Didier Picard – 03/2025

HSP90 FACTS & LITERATURE

Cytosolic heat-shock protein 90

What is this?

This file is my personal attempt at capturing the Hsp90 literature. With few exceptions it contains ALL papers with and about the cytosolic forms of Hsp90 with three important exceptions: (i) Expression analyses of the Hsp90 genes (my overview is Hsp90 *protein*-centered); (ii) the exploding pharmacological literature in which Hsp90 inhibitory drugs are used without any further genetic or biochemical analyses of Hsp90 biology; (iii) medicinal chemistry, notably the development of new drugs, and the clinical literature on their use. This monster file has grown organically over quite a number of years and hence, it is not always as organized as you might wish. However, if you search with key words, chances are you'll find everything. How to cite it? Refer to the specific web link or our web site (https://www.picard.ch) and/or cite the primary papers mentioned in here.

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General: Refs

- most abundant soluble cytosolic protein (~ 1% of total protein) even before heat-shock (Lai et al., 1984), poorly induced. Concentration depending on cells is 10 - 150 µM (Nollen and Morimoto, 2002; see also Finka and Goloubinoff, 2013); about 17.5. µM in budding yeast (Ghaemmaghami et al., 2003). Hsp90α estimated to be 2.8% in colon cancer cell lines (Wang et al., 2010). htpG in *E. coli* is present at only 5.6 µM accounting for less than 0.15% of the total protein mass (Fauvet et al., 2021). Total Hsp90 levels vary widely both in tumor and in normal cell lines and in mouse tissues (Tang et al., 2022c).

- 10-20% of all cellular proteins of yeast and humans may interact with Hsp90 and/or be affected directly or indirectly by Hsp90 inhibition (Zhao and Houry, 2007; Taipale et al., 2010; Wu et al., 2012b).
- often overexpressed in cancer (e.g. Neckers, 2002; Whitesell and Lindquist, 2005; Pick et al., 2007; Kubota et al., 2010; and many more).
- isoforms / genes:
  - isoforms are highly similar (90±5%), few clear cases of isoform-specific functional differences (for possible exceptions, see below).
  - human Hsp90α (gene HSP90AA1) and Hsp90β (gene HSP90AB1)
  - yeast (*S. cerevisiae*) *HSP82* and *HSC82*
  - only one gene in *Drosophila* (Hsp83)
  - zebra fish has one Hsp90β and two clustered Hsp90α genes (Hsp90α1 and Hsp90α2 proteins only 91% identical)
  - plants typically have more of everything
  - *Giardia* has a single but split Hsp90 gene (Nageshan et al., 2011).
  - some protozoan pathogens have multiple tandem copies (Jamabo et al., 2022).
- expression of isoforms is differentially regulated (see for example Sreedhar et al., 2004):
  human Hsp90α ~ mouse Hsp86 (~ *S. cerevisiae* Hsp82): heat-inducible
  human Hsp90β ~ mouse Hsp84 (~ *S. cerevisiae* Hsc82): constitutive, growth factor inducible
- very highly conserved: identity 60% between human and yeast, 35% identity (+18% similarity) between human and *E. coli* (HtpG).
- essential for viability in all eukaryotes, where it has been tested, i.e. in yeast (one of two isoforms is sufficient) (Borkovich et al., 1989), *Drosophila* (van der Straten et al., 1997; Yue et al., 1999), *Caenorhabditis elegans* (*C. elegans*) (Birnby et al., 2000), and mouse (Voss et al., 2000; Bhattacharya et al., 2022). HtpG dispensable in *E. coli* (Bardwell and Craig, 1988), *Actinobacillus* (Winston et al., 1996), *Bacillus subtilis* (Versteeg et al., 1999) and *Porphyromonas* (Sweier et al., 2003; Kawano et al., 2004), not found in archaea and not present in all bacteria (Chen et al., 2006a).
- Hsp90 as a <u>capacitor for evolution</u> in *Drosophila* (Rutherford and Lindquist, 1998 {discussed in Cossins, 1998; Yahara, 1999}; even including epigenetic changes in an inbred background {Sollars et al., 2003}) and *Arabidopsis* (Queitsch et al., 2002; Sangster et al., 2007). Hypothesis about the evolutionary role of Hsp90 during the pre-Cambrian glaciation and Cambrian explosion (Baker, 2006b; Baker, 2006a). Hsp90 <u>potentiates</u> the rapid acquisition of drug resistance in fungi in a calcineurin-dependent fashion (Cowen and Lindquist, 2005). However, although bristle numbers in *Drosophila* depend on Hsp90, *Hsp83* mutations have no effect on phenotypic variance (Milton et al., 2003; Milton et al., 2005; see also Debat et al., 2006). Hsp90 controls both qualitative and canalized quantitative traits (Carey et al., 2006; Milton et al., 2006; Salathia and Queitsch, 2007; see also Samakovli et al., 2007). Existence of Hsp90-buffered variation and effect of Hsp90 on it and on developmental stability in plants (Sangster et al., 2008a; Sangster et al., 2008b). May be mediated at least in part by its positive and negative interactions with Trx and Pc, respectively (Tariq et al., 2009). Alternatively, Hsp90 prevents phenotypic variations in *Drosophila* by promoting the biogenesis of piRNAs that repress expression and transposition of transposons (Specchia et al., 2010); it does so by interacting with Piwi along with Hop, thus playing an important role in canalization (Gangaraju et al., 2011; discussed by Ruden, 2011). Hsp90 system as a protein-folding reservoir that promotes both evolutionary stasis and change; thermal stress and Hsp90 inhibition increase ("normalize") the <u>correlation between phenotype and genotype</u> (Jarosz and Lindquist, 2010). Higher levels of Hsp90 correlate with lower phenotypic variation of inherited mutations (Burga et al., 2011; Casanueva et al., 2012). Fitness

benefit also seen in wild *Drosophila* populations (Chen and Wagner, 2012). In gene duplicates, the Hsp90 client can evolve faster than the non-client paralog (Lachowiec et al., 2013). Hsp90 buffers phenotypic eye size changes in cavefish (Rohner et al., 2013). Hsp90 client status of kinases promotes evolutionary rate, but the ancestral kinase may not have been a client (Lachowiec et al., 2015). However, experimental evidence in yeast argues that Hsp90 is not involved in genetic canalization, does not phenotypically buffer against the effects of new mutations, but rather enhances/potentiates them (Geiler-Samerotte et al., 2016). GWAS analysis for male genital development in *Drosophila* treated with Hsp90 inhibitor reveals large numbers of SNPs (Takahashi et al., 2018). Buffer for poliovirus capsid evolution balancing protein aggregation and stability (Geller et al., 2018). Bacterial HtpG overexpression buffers the effects of deleterious mutations arising in directed evolution experiment (Iyengar and Wagner, 2022). Ago1 buffers different genetic variants than Hsp90 in *Arabidopsis* (Lemus et al., 2023). Hsp90 stress (radicicol, heat, or ethanol) in yeast selects for robustness of sugar metabolism, and this is most notable in domesticated yeast strains; ethanol was thus a major ecological driver of canalization in yeast domestication (Condic et al., 2024).

- Down-regulation of Hsc82/Hsp82 in *S. cerevisiae* drives prolonged polarized growth, a step towards multicellularity, through destabilization of Cdc28 (Montrose et al., 2024).
- Evolution of Hsp90 family: chloroplast Hsp90 may derive from ER form and not cyanobacteria while mitochondrial Hsp90 from eubacteria other than α-proteobacteria such as *E. coli* (Emelyanov, 2002; see also Stechmann and Cavalier-Smith, 2003; Stechmann and Cavalier-Smith, 2004). Use of Hsp90 sequences for single-gene phylogenetic analysis of eukaryotes (Stechmann and Cavalier-Smith, 2003). Further analyses indicate that organellar Hsp90s are *not* derived from endosymbionts, that mitochondrial Trap1 (only in animalia and protista) and Grp94 (lost in some fungi) originated separately from ancestors of HtpG early in the formation of eukaryotic cells whereas the cytosolic Hsp90s (duplicated in vertebrates) and chloroplast Hsp90 (duplicated in higher plants) arose from Grp94 (Chen et al., 2005a; Chen et al., 2006a). These also define subfamily-specific signature sequences (Chen et al., 2006a). Coevolution with Hop (Travers and Fares, 2007). Evolutionary plasticity of Hsp90 and cochaperones (Johnson and Brown, 2009). Essentially absent from archae (Chen et al., 2006a; Large et al., 2009). A naturally occuring *Drosophila* variant in charged linker affects genetic variation of canalized traits (Sgrò et al., 2010). Duplication event in vertebrates timed (Pantzartzi et al., 2013). Duplication in plants occurred before monocot eudicot split, and vertebrates and seed plants used different mechanisms for functional diversifications (Carretero-Paulet et al., 2013). Bioinformatic analysis reveals that human and parasite Hsp90s differ by several distinct features (Faya et al., 2015). Experimental testing in yeast of fitness of reconstructed ancestral Amorphea Hsp90 and its substitutions shows pervasive contingency and irreversibility (Starr et al., 2018). Evolutionary history in plants (Li et al., 2020d). Hsp90 evolved in prokaryotes, probably around or after emergence of terrestrial prokaryotes and after Hsp70 (Rebeaud et al., 2021).
- for more genetic and biochemical interactions of yeast Hsp90 isoforms Hsp82 and Hsc82, see http://www.yeastgenome.org; for yeast 2-hybrid interactions of *C. elegans* Hsp90 (C47E8.5), see Li et al., 2004.
- By global analysis in yeast, the Hsp90 complex can be classified as a stress-inducible chaperone complex as opposed to a chaperone linked to protein synthesis (CLIPs) which also associates with nascent polypeptides (Albanèse et al., 2006). A minor proportion (~0.1%) of nascent chains in *E. coli* associate with HtpG (Zhao et al., 2021).
- Network analysis highlights Hsp90-FKBP complexes as important in responses of circadian rhythms to environmental signals (Yan et al., 2008).

- Coevolutionary analysis of Hsp90 in bacteria reveals role in flagellar assembly, chemotaxis and secretion, and association of gain/loss of Hsp90 with preference for multiple habitats (Press et al., 2013).
- *Catarrhini* primates (including humans) may also have an N-terminally (122 aa) extended version of Hsp90α (encoded by two far upstream exons), which still binds co-chaperones normally but has only half the normal ATPase activity (Tripathi and Obermann, 2013).
- Hsp90β is part of a chaperome subnetwork that is reduced in aging as well as diseased brains (Brehme et al., 2014).
- Interaction network with Hsp90, Hsp70 and Hsp40 are part of the very small core of Hsf1-dependent genes in yeast and upon heat-shock in mammalian cells (Solís et al., 2016).
- Methods (reviews and source articles): General biochemistry (Buchner et al., 1998); single molecule FRET (Gotz et al., 2016; Vermeer et al., 2024). Whole range of chaperone-related methods in a Methods Mol. Biol. volume, 1st edition (Calderwood and Prince, 2018): Cortes et al., 2018; Cox and Johnson, 2018; Davenport et al., 2018; Hoskins et al., 2018; Kumar et al., 2018; Reidy, 2018; Sager et al., 2018b; Taipale, 2018; Verkhivker, 2018; Voruganti et al., 2018; Yoveva and Sawarkar, 2018; Yuno et al., 2018. See also updated 2nd edition (Calderwood and Prince, 2023). Single-molecule analysis with optical tweezers (Tych and Rief, 2022). Ribosome profiling for interaction of Hsp90 with translating ribosome (Günnigmann et al., 2023). Use of yeast as tool (Backe et al., 2023a). FRET assays for screening for inhibitors of fungal versus human Hsp90/p23 interactions (Kohlmann et al., 2024).). Native mass spec for mapping transient interfaces of Hsp90 C-terminus with Hop TPR2A (Veale et al., 2024). Ratiometric fluorescent protein sensor (GFP-client fusion) to monitor Hsp90 client abundance without and with inhibitors in live cells (Paul et al., 2024).

Reviews:

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- General reviews: Pratt, 1990; Pratt, 1993; Smith and Toft, 1993; Jakob and Buchner, 1994; Pratt, 1997; Pratt and Toft, 1997; Csermely et al., 1998; Buchner, 1999; Caplan, 1999; Yahara, 1999; Cheung and Smith, 2000; Kimmins and MacRae, 2000; Pearl and Prodromou, 2000; Krishna and Gloor, 2001; Pratt et al., 2001; Richter and Buchner, 2001; Young et al., 2001; Mayer et al., 2002; Nollen and Morimoto, 2002; Picard, 2002 (see also Morimoto, 2002); Pratt and Toft, 2003 (see also MacLean and Picard, 2003); Prodromou and Pearl, 2003; Citri et al., 2004b; Picard, 2004; Pratt et al., 2004; Riggs et al., 2004; Sreedhar et al., 2004; Wegele et al., 2004; Pearl, 2005; Sangster and Queitsch, 2005; Terasawa et al., 2005; Whitesell and Lindquist, 2005; Zhao and Houry, 2005; Pearl and Prodromou, 2006; Picard, 2006; Stirling et al., 2006; Caplan et al., 2007; Neckers, 2007; Pearl et al., 2008; Picard, 2008; Smith and Toft, 2008; Wandinger et al., 2008; Miyata, 2009; Neckers et al., 2009a; Echeverría and Picard, 2010; Taipale et al., 2010; Trepel et al., 2010; Jackson, 2012; Röhl et al., 2013; Erlejman et al., 2014; Flynn et al., 2015; Mayer and Le Breton, 2015; Zuehlke et al., 2015; Prodromou, 2016; Vartholomaiou et al., 2016; Verma et al., 2016; Radli and Rudiger, 2017; Schopf et al., 2017; Verba and Agard, 2017; Hoter et al., 2018; Radli and Rudiger, 2018; Sima and Richter, 2018; Biebl and Buchner, 2019; Prodromou and Bjorklund, 2022; Chiosis et al., 2023; Silbermann et al., 2024; Wei et al., 2024a.
- Special review issue, edited by Didier Picard, 2012: Altieri et al., 2012; Didenko et al., 2012; Echtenkamp and Freeman, 2012; Geller et al., 2012; Hartson and Matts, 2012; Haslbeck et al., 2012; Jhaveri et al., 2012; Johnson, 2012; Kadota and Shirasu, 2012; Li et al., 2012a; Li et al., 2012c; Makhnevych and Houry, 2012; Marzec et al., 2012; Mollapour and Neckers, 2012; Prodromou, 2012; Roy et al., 2012; Sanchez, 2012; Theodoraki and Caplan, 2012; Whitesell and Lin, 2012.

- Special review book volume: Isaacs and Whitesell, 2016, including Vartholomaiou et al., 2016.
- Special review issue, edited by Chris Prodromou (Prodromou, 2023): Backe et al., 2022a; Dutta et al., 2022; Jay et al., 2022; Lynham and Houry, 2022; Maiti and Picard, 2022; Mankovich and Freeman, 2022; Omkar et al., 2022; Prodromou and Bjorklund, 2022; Xu, 2022; Ziaka and van der Spuy, 2022; van Oosten-Hawle, 2023.
- Special review issue in the book series "Subcellular Biochemistry" (volume 101), edited by Adrienne Edkins and Greg Blatch: Backe et al., 2023c; Biebl and Buchner, 2023; Chakraborty and Edkins, 2023; Ortiz et al., 2023; Prince et al., 2023; Prodromou et al., 2023; Schwarz et al., 2023.
- Reviews on Hsp90 as drug target and effects of Hsp90 inhibitors: Ochel et al., 2001; Piper, 2001; Maloney and Workman, 2002; Neckers, 2002; Workman, 2002; Isaacs et al., 2003; Maloney et al., 2003; Neckers and Ivy, 2003; Workman, 2003; Workman, 2004; Chiosis et al., 2006; Chiosis and Neckers, 2006; Sharp and Workman, 2006; Kim et al., 2009; Porter et al., 2010; Neckers and Workman, 2012; Sawarkar and Paro, 2013; Schwartz et al., 2015; Mandato et al., 2016; Tukaj and Wegrzyn, 2016; Gestwicki and Shao, 2019; Taldone et al., 2019; Zininga and Shonhai, 2019; Li et al., 2020c; Sanchez et al., 2020; Sanchez-Martin et al., 2020; Wang et al., 2021b; Ren et al., 2022b; Yadav et al., 2022a; Yu et al., 2022; Abdullah and Omran, 2024; Li et al., 2024; Saber et al., 2024; commentary on criteria for developing and validating Hsp90 inhibitors (Neckers et al., 2018); curated database (Singh et al., 2020b); on the first approved Hsp90 drug pimitespib (Doi et al., 2024); Hsp90 inhibitor patents (Liu et al., 2024a); inhibitors in clinical trials (Kim et al., 2009; Jhaveri et al., 2012; Li et al., 2013d; Jhaveri et al., 2014; Neckers et al., 2018; Yuno et al., 2018; Hoy, 2022; Maiti and Picard, 2022; Liang et al., 2024b; Liu et al., 2024g; Rastogi et al., 2024). And many many more.
- Other focused reviews:
    - Hsp90 meeting reviews: Caplan et al., 2003; Jackson et al., 2004; Richter et al., 2007a; Mayer et al., 2009; Vaughan et al., 2010; Chiosis et al., 2013; Schwenkert et al., 2014; Van Oosten-Hawle et al., 2017; Blair et al., 2019b; Edkins et al., 2023; Karras et al., 2025.
    - On proposed role of Hsp90 in chromatin remodeling and epigenetic programming relating to cancer (Ruden et al., 2005; Siegal and Rushlow, 2012; Zabinsky et al., 2019). Chromatin and DNA-related functions (Gvozdenov et al., 2019b; Wallrath et al., 2022).
    - Genome integrity (Specchia and Bozzetti, 2021).
    - Role of chaperones in evolution (Rutherford, 2003; Sangster et al., 2004; Jarosz et al., 2010; Zabinsky et al., 2019), genome stability (Kaplan and Li, 2012), and preserving genome integrity against transposable elements (Specchia and Bozzetti, 2021). Primer article on Hsp90 as buffer and potentiator of genetic variations (Schell et al., 2016). Buffer genes such as Hsp90 and mutational robustness (Tawfeeq et al., 2024). Hsp90 as global modifier of genotype/phenotype map (Aguilar-Rodríguez et al., 2024).
    - Hsp90 in plants (Krishna and Gloor, 2001; Sangster and Queitsch, 2005; Xu et al., 2012b; di Donato and Geisler, 2019; Tichá et al., 2020).
    - Hsp90-SGT1 in innate immunity of plants (Kadota et al., 2010).
    - Hsp90 for plant RNA viruses (Verchot, 2012).
    - Hsp90 and telomeres (DeZwaan and Freeman, 2010).
    - Hsp90 in neurodegenerative diseases (Luo et al., 2010; Salminen et al., 2011; Pratt et al., 2015; Bohush et al., 2019; Gracia et al., 2019; Gupta et al., 2020; Specchia and Bozzetti, 2021; Wang et al., 2021b); Hsp90 and protein aggregation and amyloid in neurodegenerative diseases (Hervás and Oroz, 2020). Folding or

holding (Rutledge et al., 2022); Aβ processing (Iqbal et al., 2023); Alzheimer's disease (Batko et al., 2024; Jeanne et al., 2024).

- Hsp90 complex and steroid receptors (Grad and Picard, 2007; Echeverría and Picard, 2010; Galigniana et al., 2010; Cano et al., 2013; Cato et al., 2014; Mazaira et al., 2018; Baker et al., 2019).
- Secreted extracellular Hsp90 (eHsp90) (Cheng et al., 2010; Li et al., 2013d; Seclì et al., 2021b; Jay et al., 2022), as biomarker (Taha et al., 2019), in the central nervous system (Calderwood et al., 2021), in cancer in general (Sager et al., 2022; Reynolds and Blagg, 2024; Singh and Jay, 2024), and the tumor microenvironment (Poggio et al., 2021). On the potential role of eHsp90α in oral squamous cell carcinoma (Abdul et al., 2023).
- Fungal Hsp90 (Leach et al., 2012; Cowen, 2013; O'Meara and Cowen, 2014; O'Meara et al., 2017; Robbins and Cowen, 2023).
- Miscellaneous parasites (Angel et al., 2014; Rochani et al., 2014; Seraphim et al., 2014; Devaney and Gillan, 2016; Woodford et al., 2016b; Angel et al., 2024).
- Single molecule analyses (Mashaghi et al., 2014; Avellaneda et al., 2017).
- Transcellular chaperone signaling and non-cell-autonomous organismal proteostasis (van Oosten-Hawle and Morimoto, 2014; Miles et al., 2019).
- Organismal role of Hsp90 (van Oosten-Hawle, 2023).
- Interaction with clients (Karagoz and Rüdiger, 2015; Rutledge et al., 2022; Babu and Freeman, 2024).
- Focus on Hsp90α and its gene *HSP90AA1* (Zuehlke et al., 2015), and on Hsp90β (Haase and Fitze, 2016).
- Innate and adaptive immunity (Tamura et al., 2016; Zininga et al., 2018).
- Cancer (Calderwood and Gong, 2016; Isaacs and Whitesell, 2016; Vartholomaiou et al., 2016; Jaeger and Whitesell, 2019; Nouri-Vaskeh et al., 2020; Birbo et al., 2021; Lacey and Lacey, 2021; Albakova et al., 2022; Alberti et al., 2022; Fu and Jia, 2022; Li and Luo, 2023; Albakova, 2024; Liang et al., 2024b; Sollars et al., 2024; Somu et al., 2024).
- Structure by SAXS (Borges et al., 2016).
- Proteomics (Weidenauer et al., 2017).
- Hsp90 and co-chaperones in tauopathies (Shelton et al., 2017b), and various clients with intrinsically disordered domains (Ramirez and Zweckstetter, 2023).
- New co-chaperones (Sager et al., 2018a; Backe et al., 2022a).
- p53 (Alexandrova and Moll, 2017).
- Stress response and adaptation (Joshi et al., 2018); buffering stress and environmental impact to prevent birth defects (Zohn, 2020).
- Hsp90/Hsp70 collaboration (Genest et al., 2019; Morán Luengo et al., 2019).
- Epichaperome and epichaperomics (Joshi et al., 2018; Taldone et al., 2019; Wang et al., 2019c; Ginsberg et al., 2022).
- Signal transduction (Streicher, 2019).
- Mitochondrial import (Becker et al., 2019).
- Hsp90-Cdc37 (Li et al., 2018; Gracia et al., 2019), and targeting interaction (Zhang et al., 2022e).
- R2TP of *Plasmodium falciparum* (Seraphim et al., 2019).
- Hsp90, R2TP and dynein assembly (Fabczak and Osinka, 2019).
- R2TP assembly (Rodríguez and Llorca, 2020), and role in maturation and assembly of macromolecular complexes (Lynham and Houry, 2022; López-Perrote et al., 2024).
- Hsp90 and other Hsps in STAT3/STAT5 signaling pathway (Jego et al., 2019).
- Aha-like co-chaperones (LaPointe et al., 2020).

- Lung diseases (Barabutis, 2020) and non-small cell lung cancer (NSCLC) (Zhu and Dai, 2024).
- Membrane-associated Hsp90 (Shevtsov et al., 2020).
- Post-translational modifications (PTMs) and their functions (Backe et al., 2020; Stewart and Schisler, 2024). Hsp90 and HDAC6 (Liu et al., 2021b).
- Regulation of Hsf1 activity (Masser et al., 2020).
- Hsp90 in pulmonary arterial hypertension (Hu et al., 2020).
- Tissue-specificity of co-chaperones (Dean and Johnson, 2021).
- Co-chaperones in disease (Altinok et al., 2021; Johnson, 2021).
- Stimulating immunotherapy with Hsp90 inhibitors (Graner, 2016; Graner, 2021).
- Hsp90 as adjuvants for immunization (Corigliano et al., 2021).
- Hsp90 in malaria and targeting it (Shonhai et al., 2021; Stofberg et al., 2021; Dutta et al., 2022).
- Hsp90-immunophilin complexes in nuclear transport (Mazaira et al., 2021; Mazaira et al., 2023).
- Bacterial Hsp90 (Wickner et al., 2021; Wickramaratne et al., 2024).
- Hsp90/Hsp70 for viral infection (Lubkowska et al., 2021).
- Fungal Hsp90 interactomes (Crunden and Diezmann, 2021).
- Regulator of extracellular matrix (Chakraborty and Edkins, 2021).
- Hsp90 function for hemeproteins and improving Hsp90 inhibitor treatments in disease (Sumi and Ghosh, 2022; see also Stuehr et al., 2022).
- Comment on complexity of Hsp90-mediated chaperoning of GR and on variety of co-chaperones (Clerico and Gierasch, 2022).
- Isoform-specific inhibitors (Yu et al., 2022).
- Isoform-specific functions (Maiti and Picard, 2022; Chang et al., 2023a).
- Retinal proteostasis and disease (Ziaka and van der Spuy, 2022).
- Role of Hsp90 in protein transport (Mankovich and Freeman, 2022).
- Role for cellular uptake of bacterial AB-type toxins (Ernst, 2022).
- Role of Hsp90 and inhibitors in cardiovascular diseases (Qi et al., 2022).
- Hsp90 as common node in multiple types of programmed cell death (Peng et al., 2022a).
- Opposite correlation of serum levels with atopic dermatitis and bullous pemphigoid (Tukaj, 2022).
- Role of putative Hsp90 co-chaperone Pin1 and Hsp90 in recruiting Nrf2 and other MAPK-regulated targets to dynein and importin-α5 for nuclear import (Ishii et al., 2023).
- On association with p53 and Cdh1/Fzr and its impact on metaphase/anaphase transition (Chowdhury et al., 2023).
- Hsp90 and metabolic enzymes (Binder and Pedley, 2023).
- In stroke-induced immunosuppression (Qiao et al., 2023).
- Dual inhibitors for cancer therapy (Xie et al., 2023).
- Effects of client PTMs on chaperone engagement (Omkar et al., 2023).
- Structural insights in into FKBP51 as co-chaperone (Baischew et al., 2023a).
- Hsp90 and non-coding RNAs (Xu et al., 2023c), and prospects for cancer therapy (Mattoo et al., 2024).
- Lessons from yeast studies (Rios et al., 2024b).
- Role for kinases (Spencer-Smith and Morrison, 2024).
- Computational and theoretical framework for understanding Hsp90 function, including its regulation by co-chaperones, ligands, and PTMs (Guarra et al., 2024).
- CFTR folding and trafficking (Scalia et al., 2024).

- Challenges for clinical trials because of large variations in Hsp90α/β isoform levels (Chang et al., 2024b).
- As guardian of tumor suppressors (Heritz et al., 2024).
- Geldanamycin and derivatives (Abdullah and Omran, 2024; Kitson et al., 2024).
- Hepatocellular carcinoma (Praveen Kumar et al., 2024).
- Fungal extracellular Hsp90 as potential target (Fang et al., 2025).
- Hsp90 in depression (Fan et al., 2025).
- Hsp90/Hsp70-dependent and independent interactions of tetratricopeptide repeat (TPR) proteins containing carboxylate clamps (Garcia-Toscano et al., 2024).
- NMR to investigate allosteric regulation (Goričan and Grdadolnik, 2025).
- Possible connection between Hsp90 modified by advanced glycation end-products and formation of urinary stones (Takata et al., 2025).

Genetics:

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- genetic analyses in budding yeast (*S. cerevisiae*) of *in vivo* functions for viability (Borkovich et al., 1989; Picard et al., 1990; Kimura et al., 1994; Minami et al., 1994; Nathan and Lindquist, 1995; Palmer et al., 1995; Louvion et al., 1996; Obermann et al., 1998; Panaretou et al., 1998; Panaretou et al., 1999; Meyer et al., 2003; Piper et al., 2003b; Francis and Thorsness, 2011; Jiang et al., 2013), spindle pole body duplication (Zarzov et al., 1997), steroid receptor regulation (Picard et al., 1990; Bohen and Yamamoto, 1993; Bohen, 1995; Nathan and Lindquist, 1995; Fang et al., 1996; Panaretou et al., 1999; Fang et al., 2006), retinoid receptors (Holley and Yamamoto, 1995), dioxin receptor (AhR) regulation (Carver et al., 1994; Whitelaw et al., 1995; Cox and Miller III, 2003; Cox and Miller III, 2004; Yao et al., 2004), src activity (Xu and Lindquist, 1993; Nathan and Lindquist, 1995; Nathan et al., 1997; Xu et al., 1999), p53 folding (Blagosklonny et al., 1996), *de novo* folding and recovery after heat inactivation of few proteins (Nathan et al., 1997), heme regulation of Hap1 (Zhang et al., 1998; Lee et al., 2002; Lee et al., 2003), HSF function (Duina et al., 1998; Harris et al., 2001), pheromone signaling and Ste11 accumulation (Louvion et al., 1998; Panaretou et al., 1999), regulation of Gcn2 (Donzé and Picard, 1999), α-complementation of β-galactosidase (Abbas-Terki and Picard, 1999), sensitivity to high salt (Imai and Yahara, 2000) and heat (Cheng et al., 1992; Imai and Yahara, 2000), sensitivity to Hsp90 inhibitors (Piper et al., 2003a; Piper et al., 2003b), maltose utilization via Mal63 (Bali et al., 2003). Microtubules aberrant in mutant strains (Yue et al., 1999), and assembly and maintenance of proteasome (Imai et al., 2003; see also Bhattacharya et al., 2020). Overexpression (Grandin and Charbonneau, 2001), deletion (Askree et al., 2004; Toogun et al., 2008), or point mutations (Toogun et al., 2008) shorten telomere length. E381K mutation shortens replicative and extends chronological life span (Harris et al., 2001). Mutations stabilize an Hsp90 degradation substrate (McClellan et al., 2005). Role in acquiring resistance to anti-fungal drugs (Cowen and Lindquist, 2005). Activating role of Ppt1 (Wandinger et al., 2006). Required for adaptation to high osmolarity by a Hog1-independent pathway; osmosensitivity of *hsp90* mutant strains suppressed by Cdc37 overexpression (Yang et al., 2006b). Comprehensive survey of effects of Hsp82 point mutants on ATPase activity, co-chaperone interaction, and GR and v-Src function (Hawle et al., 2006), and molybdate sensitivity (Millson et al., 2009). Survey of complementation and co-chaperone interactions of Hsc82 mutants (Johnson et al., 2007). Ability of Hsp90 isoforms to complement various functions (Millson et al., 2007; see also Girstmair et al., 2019; Reidy and Masison, 2020). Hsp90 mutants show secretion and vacuole targeting defects (McClellan et al., 2007). Monomeric Hsp82 is defective (Wayne and Bolon, 2007) but forced dimer is superstabilized and functional

(Wayne et al., 2010; Pullen and Bolon, 2011). Hsp90/Hsp70 machineries required for rapid galactose induction, possibly for removal of nucleosomes at target promoters (Floer et al., 2008). *Plasmodium* Hsp90 and human Hsp90α and Hsp90β support viability and confer differential sensitivities to Hsp90 inhibitors (Wider et al., 2009). *In vivo* requirements of Ydj1 for Hsp90 clients such as GR and Ste11 include farnesylation (Flom et al., 2008). Hsp90 function, possibly nuclear, is required for sporulation (Tapia and Morano, 2010). AtHsp90.1 and AtHsp90.2 (Song et al., 2010a), and AtHsp90.3 (Xu et al., 2010) complement. Required, and in particular ability to interact with Sti1, for Hsp104-mediated curing of prions (Reidy and Masison, 2010; Gorkovskiy et al., 2017). L34I mutant mimics radicicol resistance of H. fuscoatra Hsp90 (Prodromou et al., 2009). Other point mutants can partially mimic the GA resistance of *S. hygroscopicus* htpG (Millson et al., 2011). Non-phosphorylatable Hsp82 mutant Y24F is viable (Mollapour et al., 2010). Use of Hsp82 complementation to study fitness of mutant library (Hietpas et al., 2011) and relationship between expression levels and fitness of mutants (Jiang et al., 2013). Lowest Hsp90 levels still viable are 1 to 5% (Picard et al., 1990; Jiang et al., 2013). Both ts mutant and overexpression perturbs Sir2 homeostasis and gene silencing (Laskar et al., 2011). Hsp82 point mutant T101I shows unstable polysomes at low temperature (Franzosa et al., 2011). Viability and chaperone function of phosphorylation sites (Soroka et al., 2012). Aha1 overexpression can suppress impaired activity of yeast Hsp82 with charged linker from *Plasmodium* Hsp90 (Tsutsumi et al., 2012). *hsc82 W296A* affects cAMP signaling (Flom et al., 2012). A Δ*hsp82* strain is hypersensitive to Hsp90 inhibitor-induced aneuploidy (Chen et al., 2012a) and conversely, Hsp90 function is compromised in aneuploid strains (Oromendia et al., 2012). Hsp90 mutations and inhibitors destabilize hepatitis C virus core protein and its growth inhibitory effects (Kubota et al., 2012). Point mutants modeled on htpG substrate binding mutants affect various chaperone functions (Genest et al., 2013). Low levels of Hsp90 or higher temperature lead to morphological heterogeneity (elongated buds in a subset of cells) because of compromised Cla4 and Cdc28 functions, and strain ∑1278b becomes invasive (Hsieh et al., 2013). Hsp90 isoforms selectively, and in opposite ways, control the balance between resistance, apoptosis and necrotic cell death in response to acetic acid stress (Silva et al., 2013). ATP binding and ATPase requirements *in vivo* (Panaretou et al., 1998; Mishra and Bolon, 2014). Differential effects of Δ*sgt2* and SGTA/Sgt2 overexpression on steroid receptor functions (Paul et al., 2014). *CDC37* and *HSP82* are required for normal nutrient starvation response as suggested by proteomic analysis (Rødkaer et al., 2014). Slow growth phenotype of yeast complemented with human Hsp90α is exacerbated by deletion of *aha1* but not *hch1* (Synoradzki and Bieganowski, 2015). Required for homologous-recombination mediated DNA repair of double-strand breaks, rendering a panel of *hsp82* mutant strains more sensitive to MMS and UV (Suhane et al., 2015). Hsp82 overexpression upregulates Cup9 expression (Laskar et al., 2015). No isoform-selectivity or effect of overexpression on {URE3} prion, but MEEVD truncation mutant is defective (Kumar et al., 2015). Comprehensive mapping of amino acid requirements in N-terminal domain for growth and some clients indicate a number of constraints and intriguing client-specific requirements (Mishra et al., 2016; see comments in Zuehlke and Neckers, 2016). Phosphorylation by Mps1 modulates client chaperoning and sensitizes yeast to Hsp90 inhibitors (Woodford et al., 2016c). Hsp90 represses *RAD53* expression thereby augmenting genomic instability (Khurana et al., 2016). Combinatorial exploration of the fitness landscape of the 582-590 region of Hsp82 (Bank et al., 2016). Mutations in allosteric regulation points are viable but E431K ad F364A/F421A are defective for GR activity (Rehn et al., 2016). Initially reported lethality of ATPase-defective mutant E33A (Obermann et al., 1998; Panaretou et al., 1998), unlike that of the ATP binding mutant D79N (Obermann et al., 1998; Panaretou et al., 1998), could not be confirmed (Zierer et al., 2016; Reidy et al., 2023). ATPase activity and *in vivo* activity in yeast do not correlate

(Zierer et al., 2016; see also Maharaj et al., 2016; Reidy et al., 2023); what is important is a certain dwell time in the open state (Zierer et al., 2016). Hsp82 chimeras with Grp94 N- or M2-C domains are viable (Maharaj et al., 2016). Y606 mutant, notably phosphoserine mutant Y606E (equivalent of phosphorylated Y627 in human Hsp90α), impairs client accumulation and actvity (Zuehlke et al., 2017). A107N, which stabilizes the closed state, suppresses defects of W585T and *HCH1* overexpression (Zuehlke et al., 2017). Overexpression of human Tsc1 leads to toxicity, which can be suppressed by phosphomimetic Aha1 Y223E high Hsp90 affinity mutant (Woodford et al., 2017). Co-chaperones are differentially required for the activity of exogenous clients and conformation of GR (Sahasrabudhe et al., 2017). Series of temperature-sensitive mutants in M domain point out regions required for direct interaction with Hsp70 (Kravats et al., 2018); these and mutants notably in a C-terminally located region lead to Sti1-dependence (Reidy et al., 2018). *Drosophila* Hsp83 complements (Lauwers et al., 2018). *HSC82* (not *HSP82*) is required for K48-ubiquitination-mediated degradation of cytoplasmic proteins, but not K11-ubiquitination-mediated degradation of nuclear proteins (Samant et al., 2018). Δ*sti1* and Δ*hgh1* cause large decrease in Hsp90 "availability", as assayed with GR reporter (Alford and Brandman, 2018). Impact of the NxNNWHW motif of Aha1 on growth and chaperoning of cells with Hsc82 S25P (Mercier et al., 2019). Growth with either Hsc82 or Hsp82 (at similar levels) similar, but strain with Hsc82 is more affected by high temperature and by radicicol (Girstmair et al., 2019). Impact of short or long-term inactivation of Hsp90 on genome-wide DNA binding Gvozdenov et al., 2019a). Impact of mutating methylation site K594 (Rehn et al., 2020). Comprehensive fitness map of almost all possible amino acid changes in Hsp82 under different environmental conditions shows that most are fine in standard conditions (notable exceptions are a few at positions required for ATP binding or ATP-dependent conformational changes), that low Hsp90 levels are most deleterious at elevated temperature, that environmentally sensitive sites are enriched in co-chaperone/client/intramolecular contact sites and that current day Hsp90 sequences have been selected to be optimal for a range of environmental conditions (Flynn et al., 2020; Cote-Hammarlof et al., 2021). Ssa4 (and probably Ssa3) support Hsp90 client maturation less efficiently than Ssa1 or Ssa2 (Gaur et al., 2020). Hsp90 inhibition in cells transiently overexpressing human CPEB2 triggers persistent nongenetic inheritance of translational activation of some mRNAs (Tsvetkov et al., 2020). Poor complementation by human Hsp90α compared to Hsp90β mapped to N-terminus, and contributions of Sba1, Cpr6/7 to promote the closed state of α relative to β and yeast Hsp90 (Reidy and Masison, 2020). Far C-terminal α-helical region of Sba1/p23 transiently interacts with Hsp90 MC domains and required for GR activation (Biebl et al., 2021). Analysis of new series of ts mutants of Hsc82 indicate disruption at different steps and client-specific defects (Hohrman et al., 2021). Δ*hsc82* but not Δ*hsp82* is unable to grow with non-fermentably carbon source and has defective mitochondria (Jiang et al., 2021). Contact sites revealed by the cryo-EM loading complex with GR tested in yeast (Wang et al., 2022b). Exogenous expression of dual combinations of FNIP1/FNIP2 and Tsc1 promote endogenous and exogenous (e.g. steroid receptors) client stability and activity (Backe et al., 2022b). Hsp90 of *Entamoeba histolytica*, *Cryptococcus neoformans*, and *S. pombe* complement (Reidy et al., 2023). Mutants equivalent to E33A but not D79N of heterologous Hsp90, except *S. pombe*, all complement for viability; while E33A is viable, it is defective for some non-essential clients; second-site mutations within Hsp90 rescue growth defect of human Hsp90β strain with "E33A" mutation and non-essential client functions within budding yeast Hsp82 and *S. pombe* Swo1 (Reidy et al., 2023). Not required for cytosolic iron-sulfur protein assembly, but Hsp90 depletion increases mitochondrial metabolism (Carvalho et al., 2023). Hsp82 S485A mutant (in wt *HSC82* background) has *petite* phenotype, cannot grow on non-fermentable carbon sources,

and has severely defective mitochondria with complete loss of mitochondrial DNA (Peng et al., 2023). Non-permissive temperature with G170D reduces fidelity of translation initiation (Kolhe et al., 2023). Impact of Hsp82 K27 acetylation on Rad51 and DNA repair (Rani et al., 2024). The hypomorphic Hsp82 mutants A587T, G313S, or T101I as the sole source of Hsp90 compromise palatinose metabolism, whereas overexpression of Hsc82 are more resistant to Hsp90 stress in this respect (Condic et al., 2024). Differential impact of Y38, 61, and 197 mutants of human Hsp90α on growth and clients (Huo et al., 2024). Mutational scanning screen for dominant-negative mutants in N-terminal domain; beyond impairing growth, they display ATP hydrolysis in a partially open state, and promote client degradation (Flynn et al., 2025).

- genetic interactions in <u>budding yeast</u>: synthetic lethality between Δ*hsc82* and *cdc37-1* (Kimura et al., 1997), and Δ*cpr7* and Δ*hsc82* or *hsp82*^{G170D} (Duina et al., 1996). A Δ*hch1* Δ*aha1* strain with low levels of Hsp90 is temperature-sensitive (Lotz et al., 2003). Cdc37 overexpression can rescue v-Src but not GR activity in a strain with the Hsp82 G170D ts mutant (Kimura et al., 1997). Synthetic effects between Δ*cpr7* and Δ*hsc82* on HSF activity (Duina et al., 1998) and growth on maltose (Bali et al., 2003). Synthetic lethality and allele-specific complementation between *HSP90* and *STI1* (Chang et al., 1997, see also Flom et al., 2005; Flom et al., 2006). A fragment of Hsp82 suppresses the Ste4-induced growth arrest (Edwards et al., 1997). Synthetic lethality between *mps1-1* and *hsc82* (Jones et al., 1999), and *skp1* and *hsp90* (Stemmann et al., 2002). Overexpression (perhaps in a subtly isoform-specific fashion) suppresses ts cell cycle arrest and GA hypersensitivity of a *hsf* mutant (Morano et al., 1999). Δ*hsc82* derepresses invasive growth in *KSS1*-dependent way (Palecek et al., 2000). In a Δ*sti1* strain, *C. elegans* Hsp90 and human Hsp90β cannot support viability (Piper et al., 2003b). Synthetic effects of *hsp82* mutation and overexpression with *rpn* (genes for 19S proteasome subunits) mutations (Imai et al., 2003). Temperature-dependent synthetic lethality between *cns1-1* and *hsp82*ΔEEVD (Tesic et al., 2003). Overexpression of Sba1 is growth inhibitory in a Δ*hsc82* strain, and this depends on Hsp90 binding (Oxelmark et al., 2003). In contrast, Sba1 overexpression suppresses temperature-sensitivity and dioxin receptor signaling defect of Hsp82 G170D mutant (Cox and Miller III, 2004). p23 partially suppresses GR signaling defects of certain Hsp82 mutants (Hawle et al., 2006). Hsc82 G309S mutant particularly dependent on Sti1 to mediate interaction with Hsp70 (Flom et al., 2007). *HSP82* suppresses α-synuclein toxicity (Liang et al., 2008). Genetic interactions indicate that Hsc82/Hsp82 are involved in assembly of the mitochondrial F1F0-ATPase synthase complex (Francis and Thorsness, 2011). *CPR7* essential when the charged linker of Hsp90 is deleted; this synthetic lethality can be suppressed by Cns1 overexpression as well (Zuehlke and Johnson, 2012). Δ*cpr6* is synthetic sick with *hsp90-A587T* (Zuehlke et al., 2013). *utp21* mutation is synthetically sick with Δ*hsc82* (Tenge et al., 2014). Overexpression of Hch1 impairs growth of some Hsp82 mutants (including phosphoserine mimic Y606E; Zuehlke et al., 2017)and increases sensitivity to Hsp90 inhibitors; Δ*hch1* is hyperresistant (Armstrong et al., 2012). Δ*hch1* is lethal in a yeast strain with *hsp82* E381K (Horvat et al., 2014), but suppresses growth phenotype and reduced client accumulation and activity of Hsp82 W585T mutant (Zuehlke et al., 2017). *sgt* and *cns1* point mutants are hypersensitive to overexpression of other co-chaperones, which must be able to bind Hsp90 but not necessarily compete directly (Johnson et al., 2014). Expression of both *HSC82* and *SSA2* rescue lethality of Δ*hsf1* in non-stressed cells (Solís et al., 2016). Series of temperature-sensitive mutations in M domain, which are defective for interaction with Hsp70, are synthetic lethal with Δ*sti1* (Kravats et al., 2018). Hsp82 overexpression can maintain Tor1 activity in cells overexpressing molecular chaperones (Peric et al., 2017). Two N-terminal and C-terminal clusters of point mutants lead to Sti1-dependence, and additional co-chaperone deletions

differentially affect growth; Sti1-dependence can be relieved by intramolecular suppressing point mutants (Reidy et al., 2018). Hsp90 mutants genetically interact with Δ*emc2* and multiple emc (components of ER membrane complex) deletions are hypersensitive to Hsp90 inhibitors and defective for GR function (Kudze et al., 2018). Complementation experiment with Hsp90 from other yeasts (*N. castelli, K. lactis* and *Y. lipolytica*) shows relative salt resistance for strain with *Y. lipolytica* Hsp90 and a wider phenotypic variation and Hsp90-related protein network adaptations in a laboratory evolution experiment than with wild-type (Koubkova-Yu et al., 2018; see also discussion in Helsen et al., 2019). Comprehensive analysis of co-chaperone double mutants for growth and specific Hsp90 clients (Biebl et al., 2020). Sti1 becomes essential in strains with certain Ssa1 point mutants (with Ssa1 as sole Hsp70), potentially because Ydj1 competes more efficiently with Ssa1-Hsp90 interaction (Gaur et al., 2022). Deletions of *HSP82* or *HSC82* exacerbate toxicity of mammalian Nrf2 (Ngo et al., 2022). Overexpression or deletion of *HCH1*, *AHA1*, *CPR6*, *SBA1*, *STI1*, and others, or of the Hsp90 inhibitor NVP-AUY922 differentially affect Hsc82 mutants affected at different stages of the chaperone cycle, indicating that cochaperones tightly regulate the transitions between open and closed Hsp90 states (Mercier et al., 2023). Hsc82 point mutants W296A and G424D, which affect non-overlapping sets of soluble proteins, complement each other for growth (Rios et al., 2024a). Hsp90 reopening mutants have biggest effect on eEF2 levels and growth, the latter being compounded by Δ*hgh1*, and loading/closing mutants reduce sensitivity to diphtheria toxin but enhance it in absence of *STI1* (Fulton et al., 2024).

- genome-wide 2-hybrid screen and interaction with Cdc37 in budding <u>yeast</u> (Millson et al., 2004).
- suppressors in <u>yeast</u>: Protein phosphatase 2C is a multicopy suppressor of Hsp90 ts mutation in *S. pombe* (Shiozaki et al., 1994). Budding yeast: allele-specific complementation between *HSP90* and *STI1* (Chang et al., 1997). Allele-specific suppression of *hsp90* ts mutations by *SSF1*, *HCH1*, and *CNS1* (Nathan et al., 1999). Deletion of *SCH9* (codes for a PKB-like kinase) suppresses defects of strain with low levels of Hsp90 (Morano and Thiele, 1999). Cna2 overexpression suppresses salt sensitivity of Hsc82 overexpressor strains (Imai and Yahara, 2000).
- genetic analyses in <u>fission yeast</u> (*S. pombe*): a point mutation in Swo1 (Hsp90) suppresses lethality of Wee1 overexpression, is synthetically lethal with cdc2 mutations (but does not affect Cdc2 levels and in vitro kinase activity) (Muñoz and Jimenez, 1999) and suppresses effects of overexpressed Mik1 and Swe1 from budding yeast (Goes and Martin, 2001). Synthetic lethality between *swo1* and Wos2 (p23) overexpression (Muñoz et al., 1999). Swo1 overexpression suppresses some radicicol effects (Ki et al., 2001). Genetic and biochemical interactions with *rng3* and *myo2* indicate role in formation of actomyosin ring (Mishra et al., 2005). Hsp90 required in glucose/cAMP repression pathway (Alaamery and Hoffman, 2008). Required as silencing factor for the formation of heterochromatin at pericentromeric regions through siRNA loading of Ago1 (Okazaki et al., 2018; Kato et al., 2019; see also Kato et al., 2019). Hsp90 required with co-chaperone TTT to promote incorporation of PIKK pseudokinase Tra1 into SAGA (Elías-Villalobos et al., 2019). Requirement for TTT for cotranslational maturation of PIKKs (Toullec et al., 2021). Hsp90 required for RNAi-dependent and -independent heterochromatin assembly and silcencing by promoting assembly/maintenance of the Ago1-associated complexes ARC and RITS, and Fft3 and SHREC, respectively (Sun et al., 2020b). *S. pombe* Swo1 mutant equivalent to E33A of budding yeast complements, and *S. cerevisiae* wild-type but not E33A Hsc82 or Hsp82 complement (Reidy et al., 2023).

- genetic analysis in the fungus <u>*Podospora*</u> *anserina*: mod-E1 mutation in single Hsp90 gene gives thermosensitivity, developmental defects and suppresses vegetative incompatibility (Loubradou et al., 1997).
- genetic analyses in <u>*Drosophila*</u>: Hsp83 (and Cdc37) mutations impair signaling by torso (Doyle and Bishop, 1993), sevenless (Cutforth and Rubin, 1994; van der Straten et al., 1997) and Raf (van der Straten et al., 1997). Mutant Hsp83 alleles are embryonal lethals over a deficiency of locus, but some complement other mutant alleles (van der Straten et al., 1997; Yue et al., 1999). Second-site non-complementation between *Hsp83* mutations and a *Cdc37* null allele (Kimura et al., 1997). When Hsp90 is mutant (heterozygous) or inhibited by geldanamycin or challenged at higher temperature, phenotypic variations in nearly all adult structures become apparent because of the expression of previously silent genetic determinants (Rutherford and Lindquist, 1998, discussed in Cossins, 1998). Spermatogenesis seems to be particularly sensitive to reductions in Hsp90 functions and correlates with defect in microtubule dynamics (male sterility in viable transheterozygotes and when Hsp90 is reduced) (Yue et al., 1999). Depletion of Hsp90 and Droj1 with RNAi in SL2 cells induces heat-shock response (Marchler and Wu, 2001). Hsp83 mutant flies show exaggerated homeostatic response and die after sleep deprivation (Shaw et al., 2002). Hsp83 is required for localization of some mRNAs in embryos, possibly through maintenance of Lkb1 (Song et al., 2007). Required for Trithorax (Trx) function and co-recruited to actively transcribed genes (Tariq et al., 2009; see also Sawarkar et al., 2012). Required for full female fertility (Yue et al., 1999) and proper oogenesis, in particular for "dumping" and in combination with *cup* alleles (Pisa et al., 2009). Hsp90 buffers circadian behavioral activity patterns (Hung et al., 2009). Mutations and RNAi interfere with cell cycle exit suggesting the APC/C activator Cdh1 may be an Hsp90 client (Bandura et al., 2013). SNPs associated with micro-environmental plasticity of female startle response (Morgante et al., 2015). Increased autophagy and degenerating egg chambers in transheterozygotes (Choutka et al., 2017). RNAi-mediated KD leads to loss of ovarian germline stem cells and heterozygous mutations accelerate loss in *spag* KD ovaries (Chen et al., 2018a). KD and overexpression in neural stem cells blocks and promotes reactivation, respectively, through insulin signaling pathway (Huang and Wang, 2018). KD impairs axon injury signaling through the DLK ortholog Wallenda (Karney-Grobe et al., 2018). Exposure of early embryos to ether challenges Hsp90, reduces the levels of its client Trx and thereby a homeotic transformation, which is also aggravated in an heterozygous Hsp83 mutant or upon exposure to geldanamycin (Snir et al., 2024).
- <u>*Cyanobacteria*</u>: HtpG is essential for thermotolerance (Tanaka and Nakamoto, 1999), cold acclimation (Hossain and Nakamoto, 2002), and protection against oxidative stress (Hossain and Nakamoto, 2003). Overexpression is growth inhibitory; normal levels of htpG, which is localized to the membrane fraction, is required for normal levels of its client uroporphyrinogen decarboxylase (HemE) (Watanabe et al., 2007). Thermotolerance is impaired by cyclic lipopeptide antibiotics that bind htpG (Minagawa et al., 2011).
- <u>*E. coli*</u>: htpG is essential for swarming (Inoue et al., 2007) and in a competitive swimming/chemotaxis assay (Press et al., 2013). Becomes more thermotolerant upon overexpression of Hsp90 from rice (Liu et al., 2009a). *E. coli* is hypersensitive to SDS upon overexpression of htpG, which also leads to filamentation, and a panel of substrate binding mutants alleviates this (Genest et al., 2013). Δ*htpG* mutant has reduced β-lactamase and alkaline phosphatase activity, and impaired biofilm formation and protein at elevated temperature (Grudniak et al., 2013). Required for stability of Cas3 and its function in CRISPR system (Yosef et al., 2011). Required for production of genotoxic secondary metabolites such as colibactin and yersiniabactin and associated virulence; might protect a substrate in this pathway against degradation by ClpQ protease (Garcie

et al., 2016). Overexpression of eukaryotic Hsp90 renders cells more heat-resistant (Vishwakarma et al., 2018). Δ*htpG* partially rescues stress-induced growth and proteomic defects of Δ*KJ* mutant (Fauvet et al., 2018). Overexpression leads to filamentation because htpG binding to the tubulin homolog FtsZ prevents it from polymerization; Δ*htpG* cells are slightly shorter (Balasubramanian et al., 2019). htpG deletion and overexpression suppresses and aggravates, respectively, the growth defect of a ΔdnaKΔdnaJ strain; htpG may promote degradation of aggregation-prone metabolic and respiratory enzymes, possibly through the HsIUV protease (Fauvet et al., 2021). Direct interaction between HtpG and DnaK is essential for production of colibactin by pathogenic *E. coli* (Corteggiani et al., 2022).

- In *Edwardsiella tarda*, a htpG mutation affects growth and resistance to oxidative stress (Dang et al., 2011).
- In *Bacillus subtilis*, recovery from heat shock is retarded without htpG (Versteeg et al., 1999).
- Hsp90 inhibitors affect viability and cold adaptation (slightly) of γ-proteobacteria (Garcia-Descalzo et al., 2011).
- htpG overexpression improves butanol tolerance and adaptation in Clostridium (Mann et al., 2012).
- htpG required for virulence in *Leptospira interrogans* (Marcsisin et al., 2013; King et al., 2014).
- *HtpG* of *Salmonella typhimurium* is required for intestinal persistence in pigs (Verbrugghe et al., 2015).
- Required in *Shewanella oneidensis* for growth under heat stress; involves TilS as client (Honoré et al., 2017); Hsp90 and HsIVU protease have antagonistic effects for TilS (Honoré et al., 2019). Growth under heat stress and TilS activation require direct interaction of Hsp90 with DnaK (Corteggiani et al., 2022).
- Δ*htpG* of *Pseudomonas aeroginosa* is temperature-sensitive and displays several other phenotypes (Grudniak et al., 2018).
- *HtpG* modulates cell envelope in *Vibrio mimicus*, affecting antibiotic resistance (Qin et al., 2024).
- Mouse: Hsp90β knock-out embryos are normal till E9/9.5, then die because of defective allantois and allantois-trophoblast interaction (Voss et al., 2000). Hypoxia-induced accumulation of HIF-1α is delayed in null fibroblasts (Katschinski et al., 2004). Spermatogenesis is disrupted in Hsp90α mutant mice because of a specific meiotic arrest in pachytene; Hsp90β levels unchanged in a panel of tissues (Grad et al., 2010; see also Kajiwara et al., 2012; Tang et al., 2021). Hsp90α KO have defective antigen cross-presentation by dendritic cells (Imai et al., 2011); however, MHC class II antigen presentation is increased (Li et al., 2012d). Hsp90α KO have defects in piRNA biogenesis and the PIWI protein MIWI2 is mislocalized, resulting in an increased expression of the L1 retrotransposon ORF1 in testes (Ichiyanagi et al., 2014). Hsp90α KO mice have reduced myocardial fibrosis upon pressure overload and myocardial fibroblasts produce less collagen (García et al., 2016; see also Cáceres et al., 2018). Hsp90α not absolutely required for development of tumors and metastasis in PyMT mammary carcinoma model; without Hsp90α tumor burden, but not numbers, and metastasis are reduced and proliferation and migration of isolated primary carcinoma cells is impaired (Vartholomaiou et al., 2017). Hsp90α KO mice display reduced support for development of pulmonary metastasis of injected melanoma cells (van der Weyden et al., 2017). AAV-mediated overexpression of Hsp90β exarcebates epileptic seizures in mouse model; suppressed by GA (Sha et al., 2017). Note that the original Hsp90α KO of Udono and colleagues expresses a chaperone-defective C-terminal truncation of 232 AA, but have normal extracellular Hsp90α function in skin wound healing (Bhatia et al.,

2018). Hsp90α KO mice show retinitis pigmentosa and progressive blindness from week 3 after birth, correlated with photoreceptor death, defective intersegmental transport and tubulin deacetylation (Wu et al., 2020b); another study found that Hsp90α is specifically required in rod and not cone photoreceptor cells, possibly through stabilization but not assembly of PDE6, without the afore-mentioned other photoreceptor defects (Munezero et al., 2023). Hsp90α KO mice are less sensitive to DNCB-induced skin contact hypersensitivity (Kim et al., 2022). Upon manipulating Hsp90 alleles, total Hsp90 protein levels must remain 50-70% of wt levels depending on tissue; with only one Hsp90β allele remaining, only embryos develop, which have been able to increase translation of that allele (Bhattacharya et al., 2022). *fkbp5* TPR-mutant mice, in which FKBP51 is Hsp90 interaction-deficient, display reduced corticosterone and ACTH levels after acute stress, and females gain weight in high fat diet (Wang et al., 2024e).

- *C. elegans*: null mutation of very highly expressed *daf-21* (called *hsp-90* as of 2018) gene is an early larval lethal; point mutation E292K shows defects in chemosensory responses in a dosage-dependent fashion (Birnby et al., 2000; see also Vowels and Thomas, 1994; Horikawa et al., 2015). Knock-down results suggest daf-21 is required for Wee1 function and meiotic prophase/metaphase transition in oogenesis (Inoue et al., 2006). Knock-down impairs development of gonadal arms, a Hop-like phenotype (Gaiser et al., 2009). Hsp90 genes from other nematodes rescue at best partially (Gillan et al., 2009). *daf-21* mutation causes muscle defects (Gaiser et al., 2011). Higher levels of Hsp90 promoter activity correlate with lower phenotypic variation, higher thermotolerance and lower reproductive fitness (Casanueva et al., 2012). Genetic evidence for repression of Hsf1 by Hsp90 (Barna et al., 2012). Compromising Hsp90 functions by proteotoxic stress, knock-down or overexpression in one tissue affects Hsp90 functions, e.g. in heat-shock response, systemically (non-cellautonomously) in other tissues through transcellular chaperone signaling (van Oosten-Hawle et al., 2013); requires the GATA factor PQM-1 in the sender tissue (O'Brien et al., 2018). Knock-down of Hsp90, Hsp70, Sgt1 and Unc45 induce Hsf1 reporter (Guisbert et al., 2013). Daf-21 interacts with the EBAX-1 gene for quality control of the SAX-3/Robo receptor involved in axon guidance (Wang et al., 2013e). Knock-down aggravates protein aggregation toxicity and reduces lifespan (Brehme et al., 2014). Hsp90 and its co-chaperones Aha1, Hop, and p23 are required for muscle integrity and motility in a unc45 mutant background (Frumkin et al., 2014). Knockdown indicates Hsp90 is required for age-dependent cilia recovery (Cornils et al., 2016). Mutation of HLH-1 transcription factor binding site in *daf-21* promoter severely reduces myogenic expression and muscle proteostasis ("muscle-specific Hsp90 knock-down") (Bar-Lavan et al., 2016). Hsp90 suppresses the mobility of transposable elements unless challenged, e.g. by moderate environmental stress (Ryan et al., 2016). RNAi affects genes involved in innate immune response and gonadal and larval development (Eckl et al., 2017). *daf-21* mutants are hypersensitive to infection by the bacterial pathogen *Proteus mirabilis* (JebaMercy et al., 2016). Promotes Notch signaling in the germline (Lissemore et al., 2018). *daf-21* required for normal longevity, mitigated by *daf-16* LOF (Somogyvari et al., 2018). Weaker and/or later *daf-21* KD extends lifespan (Janssens et al., 2019). Mutations of *hsp-90* or co-chaperone genes suppress the neurite growth defect of mutations of *mec-15*, which encodes an F-box protein targeting the Hsp90 client DLK-1 (Zheng et al., 2020a). Overexpression of Hsp90 protects against toxicity of Aβ peptide (Lackie et al., 2020). Extensive transcriptomic analysis of impact of *hsp90-90* RNAi (Schmauder and Richter, 2021). Mutation affects adaptation to chemically induced hypoxia and mitochondrial function (Pant et al., 2021). Mutation or pharmacological inhibition of Hsp90 protects against TDP-43 neurotoxicity in a manner dependent on normal expression of the small Hsp gene *hsp-16.1*, and upregulates heat-shock pathways (Garcia-Toscano et al., 2024).

- Chicken cells lacking Hsf1 and Hsf3 have 4x reduced Hsp90α and are hypersensitive to stress and GA (Nakai and Ishikawa, 2001).
- Chicken cells lacking Hsp90β grow more slowly and have defective B-cell receptor signaling; Hsp90α can complement, too (Shinozaki et al., 2006).
- *Leishmania* promastigotes overexpressing Hsp90 are more resistant to GA (Wiesgigl and Clos, 2001). Overexpression of radicicol-resistant point mutant allows the demonstration that Hsp90 is required at multiple life stages and that growth is improved by mutation to canonical MEEVD and that Sti1 interaction is important (Hombach et al., 2013). Impact of mutations of phosphorylation sites on viability, growth and infectivity (Hombach-Barrigah et al., 2019). Overexpression of Hsp90 increases PKA activity (Nation et al., 2023).
- Human polymorphism (SNPs) - first survey of 73 caucasian samples (Passarino et al., 2003). One of these polymorphisms in Hsp90α encodes a functionally defective point mutant (MacLean et al., 2005). The same one, Q488H, as homozygote correlates with increased breast cancer risk (Zagouri et al., 2012). Correlation of particular polymorphisms in Hsp90α and β genes and NSCLC (Coskunpinar et al., 2014) and high expression of Hsp90β with poor survival (Kim et al., 2015a). A SNP in *HSP90AA1* correlates with reduced risk of recurrent ischemic stroke (Kobzeva et al., 2024).
- Knock-outs of Hsp90α and Hsp90β in human MDA-MB-231 breast cancer cells abolishes migration/invasion and proliferation, respectively (Zou et al., 2017).
- Polymorphism in flanking regions of the sheep Hsp90α gene correlate with susceptibility to scrapie (Marcos-Carcavilla et al., 2008; Marcos-Carcavilla et al., 2010), to DNA fragmentation in sperm (Ramon et al., 2014), and perhaps to climate adaptation (Salces-Ortiz et al., 2015).
- Plants: silencing of NbHsp90c-1 gene in tobacco leads to a stunted phenotype and a compromised hypersensitive response to pathogens, including resistance mediated by the Pto, N and Rx genes (Kanzaki et al., 2003; Lu et al., 2003). Silencing of an organellar Hsp90 also causes loss of the *Pto*-mediated response but not resistance (Lu et al., 2003). Point mutations in *HSP90.1* and *HSP90.2* of *Arabidopsis* specifically compromise RPS2 (Takahashi et al., 2003) and RPM1 functions (Hubert et al., 2003), respectively. Also required for RPS4- (Zhang et al., 2004c), and I-2-dependent resistance (de la Fuente van Bentem et al., 2005). Hsp90.2 and Hsp90.3 required for RPP4-mediated resistance (Bao et al., 2014). In contrast, Hsp90 reduction increases resistance to herbivores (Sangster et al., 2007). Dominant-negative Hsp90.2 induces heat-shock response (Yamada et al., 2007). Compensatory changes in Hsp90 and SGT1 prove this interation to be essential for pathogen resistance (Kadota et al., 2008; reviewed in Picard, 2008; Shirasu, 2009). Overexpression of cytosolic or organellar Hsp90 in *Arabidopsis* increases sensitivity to salt and drought stresses (Song et al., 2009; see also Xu et al., 2010). Specific mutations in *Arabidopsis HSP90.2* that suppress all *rar1* phenotypes; mutants may be independent of RAR1 co-chaperone because of increased cycling between open and closed lid conformation, independent of ATPase (Hubert et al., 2009). The 4 genes for cytosolic Hsp90 in *Arabidopsis* must ensure a minimal level of Hsp90 (Hubert et al., 2009). Reduced *HSP90.2* activity compromises stomatal closure and ABA signaling in *Arabidopsis* (Clément et al., 2011). Differential effects of virus-induced silencing different *HSP90* genes on seedling growth and the hypersensitive response in wheat (Wang et al., 2011). *HSP90* silencing abolishes accumulation of R proteins I-2 and Mi-1 in tobacco (Van Ooijen et al., 2010). Transgenic expression of soybean Hsp90s in *Arabidopsis* protects against abiotic stresses and perturbs proline metabolism (Xu et al., 2013). Mutants of *Arabidopsis* Hsp90.2 and Hsp90.3 display enhanced disease resistance associated with increased levels of immune receptors SNC1, RPS2 and RPS4 (Huang et al., 2014). Hsp90 (RAR1 and SGT1) contribute to

suppressing (!) disease tolerance/defenses to bacterial wilt disease (Ito et al., 2015). Knock-down or overexpression of HSP90.1 in *Arabidopsis* T-DNA integration and transformation (Park et al., 2014). Hsp90 orchestrates regulatory network for flowering (Margaritopoulou et al., 2016). Impact of *hsp90.2* and Hsp90 inhibitor on circadian period (Davis et al., 2018). *hsp90.2-3* mutation in *Arabidopsis* promotes membrane association of Ago1 (Sjögren et al., 2018). Hsp90 is involved in controlling retrograde communication between chloroplast and nucleus sustaining photosynthesis-associated nuclear gene expression when preproteins accumulate (Wu et al., 2019b). Mutation or knock-down of Hsp90 in *Arabidopsis* increases levels of soluble polyamines (Toumi et al., 2019). MeHSP90.9 of Cassava is required for drought resistance through stimulating the transcription factor MeWRKY20, which induces ABA synthesis, and MeCatalase1 activity to reduce H_2O_2 (Wei et al., 2020b). Also required for modulating immune responses by stimulating salicylic acid synthesis through its client MeSRS1 and inhibiting auxin production through its client MeWRKY20 (Wei et al., 2021b). Knock-down, or *hsp90.1* and *hsp90.2* mutations show that Hsp90 is required for stomatal development in *Arabidopsis thaliana* (Samakovli et al., 2020b; Samakovli et al., 2020c). Cold-sensitive lethality of interspecific *Nicotiana* hybrids, and cell lines derived them, can be traced to their SGT1 and RAR1, possibly differentially affecting their R proteins (Katsuyama et al., 2021). In tomato, different expression levels of HSP90.2 of cultivars correlate with root development and overexpression leads to increased root biomass and architecture (Yadav et al., 2021). Impact of *hsp90* mutations and KD on *Arabidopsis* embryogenesis (Samakovli et al., 2021b); KD also affects asymmetrical membrane distribution of auxin transporter PIN1 (Samakovli et al., 2021a). Overexpression and KD of *Cassava* MeHSP90.9 augments and reduces, respectively, autophagy and disease resistance (Wei et al., 2021a). Hsp90 required for CHS3-mediated defense signaling and more broadly in other NLR-mediated defense (Lu et al., 2022a). Silencing of HSP90.1 or HSP90.2 in *A. thaliana* impairs signaling of the brassinosteroid receptor BRI1/BAK1 (Samakovli et al., 2022). Hsp90 regulates crosstalk of gibberellin and brassinosteroid signaling; gibberellin-induced degradation of DELLA proteins depends on Hsp90 ATPase (Plitsi et al., 2022). Overexpression of *Dianthus caryophyllus* Hsp90-6 in *Arabidopsis* renders it more thermotolerant (Xue et al., 2022b). A single amino acid change in the ATPase domain of HSP90.6 of *Zea mays* leads to small kernels, and affects nitrogen and carbon metabolism through the proteasome and the 14-3-3 protein GF14-4, respectively (Xu et al., 2023b). HSP90.2 mutant durum wheat impairs CO_2 assimilation, photosynthesis, and grain weight gain, and overexpression increases kernel weight (Yan et al., 2023b). *hsp90.2* KO in wheat is more sensitive to powdery mildew and overexpression makes wheat more resistant (Yan et al., 2023a). KD show that HSP90s required for hypocotyl elongation during both skoto- and thermomorphogenesis through ELF3 in *Arabidopsis* (Zeng et al., 2023; commented on by Somers, 2023).

- <u>Dominant-negative Hsp90</u>: ATP binding mutant blocks eNOS and Akt function in transfected tissue culture cells (Miao et al., 2008; see also Chen et al., 2017b). A point mutant of *Arabidopsis* Hsp90.3 behaves as a dominant-negative mutant (Huang et al., 2014). DN mutant affects HIF1/2α levels (Filatova et al., 2016). Dominant-negative mutants in N-terminal domain of budding yeast Hsp90 impair growth, display ATP hydrolysis in a partially open state, and promote client degradation (Flynn et al., 2025).
- Hsp90 and IGF1R expression correlate in Ewing sarcoma, and Hsp90 overexpression with drug resistance in cell lines (Martins et al., 2008).
- <u>*Candida albicans*</u>: Hsp90 represses an environmentally triggered, and Ras1-PKA-dependent morphogenetic transition (Shapiro et al., 2009), which depends on its interaction with Cdc28 (Senn et al., 2012). Inhibition of Pkc1 phenocopies inhibition/reduction of Hsp90 in rendering cells hypersensitive to drugs (LaFayette et al.,

2010). Hsp90 is required for biofilm growth, maturation and dispersal both in *Candida* and *Aspergillus*; reduction of Hsp90 reduces matrix glucan levels and increases sensitivity to anti-fungal drugs (Robbins et al., 2011). Chemical genomics screen reveals extensive Hsp90 network and regulation by CK2 (Diezmann et al., 2012). Sgt1 is also involved (Shapiro et al., 2012). Compromised Hsp90 reduces calcineurin levels (Shapiro et al., 2012) and through that renders cells more resistant (!) to apoptosis (Dai et al., 2012). Pharmacological and genetic evidence suggests trehalose as negative regulator of Hsp90 (Serneels et al., 2012). Amphotericin B resistance requires high levels of Hsp90 to compensate for reduced fitness of mutants (Vincent et al., 2013). Genetic and biochemical interactions with transcription factors for biofilm formation and morphogenesis highlights Tup1 (Diezmann et al., 2015). Hsp90 depletion increases Hsf1 activity before heat-shock but compromises early heat-shock responses (Leach et al., 2016). Chemical genetic screen covering 10% of genome reveals that defects in ergosterol biosynthesis and actin remodeling overwhelm Hsp90 (O'Meara et al., 2016). Depletion of Hsf1 somehow compromises Hsp90 function independent of its effect on Hsp90 expression (Veri et al., 2018). Reduction of Hsp90 levels induces homothallic mating response (Guan et al., 2019). Hsp90 impairment affects P-body and stress granule formation in response to antifungals (O'Meara et al., 2019). Phosphorylation of S530 and mutation of T25 (equivalent to budding yeast T22) compromise virulence traits, (Alaalm et al., 2021). DNA polymerase ε mutants are multidrug resistant in an Hsp90-dependent way, possibly because of replication stress-induced Hsp90 expression (Utkalaja et al., 2024).

- Selection for resistance to azole antifungals and geldanamycin with budding yeast and *Candida* also leads to point mutations in Hsp90 (Hill et al., 2013). Adaptation and resistance to drug combinations, including Hsp90 inhibitors, is associated with reduced fitness in *Candida albicans* (Hill et al., 2015).
- Essential for growth of *Candida auris*; Hsp90 depletion induces filamentous growth in several *Saccharomycetales* species of the CUG clade (Kim et al., 2019b; see also Hossain et al., 2020).
- Required in *Aspergillus fumigatus* for viability, cell wall and various other functions (Lamoth et al., 2012). Acetylation of two lysine residues compromises Hsp90 function, drug resistance and virulence (Lamoth et al., 2014).
- Knock-down in mosquito reduces dehydration tolerance (Benoit et al., 2010).
- Knock-down in planarians is lethal suggesting a cytoprotective role in the gastrodermis (Conte et al., 2011).
- In *Giardia lamblia*, Hsp90 is encoded in two pieces through trans-splicing of the mRNA (Kamikawa et al., 2011; Nageshan et al., 2011; Nageshan et al., 2014; Iyer et al., 2019; Iyer et al., 2021; Tushir et al., 2024). Full-length Hsp90 is down-regulated during encystation and Hsp90 inhibitors stimulate encystation (Nageshan et al., 2014).
- Silencing in the beetle *Tribolium castaneum* shows Hsp90 is required at all developmental stages (Knorr and Vilcinskas, 2011).
- Aneuploid human cells have reduced Hsp90 levels (and function) because of reduced Hsf1 expression (Donnelly et al., 2014).
- Plant-mediated knock-down of Hsp90 in root-knot nematode protects plants (Liu et al., 2015).
- Neurospora: Hop/Sti1, Aha1 and p23 are required for resistance to antifungals and heat stress, possibly by regulating transcription of key resistance genes; Hop/Sti1 and p23 also required in *Fusarium verticilliodes* (Gu et al., 2016).
- Pea aphid *Acyrthosiphon pisum*: KD reduces longevity and fecundity (Will et al., 2017).

- In the grasshopper *Locusta migratoria*, an Alu-like transposable element has been found to disrupt the Hsp90 gene; there are no homozygotes, but heterozygotes have a competitive advantage (Chen et al., 2017a).
- Hsp90 inhibition or *daf-21* knockout (viable with pleiotropic phenotype?) in nematode *Pristionchus pacificus* reveals role of Hsp90 in canalizing the developmental plasticity of mouth-forms (Sieriebriennikov et al., 2017).
- KD in planarian *Dugesia japonica* has phenotype (Dong et al., 2018).
- HtpG mutant *Mesorhizobium huakuii* affects lipid abundance and is defective for symbiotic root nodule formation; HtpG associates with plant non-specific lipid transfer proteins in the plasma membrane of nodule cells (Zhou et al., 2019a).
- *Mycobacterium tuberculosis*: HtpG not required for growth at normal and heat shock temperatures, but depletion/inhibition is synthetically lethal with a clpB mutation under host-like stresses (Harnagel et al., 2021).
- Nematode *Heterorhabditis bacteriophora*: knock-down of hsp90-1 gene affects motility and infection of its host (Fanelli et al., 2021).
- Knock-down in *Trypanosoma brucei* impairs cytokinesis and segregation of kinetoplast (Meyer and Shapiro, 2021).
- Depletion in human pathogenic fungus *Cryptococcus neoformans* impairs growth, sensitizes to stressors such as antifungals, and reduces virulens in mouse model (Fu et al., 2022).
- Hsp90β KD in zebrafish promotes cataractogenesis, which cannot be suppressed by other Hsp90 isoforms (Fu et al., 2023).
- KD of Hsp90α and Hsp90β in yellowtail kingfish leads to redox stress in the liver under high-temperature stress (Wang et al., 2024c).
- In the extremophile crustacean *Artemia franciscana*, knock-down of Hsp90 slows the development of nauplius embryos and reduces tolerance to desiccation and low temperature of cysts (Fatani et al., 2024).
- Hsp90 KD and overexpression in the intestine of *C. elegans* promote and reduce thermotolerance, respectively (Bardan Sarmiento et al., 2024).

Hsp90 interacting proteins:

Top Refs

- *Note that non-proteinaceous interactors are mentioned in other chapters*.
- **Hsp90Int.db:** the comprehensive interactome built with data from public protein-protein interaction databases and the literature (Echeverría et al., 2011a; see also its associated and continuously updated database at https:/www.picard.ch/Hsp90Int).
- Introduction of the term "molecular chaperone ensemble" for the multitude of Hsp90-cochaperone complexes that can dynamically coexist in the same cell or across different cell types (Echeverría et al., 2016).
- Yeast 2-hybrid with C-terminal 100 AA of human Hsp90α yielded only FKBP51, FKBP52 and TOM34 (Young et al., 1998). Yeast 2-hybrid with Cyp40 TPR yielded only C-terminal portion of murine Hsp90 (Carrello et al., 1999).
- Global analyses in budding yeast: Zhao et al., 2005; also genome-wide 2-hybrid screen with an Hsp90 ATPase mutant for yeast interactors (Millson et al., 2005). Chemical genetic screens with homozygous and heterozygous deletion libraries at different temperatures reveal roles in secretory pathway and cellular transport under normal conditions, in cell cycle, meiosis and cytokinesis at elevated temperature, as well as in transcription, ribosome biogenesis and GTP binding proteins (McClellan et al., 2007; Franzosa et al., 2011). TAP-tagged yeast Hsc82 and Hsp82 pull down large and distinct sets of proteins, and chaperone-centric systems analysis suggests a multitude of

overlapping chaperone modules (Gong et al., 2009). Proteins (e.g. Gln1) that form foci in response to stress and co-IP with Hsp82 (O'Connell et al., 2014; see also Chen et al., 2018b). Proteomic analysis of Hsp90-dependent proteome with reduced Hsp90 levels indicates that a large fraction changes with an overrepresentation of conserved, unstable, large and hub proteins (Gopinath et al., 2014). Proteomic analysis of interactions in response to DNA damage (Truman et al., 2015). Integrated genetic and physical interaction mapping reveals chaperone supercomplex and enrichment of interactions with proteins forming foci under stress (Rizzolo et al., 2017; see also Rizzolo et al., 2018). Isoform-specific interactome of C-terminally tagged Hsp90 shows few differences and an overall bias towards proteins with lower than average pI (Girstmair et al., 2019). Interactome probed by UV-crosslinking of non-natural amino acid incorporated into several sites of Hsc82 (Kolhe et al., 2023). Hsc82 point mutants affecting different steps in the Hsp90 cycle affect the levels of distinct sets of soluble proteins (Rios et al., 2024a).

- Global analyses in mammalian cells: co-IP with Hsp90 (Falsone et al., 2005; Te et al., 2007; Wang et al., 2010; Skarra et al., 2011; Wu et al., 2012b); pharmacological survey of kinases (Citri et al., 2006; Haupt et al., 2012); accumulation of detergent-insoluble ubiquitinated proteins in presence of GA (Falsone et al., 2007); pull-down with Hsp90 inhibitor beads (Caldas-Lopes et al., 2009). Comparative approach with IP, GA-biotin beads and Hsp90β-sepharose yields a total of 42 proteins including a modest set overlapping proteins (Tsaytler et al., 2009). TAP-tagged Hsp90 pulls out 37 known and 24 novel proteins in ligand-dependent fashion (Gano and Simon, 2010; see also Manissorn et al., 2018). Proteomic analysis of the autophagy protein network around ATG8 proteins reveals Hsp90α/β (Behrends et al., 2010; see also Joo et al., 2011; Seguin-Py et al., 2012; see also Cassava ATGs below). Proteomics with Hsp90 complexes pulled down with PU-H71-beads identifies many cancer-specific signaling complexes (Moulick et al., 2011); these are preferentially pulled out from AML cells with hyperactivated signaling pathways (Zong et al., 2015). Survey of kinases, E3 ligases and transcription factors, and of Cdc37-dependence by immunoprecipitation (Taipale et al., 2012; see also Buljan et al., 2020). Extensive biochemical probing of the chaperone network reveals global features, Hsp90-independent co-chaperone interactions, co-chaperone-mediated substrate specificities, specificity of the NUDC family of co-chaperones for proteins with β-propeller folds and an evolutionary expansion of proteins with folds correlating with respective co-chaperones (Taipale et al., 2014). See also Aha1-based proteomics (Sun et al., 2012; Sun et al., 2015). No correlation between Hsp90 inhibitor-induced degradation and co-immunoprecipitation for a panel of kinases (Jin et al., 2016). Mass spec survey of a panel of DNA/RNA helicases (Miao et al., 2018) and kinases (Miao et al., 2019). Chemical genetic screen with targeted shRNA library, affinity purification of nuclear Hsp90α and cancer co-expression analysis yields 5 components of three complexes (HCFC1, NuRD, and BAF) (Antonova et al., 2019). Survey of RNA binding proteins by LUMIER (Tsvetkov et al., 2020). Hop interactions with cellular proteins largely dependent on interaction with Hsp90-Hsp70, i.e. formation of the ternary complex (Bhattacharya et al., 2020). Impact of Aha1 knockdown on Hsp90 proximity labelling (Liu et al., 2022c).
- Large-scale screen of disease-associated mutant alleles shows that a higher % tends to have increased binding to Hsp90 (and Grp94), and more of these are unstable and have lost their protein-protein interactions (Sahni et al., 2015).
- Global analyses in *E. coli*: htpG associates with a number of proteins including several ribosomal proteins (Butland et al., 2005). Deletion of htpG leads to no significant proteome changes in wt cells (Fauvet et al., 2021). A minor proportion of nascent chains,

including for metabolic enzymes, associate with HtpG, which partially compensates for loss of DnaK (Zhao et al., 2021).

- Global analyses in γ-proteobacteria (Garcia-Descalzo et al., 2011) and ΔhtpG *M. tuberculosis* (Mangla et al., 2023).
- Computational prediction of chaperone networks in *Plasmodium* (Pavithra et al., 2007).
- The composite Sba1 interaction network shows relatively little overlap with that of Hsp82, but there is a remarkable number of multiprotein complexes where Sba1 and Hsp82 affect adjacent subunits (Echtenkamp et al., 2011).
- Global analysis with TAP/GFP-tagged Hsp90 in *Candida albicans* and impact of anti-fungal drugs (O'Meara et al., 2019).
- Genome-wide Y2H screen with wheat (Yan et al., 2023a; Guo et al., 2024).
- Global analysis in *C. elegans*: Tissue-specific and stress-specific interactomes probed by UV-crosslinking of non-natural amino acid incorporated into proteins followed by immunoprecipitation of C-terminally tagged Hsp90 (Huang et al., 2024b).

Co-chaperones/chaperones

- Proteins with TPR motifs: FKBP52 (=p59=hsp56=HBI=FKBP4) (Sanchez et al., 1990; Callebaut et al., 1992; Czar et al., 1994; Radanyi et al., 1994) and its high MW and membrane-associated plant homologs (Reddy et al., 1998; Kamphausen et al., 2002) including FKBP42 = TWISTED DWARF1 (TWD1) (Zhu et al., 2016b) and others, FKBP51 (=FKBP54=FKBP5) (Smith et al., 1993a; Nair et al., 1997), ceFKB-6 (Richardson et al., 2007), FKBP8 (=FKBP38) (Okamoto et al., 2006) but only as CaM-Ca^{2+} complex (Edlich et al., 2007), FKBP36 (=FKBP6 = Shutdown in *Drosophila*) (Jarczowski et al., 2009), *Plasmodium* FKBP35 (Kumar et al., 2005; Alag et al., 2009), cyclophilin-40 (= PPID = Cpr6 and Cpr7 in yeast) (Nadeau et al., 1993; Chang and Lindquist, 1994; Hoffmann and Handschumacher, 1995; Duina et al., 1996; Ratajczak and Carrello, 1996; Warth et al., 1997; Dolinski et al., 1998; Faou and Tropschug, 2003), Hop (=p60=STIP1=STI1 in yeast) (Perdew and Whitelaw, 1991; Smith et al., 1993b; Chang and Lindquist, 1994; Chen et al., 1996c; Owens-Grillo et al., 1996a), plant, Tom70 (Owens-Grillo et al., 1996a; Young et al., 2003; and comments by Voos, 2003; Fan et al., 2006; see also Bhangoo et al., 2007), probably also related Tom71=Tom72 (Li et al., 2009), protein phosphatase 5 (PP5) (Chen et al., 1996b; Silverstein et al., 1997) and its yeast ortholog Ppt1 (Wandinger et al., 2006), Ah receptor-interacting protein (AIP = XAP-2 = ARA9=FKBP37.7) (Ma and Whitlock, 1997; Meyer and Perdew, 1999), Cns1 (Dolinski et al., 1998; Marsh et al., 1998; Tesic et al., 2003; Hainzl et al., 2004) and its *Drosophila* and human relatives Dpit47 (Crevel et al., 2001) and TTC4 (Crevel et al., 2008), CHIP (Connell et al., 2001), *C. elegans* UNC-45 (Barral et al., 2002), GCUNC-45 (=Unc45a) (Chadli et al., 2006), Unc45b (Taipale et al., 2014), zebra fish Steif/Unc-45b (Etard et al., 2007), DnaJC7 (=Tpr2=mDj11=CCRP) (Brychzy et al., 2003; Kobayashi et al., 2003), CRN (Hatakeyama et al., 2004), WISp39 (=FKBPL) (Jascur et al., 2005; McKeen et al., 2010; Howell et al., 2015), NASP (Alekseev et al., 2005; see also Campos et al., 2010), Tah1 (Zhao et al., 2005) (= Spaghetti {Giot et al., 2003; Boulon et al., 2008; Benbahouche et al., 2014} = RPAP3; see also Millson et al., 2008), Spag1 (Maurizy et al., 2018), chloroplast Toc64 (Qbadou et al., 2006) and its close plant mitochondrial homolog OM64 (Schweiger et al., 2013), TPR1 (=Ttc1) (Te et al., 2007; Lotz et al., 2008). SGT (for "Small glutamine-rich tetratricopeptide repeat-containing protein"; also Vpu-binding protein or α-SGT or, confusingly, even SGT1; human gene name is SGTA; SGT2 in yeast): mammalian (Liou and Wang, 2005), yeast (Liou et al., 2007), and *Leishmania* protein (Ommen et al., 2010; Coto et al., 2018); chemical genetic interaction with Δ*hsp82* in yeast (McClellan et al., 2007). DYX1C1, which also contains a CS domain (Chen et

al., 2009c; see also Maurizy et al., 2018). *Arabidopsis* proteins AtTPR1 and AtTPR2 besides many other predicted ones (Prasad et al., 2010). AtTPR7 (Schweiger et al., 2012; Schweiger and Schwenkert, 2013). AIPL1 (Hidalgo-de-Quintana et al., 2008; Li et al., 2013c; Sacristan-Reviriego et al., 2017; Sacristan-Reviriego et al., 2020). Tom34 of Tom70 pathway (Faou and Hoogenraad, 2012; see also Trcka et al., 2014). Some but not all TPR proteins of *C. elegans* (Haslbeck et al., 2013). Tetrahymena Coi12p (Woehrer et al., 2015). Direct interactions between *E. coli* htpG and J-domain proteins CbpA and DnaJ, and yeast Hsp82 and Ydj1 (Wickramaratne et al., 2023).

- Binding of TPR proteins to one Hsp90 subunit is mutually exclusive (Owens-Grillo et al., 1995; Owens-Grillo et al., 1996a; Young et al., 1998) and requires TPR motifs (Radanyi et al., 1994; Hoffmann and Handschumacher, 1995; Owens-Grillo et al., 1996a; Ratajczak and Carrello, 1996). But: evidence for Hsp90-FKBP52-Hop and Hsp90-FKBP52-p23-Hop complexes (Hildenbrand et al., 2011). Moreover, mixed Sti/Hop-PPIase-Hsp90 complexes are a favored intermediate and Sti/Hop displacement requires ATP and p23 (Li et al., 2011c). Similarly, there are ternary complexes Hsp90-Cpr6-Cpr7 (Zuehlke and Johnson, 2012). Despite mixed complexes, FKBPs clearly compete with Hop (Ebong et al., 2016). Cns1 and Cpr7 can form mixed complexes with Hsp90 dimers (Schopf et al., 2019).
- Binding of PP5 is not GA-sensitive (Shao et al., 2002).
- Binding of TPR proteins and Cdc37 are mutually exclusive to adjacent sites (Silverstein et al., 1998); are *not* mutually exclusive, and Cdc37 complexes are stabilized by substrate and also contain p23 (Hartson et al., 2000; Shao et al., 2002), or perhaps not (Siligardi et al., 2004). Indeed, Cdc37 and Sti1 can interact directly (Abbas-Terki et al., 2002). Cdc37 binds ATPase domain of Hsp90 (Roe et al., 2004).
- Cdc37 is also complexed with Hsp90 in yeast system (Abbas-Terki et al., 2000).
- Cdc37 relative Harc (= CDC37L1), mutually exclusive binding through their conserved central domains (Scholz et al., 2001a; see also Cartledge et al., 2007). Does not interact with kinases (Taipale et al., 2014).
- Binding of FKBP52 may be inhibited by phosphorylation of FKBP52 by CKII within hinge between FK1 and FK2 (Miyata et al., 1997).
- p23 (Johnson et al., 1994; Johnson and Toft, 1994; Johnson and Toft, 1995; Johnson et al., 1996). Yeast p23 = Sba1(Bohen, 1998; Fang et al., 1998); interaction stabilized by molybdate, blocked by Macbecin, dependent on ATP (Fang et al., 1998; see also Obermann et al., 1998; Grenert et al., 1999) and ATP-induced dimerization (Chadli et al., 2000; Prodromou et al., 2000). In turn, nucleotide-bound state of Hsp90 is stabilized by both p23 and molybdate (Sullivan et al., 2002; see also McLaughlin et al., 2006). Novobiocin disrupts interaction (Marcu et al., 2000a). Interaction inhibited by Hop (Johnson et al., 1998) unless Hop is also bound to Hsp70 (Hernández et al., 2002b). Mammalian p23 has been proposed to be identical to cytosolic prostaglandin E2 synthase and Hsp90 enhances cPGES activity in vitro, and in vivo stimuli that increase cPGES activity enhance association with Hsp90 and both are inhibited by GA (Tanioka et al., 2003). Stimulatory phosphorylation of p23 by CK2 is stimulated by Hsp90 (Kobayashi et al., 2004). Binds Hsp90α with 3x stronger affinity than Hsp90β (Synoradzki et al., 2018).
- p23-relative B-ind1 (=HACD3) binds Hsp90 through FXXW motif and together with FKBP8 recruits Hsp90 to HCV replication complex (Taguwa et al., 2008).
- p23-relative AARSD1 binds Hsp90 with its CS domain, independently of the name-giving alanyl-tRNA synthetase domain, competing with p23; it only binds the Hsp90β isoform (Echeverría et al., 2016).
- Aha1/Hch1 family of ATPase-stimulating co-chaperones (Panaretou et al., 2002; Lotz et al., 2003; see comments by Mayer et al., 2002). Interaction blocked by full-length

Sti1/Hop (Lotz et al., 2003; Harst et al., 2005), Cdc37 and p23 but not cyclophilins (Harst et al., 2005; see also Xu et al., 2012a), or not by p23 (Sun et al., 2012). Aha1 preferentially binds Hsp90α, and this maps to the Hsp90α middle domain (Synoradzki and Bieganowski, 2015).

- Hsc70/Hsp70: Neurospora Hsp80 binds directly to Hsp70 (Freitag et al., 1997; Ouimet and Kapoor, 1998; Britton and Kapoor, 2002). Complex with chicken Hsp90 disrupted by novobiocin (Marcu et al., 2000a). Weak Hsp90:Hsp70 complexes exist with 2:1 stoichiometry in retic. lysate (Murphy et al., 2001). Hsp70 in Hsp90 complexes in *Plasmodium falciparum* (Banumathy et al., 2003). Some binding of ΔMEEVD mutant or in absence of Sti1 in yeast (Flom et al., 2007). Hsc70 interacts preferentially, and Hsp72 only in Hsp90 complexes in mammalian cells when Hsc70 is knocked down (Powers et al., 2008). htpG interacts with DnaK (Genest et al., 2011). Single Hsp70 molecule binds Hop-Hsp90 complex between extended Hsp90 monomers (Southworth and Agard, 2011). htpG of cyanobacterium *S. elongatus* directly interacts with DnaK2 and DnaJ2 (Nakamoto et al., 2014; also in *M. tuberculosis*: Mangla et al., 2023). Interaction of *E. coli* htpG and DnaK is stabilized by client, abolished by M-domain mutations, and complex formation facilitated by J-domain protein CbpA (Genest et al., 2015; see also Doyle et al., 2019). Involves a surface of the nucleotide-binding domain of DnaK that also binds J proteins (Kravats et al., 2017; see also Doyle et al., 2019). Direct interaction between yeast Hsp82 and yeast Ssa1 (Kravats et al., 2018; Doyle et al., 2019), and human Hsp90α/β and Hsc70/Hsp70 (Bhattacharya et al., 2020).
- Sis1-like protein in *Toxoplasma gondii* (Figueras et al., 2012).
- RAR1, a CHORD-containing protein distantly related to p23 (Garcia-Ranea et al., 2002) interacts through the CHORD-I domain (Liu et al., 2002; Hubert et al., 2003; Takahashi et al., 2003). Does not regulate Hsp90 ATPase alone or in combination with SGT1 (Botër et al., 2007; Hubert et al., 2009), but may promote lid cycling (Hubert et al., 2009). Interacts also with SGT1 of peanut by yeast 2-hybrid (Yuan et al., 2021).
- SGT1 (for "Suppressor of G2 allele of SKP1 homolog"; human gene name: *SUGT1*; do not confuse with "other" SGT1) (Hubert et al., 2003; Takahashi et al., 2003; reviewed in Picard, 2008; Shirasu, 2009), is distantly related to p23 and binds Hsp90 by its CHORD and SGT1 (CS) domain, not the TPRs (Lee et al., 2004b; see also Catlett and Kaplan, 2006; Botër et al., 2007). It can form a ternary complex with Sti1, does not regulate ATPase of Hsp90 and may act to bring in substrate through TPR domain (Catlett and Kaplan, 2006). Also ternary complexes with RAR1 (Botër et al., 2007). Hsp90 promotes its dimerization and interaction with Skp1 (Bansal et al., 2009). May function as adaptor for some clients (Catlett and Kaplan, 2006; Davies and Kaplan, 2010). Interaction with Hsp90 and nuclear localization regulated by phosphorylation (Prus et al., 2011). Depends on Hsp90 for interaction with LRR domain protein Scrib (Eastburn et al., 2012). Nematode Sgt1 also binds through CS domain, is competed by p23, barely affects Hsp90 ATPase activity and binds all Hsp90 conformations (Eckl et al., 2014).
- CS-domain containing NudC (Te et al., 2007) and NudCL2 (=Nudcd2) (Yang et al., 2010), primarily through CS-domain (Biebl et al., 2022). Inhibits Hsp90 ATPase (Zhu et al., 2010; Yang et al., 2018) or not (Biebl et al., 2022). Stabilizes cohesin subunits through Hsp90 (Yang et al., 2018).
- CS-containing Siah-1-interacting protein (SIP) (Lee et al., 2004b). Direct interaction of SIP, also known as calcyclin binding protein (=CACYBP), with Hsp90, possibly to bring in a chaperone activity and to dephosphorylate it (Góral et al., 2016).
- Melusin-related mammalian CHORD-containing protein Chp1 (= *Drosophila* Morgana {Ferretti et al., 2010}) (=CHORDC1) through CS and other domains (Hahn, 2005; Wu et al., 2005; Michowski et al., 2010), in ADP- and CS-dependent manner (Gano and Simon, 2010); Morgana interacts with R2TP along with FKBP4 and Aha1 (Palumbo et al., 2020).

- Melusin (=ITGB1BP2): a CS and CHORD-containing molecular chaperone, related to Chp1/Morgana that binds Hsp90 through its CHORD domain; also binds SGT1 (Sbroggiò et al., 2008).
- CS-containing USP19 (He et al., 2016; see also Meng et al., 2019); interaction is through CS2 binding ATPase domain of Hsp90 and relieves auto-inhibition (Xue et al., 2020).
- Sse1 is part of the Hsp90 complex in budding yeast (Liu et al., 1999; see also Mandal et al., 2010). Sse2 probably as well, notably through its nucleotide binding domain; part of an early quality control step with Hsp70 (Mandal et al., 2010).
- valosin-containing protein (VCP)/p97, AAA+ chaperone, along with p23, Cdc37 (Prince et al., 2005a). Co-IP depends on presence of HDAC6 (Boyault et al., 2007).
- Co-chaperones FNIP1 and FNIP2: decelerate ATPase by competing with Aha1, promoting client loading (Woodford et al., 2016a).
- Tsc1, competes with Aha1, binds closed conformation (promoting ATP and drug binding), and inhibits ATPase (Woodford et al., 2017).
- Molecular chaperone PhLP2A (Krzemień-Ojak et al., 2017).
- ZMYND10, possibly through FKBP8 for chaperoning of axonemal dynein heavy chains (Mali et al., 2018).
- Ids2 in yeast as PKA-inactivated co-chaperone for protein folding; activated by dephosphorylation upon caloric starvation (Chen et al., 2018b); may recruit Hsc82 to complex V ATP synthase subunit Atp3 (Jiang et al., 2021).
- TIMP2 for extracellular Hsp90 (Baker-Williams et al., 2019).
- Prefoldins PFD4 and PFD6 of *Arabidopsis* (Esteve-Bruna et al., 2020).
- Cereblon, with Hsp90α, counteracts effects of Aha1 for quality control of transmembrane proteins; interaction with Hsp90α inhibited by both Hsp90 inhibitors and cereblon-targeted immunomodulatory drugs (Heider et al., 2021).
- TPR- and J-domain-containing proteins TPR15 and TPR16 with Hsp90-2 of *Arabidopsis thaliana* (Dittmer et al., 2021).

Others (notably, but not exclusively, clients/substrates)

- "stable" association with all vertebrate steroid receptors (GR, MR, ERα, ERβ, PR, AR) in the absence of hormone (Joab et al., 1984; Catelli et al., 1985; Sanchez et al., 1985; Schuh et al., 1985; Rafestin-Oblin et al., 1989; Veldscholte et al., 1992; Powell et al., 2010). Released after hormone binding. Important for high affinity ligand binding of GR (Bresnick et al., 1989), MR (Rafestin-Oblin et al., 1989). Complex confirmed by *in vivo* crosslinking (Rexin et al., 1992; Segnitz and Gehring, 1995). Comprehensive analysis with ERα (Dhamad et al., 2016).
- PPARα, along with XAP2 (Sumanasekera et al., 2003b); PPARβ more weakly (Sumanasekera et al., 2003a); Hsp90 may be inhibitory since GA enhances PPARα/β activity (Sumanasekera et al., 2003a).
- PPARγ (Nguyen et al., 2013).
- PPARδ once phosphorylated on Y108 in response to EGF (Gou et al., 2021).
- CAR (Kobayashi et al., 2003; Yoshinari et al., 2003).
- PXR (Squires et al., 2004; see also Kim et al., 2015b). Chlorogenic acid increases interaction with Hsp90 and nuclear localization (Meng et al., 2024).
- VDR (Marcinkowska and Gocek, 2010).
- Thyroid hormone receptor β (TRβ) (Fan et al., 2022b).
- Dioxin receptor (= aliphatic hydrocarbon receptor = AhR) (Denis et al., 1988; Perdew, 1988), required for ligand regulation and DNA binding (Pongratz et al., 1992; Whitelaw et al., 1993; Antonsson et al., 1995; Coumailleau et al., 1995; Whitelaw et al., 1995;

Shetty et al., 2003) and high affinity ligand binding (Pongratz et al., 1992). Ligand-dependence of Hsp90 release is p23-dependent (Kazlauskas et al., 1999). GA does not block its ligand binding but its nuclear localization (perhaps unmasking of NLS) (Kazlauskas et al., 2001). Interaction with PAS domain itself not affected by ligand (Tsuji et al., 2014). bHLH also interacts with Hsp90 (through N-terminal domain), p23 and XAP2 (Kudo et al., 2018). Some evidence for transitional state containing both Hsp90 and Arnt, before dissociation of Hsp90 (Soshilov et al., 2020). Composition of Hsp90-AhR complex may depend on AhR ligand (Narita et al., 2024).

- water mold *Achlya* steroid (antheridiol) receptor (Brunt et al., 1990).
- Sim (McGuire et al., 1995), HIF-1α (Gradin et al., 1996; Minet et al., 1999; see also Liu et al., 2007) (possibly only Hsp90α {Tang et al., 2021}), HIF-2α and HIF-3α (Katschinski et al., 2004). Released upon dimerization with Arnt. RACK1 competes with Hsp90 for HIF-1α binding (Liu et al., 2009a; Xu et al., 2021).
- cytoplasmic v-erbA (Privalsky, 1991).
- transient association with pp60 v-src (Brugge et al., 1981; Oppermann et al., 1981; for review, see Brugge, 1986). Binding to c-Src expressed in retic. lysate system (Hutchison et al., 1992a). GA transiently activates Src concomitant with Hsp90 release (Koga et al., 2006). Interaction with c-Src strongly stimulated by sepsis and LPS in neutrophils (Gupta et al., 2018).
- src related tyrosine kinases: yes, fps (Adkins et al., 1982; Lipsich et al., 1982), fes, fgr (Ziemiecki, 1986; Ziemiecki et al., 1986; Hartson and Matts, 1994; Nair et al., 1996) and lck (Hartson and Matts, 1994; Hartson et al., 1996). Required for *de novo* folding of kinase domain of lck (Hartson et al., 1998; see also Bijlmakers and Marsh, 2000). Association with a ts mutant of Hck: functionally necessary and stimulated by Cdc37 overexpression (Scholz et al., 2000); ongoing support particularly required for mutant Hck (Scholz et al., 2001b).
- Bcr-Abl, but not c-Abl (An et al., 2000; see also Peng et al., 2021) or perhaps yes a little bit (Moulick et al., 2011).
- regulation of eIF2-α kinase HRI (Kudlicki et al., 1987; Rose et al., 1987; Matts and Hurst, 1989; Matts et al., 1992; Mendez et al., 1992; Mendez and de Haro, 1994; Berwal et al., 2018). Hsp90 is essential for folding, maturation and maintaining conformation competent for activation (Uma et al., 1997).
- eEF-2 kinase (Palmquist et al., 1994; Yang et al., 2001).
- prevents aggregation of casein kinase II, binds catalytic CKIIα subunit (Miyata and Yahara, 1992; Miyata and Yahara, 1995), but may not affect CKII activity (Shi et al., 1994).
- activation of CDK4 as a complex with (and via?) CDC37(p50) (Dai et al., 1996; Stepanova et al., 1996; see also Wang et al., 2002). Association with p50 (Perdew and Whitelaw, 1991; Whitelaw et al., 1991) (now known as CDC37). Binding of Cdc37 and to Cdk4 is mutually exclusive with cyclin D (Stepanova et al., 1996) and p16 (Lamphere et al., 1997). Increased interaction of some Cdk4 mutants with Hsp90 and Cdc37 (Lambert et al., 2013). Cyclins and CKIs displace Cdc37-Hsp90 from Cdk4 (Hallett et al., 2017). Both FKBP51 and FKBP52 are required to sequester Cdk4 with Hsp90 and prevent binding to cyclin D1 (Ruiz-Estevez et al., 2018).
- in large complex with Cdk6 and Cdc37 (Mahony et al., 1998). Cyclins and CKIs displace Cdc37-Hsp90 from Cdk6 (Hallett et al., 2017).
- Cdk2 (Prince et al., 2005b).
- Cyclin B; interaction is Cdc2-independent and Hsp90 is required (nevertheless indirectly) to recruit cyclin B to centrosomes and the mitotic spindle (Basto et al., 2007).
- Cdc2 (Cdk1, ~ Cdc28 in *S. cerevisiae*) (Garcia-Morales et al., 2007); it is a Cdc37 client, and notably based on more recent evidence also an Hsp90 client (Caldas-Lopes et al.,

2009). Also in *Candida albicans* (Senn et al., 2012). Hsp90 stabilizes a complex of CDK1 with EZH2 to promote phosphorylation and degradation of EZH2 (Göllner et al., 2017).

- required for activation of Wee1 in *S. pombe* (Aligue et al., 1994; Goes and Martin, 2001), Swe1 in *S. cerevisiae* (Goes and Martin, 2001), and ortholog in *C. elegans* (Inoue et al., 2006).
- reverse transcriptase of duck hepatitis B virus (HBV) (Hu and Seeger, 1996; Hu et al., 1997; Cho et al., 2000a; Cho et al., 2000b; Hu and Anselmo, 2000; Gyoo Park et al., 2002; Hu et al., 2002; see also Liu et al., 2014a). Gets incorporated into capsid through this interaction and is essential for RNP formation and priming. However, see also Beck and Nassal, 2003. Hsp90 may only stimulate (Stahl et al., 2007).
- HBV capsid core protein dimer; Hsp90 facilitates core assembly and is incorporated into capsid through this interaction (Shim et al., 2011). Synergistic effects with Hsp70 (Seo et al., 2018).
- stabilizes p53 mutants (Blagosklonny et al., 1995; Blagosklonny et al., 1996; Sepehrnia et al., 1996; Nagata et al., 1999; see also Whitesell et al., 1998). *In vitro*, preferentially binds wild-type p53 in a BAG-1 sensitive fashion (King et al., 2001). Cancer cells with mutant p53 are more sensitive to Hsp90 and HDAC inhibitors than cells with wt p53 (Li et al., 2011a; Li et al., 2011b). Tumors with gain-of-function (GOF) p53 mutants can be inhibited with Hsp90 inhibitors and/or a combination with an HDAC inhibitor (Alexandrova et al., 2015). Hsp90 protects DNA binding-competent conformation (Boysen et al., 2019) and restores native state from Hsp70-mediated unfolding in ATP hydrolysis- and HOP-dependent manner (Dahiya et al., 2019) of wild-type and mutant p53. Hsp90α and Hsp90β preferentially bind mutant and wild-type p53, respectively (He et al., 2019). Slows down aggregation of Zinc-free DBD (Wu and Dyson, 2019). Promotes packaging of GOF p53 mutants but not wild-type into small extracellular vesicles (Ma et al., 2021).
- Mdm2; stabilization of p53 mutants presumably by blocking the E3 ubiquitin ligase activity of Mdm2 (Peng et al., 2001; see also Li et al., 2011a; Li et al., 2011b). But Hsp90 promotes p53 tetramer unfolding activity of Mdm2 (Burch et al., 2004) and degradation of wild-type p53 (He et al., 2019). Mdm2 only interacts with Hsp90β (He et al., 2019).
- stabilizes Raf-1 (= c-Raf = CRAF) (Stancato et al., 1993; Lovric et al., 1994; Stancato et al., 1994; Wartmann and Davis, 1994; Schulte et al., 1995; Schulte et al., 1996); wild-type Hsp83 required for Raf kinase activity in *Drosophila* (van der Straten et al., 1997); ternary complex both directly and through Cdc37 (Grammatikakis et al., 1999). c-Raf complex disrupted by RanBP9/RanBPM (Atabakhsh and Schild-Poulter, 2012). CRAF unlike BRAF requires continuous Hsp90 assistance with differential requirements during folding and for activation (Mitra et al., 2016).
- B-Raf (= BRAF) in PC12 cells (Jaiswal et al., 1996), and V600E mutant (da Rocha Dias et al., 2005; Grbovic et al., 2006; Fukuyo et al., 2008). Hsp90, Cdc37 and FKBP5 are primarily associated with active high MW BRAF complexes (Diedrich et al., 2017).
- A-Raf (ARAF) (Miao et al., 2019).
- stabilizes and binds Ste11 (Louvion et al., 1998).
- cytoskeletton: actin (Koyasu et al., 1986; Nishida et al., 1986; Miyata and Yahara, 1991; Kellermayer and Csermely, 1995; Park et al., 2007), tubulin (Sanchez et al., 1988; Williams and Nelsen, 1997; Garnier et al., 1998; Cambiazo et al., 1999; Weis et al., 2010) and microtubules (Fostinis et al., 1992; Williams and Nelsen, 1997; Krtková et al., 2012; see also Lange et al., 2000), and myosin (Barral et al., 2002; Srikakulam and Winkelmann, 2004; Mishra et al., 2005 Etard et al., 2008) (including Myo3B; Taipale et al., 2012), see also immunofluorescence work by Czar et al., 1996. Binds and bundles F-actin *in vitro* (Park et al., 2007). Binds ciliary β4-tubulin and promotes its polymerization (Takaki et al., 2007). Unc-45 (preferentially the *a* form) promotes Hsp90-dependent folding of the myosin motor domain (Liu et al., 2008a; Srikakulam et al., 2008). Tubulin

acetylation favors recruitment of Hsp90 and client proteins (Giustiniani et al., 2009; see also Zhong et al., 2014). Association with F-actin and α-tubulin may play a role in phagosome formation and function (Singhto et al., 2013).

- binds calmodulin in Ca^{2+}-dependent fashion (Minami et al., 1993; see also Cambiazo et al., 1999). Or perhaps rather the calcium-binding and chaperone protein S100A1 of the S100 family (Okada et al., 2004). Selectively oxidized calmodulin (Whittier et al., 2004) suggesting a role for Hsp90 in the oxidative stress response (Squier, 2006).
- Proteasome (Tsubuki et al., 1994; Wagner and Margolis, 1995; see also Verma et al., 2000). Affinity for 20S complex is 30 nM and stoichiometry of Hsp90 to 20S is 1:2 (Eleuteri et al., 2002). Proteasome is inhibited for some substrates (Tsubuki et al., 1994; Wagner and Margolis, 1995) but stimulated for others (Eleuteri et al., 2002); Hsp90 protects it from oxidative inactivation *in vitro* and *in vivo* (Conconi et al., 1998). Required for assembly and maintenance of the 19S regulatory subunit in budding yeast (Imai et al., 2003) and of the 26S proteasome in mammalian cells (Yamano et al., 2008). Hsp90 required for degradation of oxidized calmodulin (Whittier et al., 2004). Hsp90 inhibition suppresses proteasome remodeling (Nanduri et al., 2015). Hsp83 mutants in *Drosophila* have reduced proteasome activity (Choutka et al., 2017). Associated with complexes smaller than 20S (Sakellari et al., 2019). Levels of 20S components go up upon deleting/inhibiting Hsp90 in *C. albicans* (O'Meara et al., 2019). Hop KO in human cell lines affects proteasome assembly/maintenance/lid docking and activity, and proteasome components interact with Hop that is capable of forming the Hsp70-Hop-Hsp90 ternary complex (Bhattacharya et al., 2020). Proteasome components PBD2 and RPN6 in corn (Xu et al., 2023b). Hsp90 of *Plasmodium falciparum* promotes proteasome activity, possibly by affecting assembly and/or stability (Mansfield et al., 2024).
- free ßγ subunit of G protein (Inanobe et al., 1994).
- $G\alpha_0$ (Busconi et al., 2000).
- $G\alpha_{12}$ interaction required for downstream signaling, but not for closely related $G\alpha_{13}$ (Vaiskunaite et al., 2001); Hsp90 may help to target $G\alpha_{12}$ to lipid rafts (Waheed and Jones, 2002), and connect it with Src at tight junctions (Sabath et al., 2008). Some $G\alpha_{12}$ mutants have impaired binding (Montgomery et al., 2014).
- HSF1 (Nadeau et al., 1993; Nair et al., 1996; Ali et al., 1998; Duina et al., 1998; Zou et al., 1998; Bharadwaj et al., 1999), along with Ral-binding protein 1 (RalBP1) and α-tubulin (Hu and Mivechi, 2003). Release from Hsf1 is stimulated by ubiquitinated cellular aggregates and this depends on sensing and segregase activities of associated HDAC6 and VCP/p97, respectively; it is independent of HDAC6-mediated deacetylation of Hsp90 (Boyault et al., 2007). Also in plants (Yamada et al., 2007). Hsp90 reduces temperature of trimerization and broadens response window *in vitro* (Hentze et al., 2016). Unlike Hsp70, the main role notably of the closed form of Hsp90 may be to dynamically remove trimers from DNA (Kijima et al., 2018). Yeast Hsf1 may not interact and be indirectly activated through Hsp70 titration upon compromising Hsp90 (Zheng et al., 2016). Inhibition of translation prevents HSF1 activation, even upon Hsp90 inhibition, and, in line with HSF1 remaining bound to Hsp90 in response to proteotoxic stress, suggests that negative feedback of chaperones is indirect through restoration of proteostasis (Simoncik et al., 2024).
- HSF2 (Pesonen et al., 2021).
- HsfA1, HsfA2, and HsfB1 in tomato, where B1 is targeted for degradation when associated with Hsp90 (Hahn et al., 2011; Röth et al., 2017), and HsfA1a, HsfA1b and HsfA1d in *Arabidopsis* (Yoshida et al., 2011; see also Ohama et al., 2016).
- MEK (Stancato et al., 1997; not according to Jaiswal et al., 1996; but see also Shinozaki et al., 2006).

- MEKK1 and MEKK3 (Bouwmeester et al., 2004; see also Fang et al., 2009).
- Mixed-lineage kinase 3 (MLK3) (Zhang et al., 2004a).
- Insulin receptor (Takata et al., 1997), more strongly to mutants (Imamura et al., 1998). Required for maturation during trafficking through ER (Ramos et al., 2007). Also in *Drosophila* (Huang and Wang, 2018).
- Insulin-like growth factor 1 receptor (IGF1R) (Martins et al., 2008); interaction of Hsp90 with precursor promoted by PKM2 binding to it (Koo et al., 2021).
- eNOS (NOS-3): association is direct and stimulated by activators of NOS signaling, association stimulates NOS activity in vivo and in vitro (García-Cardeña et al., 1998; Gratton et al., 2000; Russell et al., 2000). Hsp90 facilitates release from caveolin in presence of calmodulin (Gratton et al., 2000), and helps to recruit Akt to eNOS (Brouet et al., 2001). Hsp90 functions as a scaffold by using its central domain to bind both Akt and eNOS (Fontana et al., 2002; for discussion, see Balligand, 2002). Hsp90 stimulates eNOS activity by increasing its affinity for calmodulin at low calcium and calmodulin-independent at high calcium (Takahashi and Mendelsohn, 2003a), and by synergizing with Akt (Takahashi and Mendelsohn, 2003b). Hsp90 increases affinity of NOS-3 for globular β-actin in a ternary complex and in turn becomes degraded more rapidly (Ji et al., 2007). Recombinant Hsp90 shifts eNOS activity from producing superoxide to NO (Sud et al., 2007). Lower amounts of Hsp90 in eNOS tissues than in neuronal tissues protects NOS insufficiently from cleavage by calpain (Averna et al., 2007; Averna et al., 2008b). Upon brief exposure to Ca^{2+}, Hsp90 promotes release of eNOS complex from caveolae and protection from recruited calpain (Averna et al., 2008a). Evidence for isoform-specific activity: eNOS associates with both Hsp90 isoforms but Hsp90α and Hsp90β overexpression increase and reduce activity, respectively, correlating with increased/reduced eNOS dimerization and Akt activation (Cortés-González et al., 2010; see also Chen et al., 2014). However, in intra-renal transfections, both isoforms protect against ischemia/reperfusion damages and effects on eNOS (Barrera-Chimal et al., 2014). IKKβ competes with eNOS for binding to middle domain and thereby attenuates eNOS activity (Natarajan et al., 2015). Association augmented by Aβ peptide correlating with reduced interaction of Hsp90 with Akt (Lamoke et al., 2015). VEGF-stimulated interaction with Hsp90 requires SDF2 (Siragusa et al., 2015). PP2A promotes dissociation of Akt-Hsp90-eNOS complex (Bharath et al., 2015). Hsp90 enhances affinity of eNOS for cofactors NADPH, L-arginine, and calmodulin (Chen et al., 2017b).
- nNOS (NOS-1): activity and accumulation of transfected but not in vitro translated nNOS depends on Hsp90 (Bender et al., 1999). Stimulates calmodulin binding in purified system (Song et al., 2001), and inhibits production of superoxide (Song et al., 2002). Estrogen promotes association of nNOS with Hsp90 and activity (Houlihan et al., 2009). Prevents CHIP-dependent nNOS ubiquitination (Peng et al., 2009) by competing against Hsp70-CHIP (Peng et al., 2012). Favors interdomain electron transfer (Zheng et al., 2020b). Hsp90α promotes superoxide production by nNOS (Zheng et al., 2021b).
- iNOS (NOS-2): Hsp90 behaves as an allosteric enhancer (Yoshida and Xia, 2003); facilitates heme insertion (Ghosh et al., 2011).
- Soluble guanylyl cyclase (sGC) through its β subunit (Venema et al., 2003; Papapetropoulos et al., 2005). Hsp90 binds heme-free sGC, promotes heme binding and dissociates in response to activation by NO allowing association with sGC-α1 (Ghosh and Stuehr, 2012; Ghosh et al., 2014). Hsp90 M domain interacts with PAS domain of sGCβ1 (Sarkar et al., 2015); more detailed study on sGC determinants and role of Hsp90 in preventing heterodimer formation with sGCα during maturation (Dai et al., 2019). Hsp90 also required for NO-mobilized heme deployment (Dai et al., 2022). Reactive oxygen or nitrogen species induce heterdimer dissociation and binding of sGCβ to Hsp90 without loss of heme (Dai and Stuehr, 2022).

- Hemoglobin α, β, and γ (Hbα/β/γ), in the apo-state to promote insertion of heme and association with Hb partner; heme insertion results in release; in erythroid cells, Hbα is chaperoned by AHSP and not Hsp90; ATPase-defective variant and inhibitors block heme insertion (Ghosh et al., 2018). The heme chaperone GAPDH may transfer the heme directly or indirectly through Hsp90 or AHSP (Tupta et al., 2022).
- Myoglobin in the apo-state along with Hop, Cdc37, Aarsd1, Aha1 and Hsp70 to promote insertion of heme, blocked by Hsp90 inhibitors (Ghosh et al., 2019). The heme chaperone GAPDH may transfer the heme directly or indirectly through Hsp90 (Tupta et al., 2022).
- reovirus σ1 homotrimer, immature form (Gilmore et al., 1998).
- Hap1, complex required for heme regulation (Zhang et al., 1998); association enhanced by heme favoring Hap1 activity (Lan et al., 2004).
- binds and stabilizes nascent CFTR (Loo et al., 1998; see also Youker et al., 2004). Hsp90 and many co-chaperones including Aha1, p23, and FKBP8 are part of the CFTR interactome (Wang et al., 2006; see also Sun et al., 2008; Okiyoneda et al., 2010). Differential sensitivities of wild-type and mutant CFTR to calpain correlate with different affinities for Hsp90 (Averna et al., 2011). Folding of ΔF508 is stalled in a chaperone trap (Coppinger et al., 2012); its thermal unfolding post-ER is partially suppressed by Hsc70 and Hsp90 (Bagdany et al., 2017).
- Telomerase: bound to and required for proper assembly (Holt et al., 1999; Forsythe et al., 2001). A key role of Hsp90 may be to maintain active Akt and TERT phosphorylation, and to prevent its dephosphorylation by PP2A (Haendeler et al., 2003), and/or to promote proper TERT folding and efficient telomere loading (Keppler et al., 2006). In yeast as well: Hsp90 promotes DNA binding of telomerase and through its continued association and processivity (Toogun et al., 2008); it also promotes switch between telomere capping and extension activities (DeZwaan et al., 2009). Nuclear localization requires FKB52 to promote interaction with dynein (Jeong et al., 2016).
- Calcineurin: co-IPs; activity stimulated by Hsp90 in a partially calmodulin-dependent fashion (Someren et al., 1999). Also Cna2 from budding yeast; Hsc82 may compete with calmodulin binding (Imai and Yahara, 2000). Interaction induced by glucocorticoids in INS-1 cells (Ranta et al., 2008). Interaction in *Candida albicans* (Singh et al., 2009). Stimulated by angiotensin II in adventitial fibroblasts (Huang et al., 2020).
- stabilizes and binds the yeast eIF2α kinase Gcn2 (Donzé and Picard, 1999).
- Facilitates folding of PKR and keeps its activity repressed (Donzé et al., 2001). β-amyloid peptide activates PKR without disrupting the Hsp90 complex (Suen et al., 2003).
- stabilizes and binds M15 fragment of β-galactosidase in yeast (Abbas-Terki and Picard, 1999).
- stabilizes Cdk9 as a complex with (and via?) Cdc37, before assembly with cyclin T1 (i.e. p-TEFb) (O'Keeffe et al., 2000; see also Pan et al., 2016).
- binds and is required for activation of c-Mos (Fisher et al., 2000).
- SV40 large T-antigen: probably required for folding (Miyata and Yahara, 2000).
- KSR (Kinase suppressor of Ras) is in a multiprotein complex with Hsp90 (Stewart et al., 1999).
- Death domain kinase RIP (RIP1 = RIPK1): complex dissociates upon activation by TNFα (Lewis et al., 2000; see also Li et al., 2015; Yang and He, 2016; see also Wu et al., 2019e).
- RIP3 (= RIPK3) (Li et al., 2015; see also Yang and He, 2016; Yu et al., 2020).
- 12(S)-HETE receptor (not cloned yet) (Herbertsson et al., 1999).
- Calponin (Bogatcheva et al., 1999; Ma et al., 2000).
- Apaf-1: Hsp90 inhibits cyt. c-mediated oligomerization (Pandey et al., 2000). GA-induced apoptosis depends on Apaf-1 (Fortugno et al., 2003). Interaction through Apaf–1 CARD

domain and weaker with S226- and S255-phosphorylated form of Hsp90β and only weak with Hsp90α (Kurokawa et al., 2008).

- Human DnaJ homolog Hsj1b (Schnaider et al., 2000).
- required for assembly of multi-aminoacyl-tRNA synthetase complex (Kang et al., 2000).
- Maintains Akt/PKB activity by preventing dephosphorylation by PP2A (Sato et al., 2000). Discrepancy with more recent study that shows that both Hsp90-Cdc37 bound and free Akt is active and dephosphorylated at same rate (Basso et al., 2002). Hsp90α and Hsp90β overexpression increase and reduce Akt activation (Cortés-González et al., 2010).
- PDK1: Hsp90 binds and stabilizes it (Fujita et al., 2002), and promotes its association with Sgk3 (Wang et al., 2014b).
- ErbB2 (=HER2): through its kinase domain; both nascent (shared with EGF receptor) and mature protein Hsp90-dependent (Xu et al., 2001; Xu et al., 2002b). A short region in the hinge that differs from the EGF receptor may be the recognition site (Tikhomirov and Carpenter, 2003). Further mapping to loop in kinase domain and demonstration that Hsp90 restrains ErbB2 from interacting with other ErbB's in absence of ligand (Citri et al., 2004a). See also Xu et al., 2005. Introducing a negative charge into this surface as present in ErbB1 (EGF receptor) destroys interaction (Citri et al., 2006). Loss of interaction activates in Src-dependent fashion (Xu et al., 2007b). Only the active conformation of ErbB2 interacts and can be targeted with Hsp90 inhibitors (Kancha et al., 2013). Low levels of HER2 need primarily Hsp90α for membrane-targeting, high levels need additionally Hsp90β, and for maintenance at the membrane also Grp94 (Patel et al., 2013). Interaction is impaired when ATM is knocked down or inhibited (Stagni et al., 2015).
- Nascent mutant EGF receptor EGFRvIII (Lavictoire et al., 2003). Wild-type receptor binds inhibitor-bound Hsp90 (Caldas-Lopes et al., 2009). Mutant EGFR is stabilized by Hsp90 and PKM2 (Yang et al., 2015b).
- Also mature wild-type EGF receptor (Ahsan et al., 2012). A peptide representing the region responsible for the differential dependence on Hsp90 between EGFR and ErbB2 interferes with Hsp90 binding and promotes degradation (Ahsan et al., 2013).
- ErbB3 (=HER3), transiently during maturation (Gerbin and Landgraf, 2010; Liu and Landgraf, 2015).
- Pim-1: required for accumulation and kinase activity (Mizuno et al., 2001).
- ANP receptor (atrial natriuretic peptide receptor = GC-A = NPR1): Hsp90 and Cdc37 associated through kinase homology domain (Kumar et al., 2001).
- Membrane receptor guanylyl cyclase C (GC-C = GUCY2C) (Caveney et al., 2023).
- Mik1: required for stability / activity, co-IP (Goes and Martin, 2001).
- MOK: associated through kinase domain, along with Cdc37 and Hsc/Hsp70 (Miyata et al., 2001).
- MOK relatives MAK and MRK, but not Erk, p38 nor JNK (Miyata et al., 2001). For JNK and p38, however, see below.
- For MAPK (Erk's) there is mostly evidence against (e.g. Miyata et al., 2001; our own unpublished data) Hsp90 complexes, but also some for (Setalo et al., 2002; Caldas-Lopes et al., 2009; Sun et al., 2021).
- Polo-like kinase 1 (Plk): C-terminal and not kinase domain is required for interaction; some disease-associated point mutations abolish it (Simizu and Osada, 2000). Also interacts with *Drosophila* Polo kinase (de Cárcer et al., 2001; see also de Cárcer, 2004), and function depends on Sgt1 (Martins et al., 2009).
- Polo-like kinase 3 (Plk3) (Ou et al., 2019).
- DNA polymerase α, inactive form, perhaps through Dpit47 (Crevel et al., 2001).

- ApoB: Hsp90 promotes its degradation after ubiquitination (Gusarova et al., 2001).
- Thrombin receptor (PAR-1) (Pai et al., 2001).
- Argonaute-1 (= Ago1) (Iwasaki et al., 2010; see also Liu et al., 2024d). In plants, with Hsp90.2, Hsp90.3 and Hsp90.4 during maturation in the nucleus before export to cytoplasm (Bologna et al., 2018). *hsp90.2-3* mutation promotes its membrane association (Sjögren et al., 2018).
- Argonaute-2 (= Ago2 = GERp95), along with p23, Hop, and Hdj2; transiently en route to Golgi (Tahbaz et al., 2001).
- Argonaute-4 (Ago4): binds and is required for loading of heterochromatic siRNAs in the cytoplasm in plants (Ye et al., 2012).
- Dicer 1, in an Aha1-dependent way (Liu et al., 2022c).
- Macrophage scavenger receptor (Nakamura et al., 2002).
- IκB kinases α, β (Chen et al., 2002), γ and ε (Bouwmeester et al., 2004) (see also Broemer et al., 2004; Lee et al., 2010; Natarajan et al., 2015). Cdc37 recruits Hsp90 to *de novo* IKK, notably IKKα, for maturation to IKK complex, and Hsp90-Cdc37 also required to generate activated state of mature IKK holocomplex following T-loop phosphorylation (Hinz et al., 2007). Interaction with IKK/Cdc37 may be reduced by HBV polymerase (Liu et al., 2014a). Impact on IKK may be promoted by binding of Hsp90α to lncRNA *AC245100.4* (Cui et al., 2020).
- Vaccinia core protein 4a: Hsp90 associates transiently with immature viral particles and is required for replication (Hung et al., 2002).
- Ctf13/Skp1: interact and are dependent for heterodimer formation and in vivo activity (Stemmann et al., 2002). Also needs the Hsp90 co-chaperone Sgt1 (Bansal et al., 2004; Lingelbach and Kaplan, 2004).
- SKP2 complexes contain Hsp90β along with SKP1, SGT1, and other proteins (Lyapina et al., 2001). Interacts with both isoforms (Cai et al., 2021).
- Aurora B, along with Cdc37 (Lange et al., 2002).
- Cytoplasmic domains of Ire1α and Perk (Marcu et al., 2002). For Ire1α interaction with Hsp90 and Cdc37, see also Ota and Wang, 2012; Zhao et al., 2019.
- In membrane rafts in complexes with caveolin-1 and STAT3; GA blocks IL-6 signaling (Shah et al., 2002), and Hsp90 co-IPs with STAT3 (Sato et al., 2003; Chong et al., 2019), stimulated by LIF (Setati et al., 2010). Interaction with STAT3 is increased in skeletal muscle of cachexia patients (Niu et al., 2021).
- RNA polymerase subunits PB1 and PB2 of Influenza A virus; Hsp90α and β interacts as required host factor through N-terminal and middle domain to promote assembly with PA in the nucleus (Momose et al., 2002; Naito et al., 2007; see also Jirakanwisal et al., 2015).
- Rab-αGDI: a chaperone complex with Hsp90 (possibly the Rab recycling factor) is associated with synaptic vesicle, and required for Rab recycling and Ca^{2+}-induced neurotransmitter release (Sakisaka et al., 2002; Chen et al., 2005b), and ER-Golgi traffic (Chen and Balch, 2006).
- Tom70-dependent mitochondrial precursor proteins (Young et al., 2003; Fan et al., 2006; Zara et al., 2009), along with Tom34, Hsp70, Hop and Cdc37 (Faou and Hoogenraad, 2012), and Toc64-dependent chloroplast precursor proteins (Qbadou et al., 2006; Fellerer et al., 2011), the latter along with Hop and FKBP73 (Fellerer et al., 2011). SARS-CoV-2 Orf9b inhibits binding of Hsp90 and associated clients to Tom70 (Brandherm et al., 2021), although there is also evidence that Tom70 and Orf9b may be able to bind simultaneously to Hsp90 (Zhou et al., 2024a).
- Mitochondrially targeted proteins with a chimeric signal can be directly directed to TOM40 as ternary complex with Hsp70 and Hsp90 (Anandatheerthavarada et al., 2008), or for some to TOM70 first in a TOM20/22 bypass mechanism (Anandatheerthavarada

et al., 2009). New study shows that TOM20 competes with chaperone binding to TOM70, thereby facilitating preprotein release (Fan et al., 2011).

- Signal-anchored proteins of the outer mitochondrial membrane (Drwesh et al., 2022).
- Aggregation-prone Tau protein (Dou et al., 2003; Luo et al., 2007). Interaction facilitates conformational change leading to phosphorylation and aggregation (Tortosa et al., 2009). Also interacts with monomeric Tau (Nguyen et al., 2025).
- Oncoprotein MTG8 (Komori et al., 1999).
- Neurotrophin receptor trkB; Hsp90 may be involved in axonal transport in retinal ganglion cells (Bernstein et al., 2001).
- TrkA splice variants I and III; Hsp90 also colocalizes with TrkAI at the cell surface and is required for TrkAI localization there (Farina et al., 2009).
- Knob complexes in the membrane of *Plasmodium*-infected erythrocytes (Banumathy et al., 2002).
- Tumor suppressor kinase Lkb1 (Boudeau et al., 2003; Nony et al., 2003; Gaude et al., 2012).
- VEGFR1 (Park et al., 2008).
- VEGFR2 (Flk-1/KDR): interaction possibly stimulated by VEGF (Masson-Gadais et al., 2003). Promotes Y300 phosphorylation of Hsp90β by Src (Duval et al., 2007; see also Park et al., 2008).
- Diphtheria toxin A for translocation into cells (Ratts et al., 2003; Dmochewitz et al., 2011); along with Hsp70/Hsc70, Cyp40, FKBP51/52 (Schuster et al., 2017).
- Histones H1, H2A, H2B, H3 and H4 (Schnaider et al., 1999). NASP (tNASP) may be a co-chaperone for the takeover from Hsp70 and assembly of the H3.1 (with K9me1) - unacetylated H4 dimer (Campos et al., 2010). Newly synthesized and unacetylated H4 binds Hsp90 along with PP32 and SET (Saavedra et al., 2017).
- ether-a-gogo-related cardiac potassium channel (ERG = HERG = KCNH2) (Ficker et al., 2003), possibly during trafficking (Walker et al., 2007). Only binds and is dependent on Hsp90α (Peterson et al., 2012). Hsp90 facilitates maturation by preventing interaction with CHIP (Iwai et al., 2013).
- KS type of glutathione S-transferase (GST) subunit 3 (Mayama et al., 2003).
- Thiopurine S-methyltransferase: GA promotes association and enhanced binding correlates with degradation (Wang et al., 2003).
- Purinergic receptor $P2X_7$: complexed with tyrosine phosphorylated Hsp90, which may be inhibitory (Kim et al., 2001; Adinolfi et al., 2003). Hsp90 required for large pore formation and autophagic cell death (Young et al., 2015). Hsp90 may work through cysteine-rich cytoplasmic domain (Migita et al., 2016).
- Plant disease resistance proteins: NB-LRR proteins RPM1 and RPS2 (Hubert et al., 2003; see also Holt III et al., 2005), and RPP4 (Bao et al., 2014).
- LRR protein I-2 (de la Fuente van Bentem et al., 2005).
- NB-LRR proteins in animals: Nod1 (Hahn, 2005; da Silva Correia et al., 2007; Mayor et al., 2007). Also the Nod-like receptors (NLRs) Nod2, NALP2, NALP3 (= NLRP3), NALP4, NALP12 and IPAF; binding to NACHT domain and with SGT1 to LRR domain (Mayor et al., 2007). Monarch-1 (Arthur et al., 2007).
- Inhibitor of apoptosis protein survivin through survivin baculovirus IAP repeat (Fortugno et al., 2003).
- Neuropeptide Y (NPY), although not clear whether this would happen physiologically (Ishiwatari-Hayasaka et al., 2003).
- G protein coupled receptor kinases GRK2 (Luo and Benovic, 2003) and GRK6 (Tiedemann et al., 2010). MAPK phosphorylation of GRK2 enhances interaction and promotes GRK2 targeting to mitochondria (Chen et al., 2013a).

- Mal63 of *S. cerevisiae* (Bali et al., 2003; Ran et al., 2008), and MalR of *Aspergillus oryzae* (Konno et al., 2018).
- Bid (Zhao and Wang, 2004).
- NFκB-inducing kinase (NIK) (Bouwmeester et al., 2004; Citri et al., 2006).
- TAK1 (Bouwmeester et al., 2004; Liu et al., 2008b).
- TBK1 (Bouwmeester et al., 2004; Yang et al., 2006a). Hsp90 brings TBK1/IRF3 to Tom70 on mitochondrial outer membrane for activation (Liu et al., 2010); the latter is counteracted by SARS-CoV-2 Orf9b (Brandherm et al., 2021).
- Chk1 (Arlander et al., 2003; Arlander et al., 2006; see also Cheng et al., 2017; Oh et al., 2017).
- Flt3 (Yao et al., 2003; Kancha et al., 2013).
- MMP2, interacts with extracellular Hsp90α (Eustace et al., 2004; Yang et al., 2008; Baker-Williams et al., 2019).
- Proenzymes and active forms of MMP2 and MMP9 interact with both isoforms (Stellas et al., 2010; see also Tukaj et al., 2015).
- MMP3 interacts with extracellular Hsp90β (Correia et al., 2013).
- Toll-like receptor 4 (TLR4): Hsp70 and Hsp90 form a cluster with TLR4 and the adaptor molecule MD-2 within lipid microdomains following LPS stimulation, and are targeted to Golgi (Triantafilou and Triantafilou, 2004).
- TLR7 and TLR9 (Saito et al., 2015).
- RET/PTC1 chimeric oncoprotein (Marsee et al., 2004).
- RET (Alfano et al., 2010).
- Annexin II (Annexin A2) (Lei et al., 2004; Díaz-Díaz et al., 2020).
- Na^+-K^+-Cl^- cotransporter 1 during early biogenesis (Simard et al., 2004).
- c-Kit (Nakatani et al., 2005; Martins et al., 2008) and Kit mutants (Mariño-Enríquez et al., 2013).
- *S. pombe* UCS protein Rng3, TPR-less relative of UNC-45 (Mishra et al., 2005).
- Cdk11 (Mikolajczyk and Nelson, 2004).
- Dengue virus (Reyes-del Valle et al., 2005), specifically proteins E, NS1, NS2B, NS3, NS4B, NS5 (Srisutthisamphan et al., 2018; see also Roby et al., 2020).
- NS5 of flaviviruses (Dengue, Zika, West Nile virus, Japanese encephalitis virus, ...) (Roby et al., 2020; see also Hajari et al., 2025).
- Histone methyltransferases SMYD1b (Tan et al., 2006; Li et al., 2013a), SMYD2 (Abu-Farha et al., 2008; Abu-Farha et al., 2011; Donlin et al., 2012; Hamamoto et al., 2014), and SMYD3 (Hamamoto et al., 2004; Abu-Farha et al., 2011; Brown et al., 2015). Associate with and are stimulated by Hsp90α. Substrate specificity of SMYD2 modified by Hsp90α (Abu-Farha et al., 2008).
- Histone arginine methyltransferase PRMT5 (Maloney et al., 2007).
- Interleukin-1 receptor-associated kinase 1 (IRAK-1), along with Cdc37 (De Nardo et al., 2005).
- The minimal kinase SSTK (= Tssk6) (Spiridonov et al., 2005), and TSSK4 (Jha et al., 2013; see also Chen et al., 2021b).
- Integrin-linked kinase (Aoyagi et al., 2005), stabilizing it and facilitating interaction with α-parvin (Radovanac et al., 2013).
- Active, dually phosphorylated MAPK Slt2 (Millson et al., 2005) and ERK5 (Piper et al., 2006; Truman et al., 2006). In contrast, Hsp90-Cdc37 is released upon activation and autophosphorylation of ERK5, and Cdc37 overexpression dissociates ERK5 inducing its nuclear localization and transcriptional but not kinase activity (Erazo et al., 2013). Hsp90 not involved in non-catalytic activation of Swi4/Swi6 by Slt2 and Mlp1 (Millson et al., 2022).

- ASK1 forms ternary complex with Akt and Hsp90, both bind middle domain of Hsp90 (Zhang et al., 2005b).
- N-WASP: binds through middle domain and promotes phosphorylation by c-src and actin polymerization activity (Park et al., 2005). Through this interaction, Hsp90 bundles branched actin filaments (Park et al., 2007).
- Hsp90 interacts with and is regulated by HDAC6 (Bali et al., 2005; Kovacs et al., 2005), and HDAC1 (Zhang et al., 2013a), and HDAC6 is a substrate (Rao et al., 2008).
- Interacts with SIR2 (SIR2RP1) in *Leishmania* (Adriano et al., 2007) and PfSir2 *Plasmodium falciparum* (Tabassum et al., 2022).
- SIRT1 (Nguyen et al., 2018; Białopiotrowicz-Data et al., 2023).
- SIRT2 (Min et al., 2018).
- misfolded VHL (McClellan et al., 2005).
- MUC1: its phosphorylation by c-Src stimulates interaction and Hsp90-dependent targeting to mitochondria (Ren et al., 2006). Fucosylation of Hsp90 promotes interaction (Guo et al., 2023).
- free ribosomal proteins S3 and S6 (Kim et al., 2006).
- Membrane-bound P450 CYP2E1 (Morishima et al., 2005; Wei et al., 2023).
- P450 CYP3A4 and CYP2D6, need Hsp90 for heme insertion (Islam et al., 2024).
- Binds and protects vimentin from caspase cleavage (Zhang et al., 2006; see also Chen et al., 2009b).
- CLC-1 chloride channel: transiently only with Hsp90β, which promotes its degradation through cullin 4 (CUL4) (Peng et al., 2016b).
- CLC-2 chloride channel (Hinzpeter et al., 2006).
- JAK1 interacts with Hsp90 and Cdc37, required for interferone signaling (Shang and Tomasi, 2006).
- α-synuclein, in Lewy bodies and neurites and glial cell inclusions (Uryu et al., 2006). In the absence and presence of ATP Hsp90 favors soluble oligomeric and fibirillar states, respectively (Falsone et al., 2009). Multiple domains of Hsp90 are able to prevent aggregation and its toxicity by interacting with the soluble oligomeric form (Daturpalli et al., 2013). Interaction with Hsp90 is through N-terminus of α-synuclein, which is disrupted by c-Abl phosphorylation of a tyrosine within it; Hsp90 contributes to preventing targeting to mitochondrial membranes and aggregation (Burmann et al., 2020).
- Mg^{2+}-dependent phosphatidate phosphohydrolase (Siess and Hofstetter, 2005).
- Bcl-2 (Cohen-Saidon et al., 2006). Stimulated by VEGF through KDR (Dias et al., 2002). CpG oligodeoxynucleotide signaling leads to increased expression of Hsp90β and association with Bcl-2 (Kuo et al., 2007). IP/MS of Bcl-2 pulls out Hsp90β (Li et al., 2017b).
- Interferon regulatory factor 3 (IRF3); Hsp90 acts as scaffold to bring the kinase TBK1 to IRF3 (Yang et al., 2006a). In the case of IRF-1, it may be indirectly through Hsp70 (Narayan et al., 2009). Hsp90 brings TBK1/IRF3 to Tom70 on mitochondrial outer membrane for activation (Liu et al., 2010) ; the latter is counteracted by SARS-CoV-2 Orf9b (Brandherm et al., 2021; see also Ayinde et al., 2022).
- DNA helicase Ssl2 (Flom et al., 2005).
- Death-associated protein kinases DAPK, DAPK2/ZIPK, and DAPK3 (Citri et al., 2006).
- Kinases that are Hsp90 substrates are typically signaling hubs except for the PI3K-Akt pathway (Citri et al., 2006).
- Perilipin (Yamaguchi et al., 2006).
- Tyrosine kinase receptor Ron (Germano et al., 2006).
- Atypical PKCλ as part of a larger complex (Brajenovic et al., 2004).

- All PKCs bind along with Cdc37; required for phosphorylation-dependent maturation and for stability in cell type-dependent fashion (Gould et al., 2009; see also Lu et al., 2014). Required for interaction of PKCδ with importin-α (Adwan et al., 2011). See also hypothesized role of Hsp90 release from PKCδ for response to proteoxic stress (Lu et al., 2021).
- TonEBP/OREBP: Hsp90 associated with protein on DNA and required for increased expression and for activity (Chen et al., 2007).
- MRE11/Rad50/NBS1 (MRN) complex involved in DNA damage response (Dote et al., 2006); critically dependent on phosphorylation of S164 of Hsp90α by Cdc7-Dbf4 for ATM/ATR signaling (Cheng et al., 2017).
- Prolactin receptor in newts (Saribek et al., 2006).
- Fused (Kise et al., 2006).
- GSK3β: Hsp90 required for autophosphorylation at a tyrosine in activation loop (Lochhead et al., 2006), stability and function (Banz et al., 2009). Another study finds that only a kinase-dead mutant but not wt interacts (Jin et al., 2016). Hsp90-Hop act as scaffold for GSK3β-mediated phosphorylation of LSD1 (Tsai et al., 2018). GSK3β binds indirectly to Hsp90 through PGK1 (Tang et al., 2022b).
- Capsid precursor protein P1 of picornaviruses (Geller et al., 2007).
- ZAP-70: possibly specifically with Hsp90 from leukemic cells as a "conditional Hsp90 substrate" (Castro et al., 2005; Bartis et al., 2007).
- platelet-derived growth factor receptor α (Matei et al., 2007).
- Msps (other orthologs: XMAP215, ch-TOG); Hsp90 is required (perhaps indirectly) to recruit Msps to centrosomes and the mitotic spindle (Basto et al., 2007).
- Cdk5 activator p35 (Luo et al., 2007).
- conserved oligomeric Golgi (COG) complex components COG5, -7, -9 (McClellan et al., 2007).
- FLICE-like inhibitory proteins $FLIP_S$ and $FLIP_L$; required for recruitment of these and RIP to DISC (Panner et al., 2007).
- CB2 cannabinoid receptor; may function as scaffold for interaction with G protein (He et al., 2007; He et al., 2012).
- mitochondrial cyclophilin D; Hsp90 and Trap1 prevent cyclophilin D from promoting mitochondrial permeability transition (Kang et al., 2007).
- JNK: Hsp90 recruited to JNK in lipid rafts in edelfosine-treated cells (Nieto-Miguel et al., 2008). Additional evidence for Hsp90 requirement for JNK-1 (Wang et al., 2009a).
- Pih1 (=Nop17) and R2TP complex (including RUVBL1): directly (Te et al., 2007)? or indirectly through Tah1 (Zhao et al., 2005 Zhao et al., 2008; Pal et al., 2014; Rivera-Calzada et al., 2017). See also Eckert et al., 2010; Izumi et al., 2012; Benbahouche et al., 2014. Also URI complex, either directly or through Pih1 and Tah1 (Izumi et al., 2012). Evidence for several R2TP-like complexes including R2SP, R2SD and others through RPAP3-like protein Spag1 and through DYX1C1 (Maurizy et al., 2018). HSP90/R2TP chaperone acts as a platform to assemble the TSC complex, using the RUVBL1/2 chaperone-like activity (Abéza et al., 2024).
- IP6K2; Hsp90 inhibits its activity and thereby protects against apoptosis (Chakraborty et al., 2008).
- Rac/Rop GTPase Rac1 of rice (Thao et al., 2007).
- Rac1, at least with Hsp90β (Cha et al., 2010).
- ATP-sensitive K^+ channel Kir6.2; Hsp90 promotes mitochondrial targeting (Jiao et al., 2008).
- MAP kinase kinase kinase Tpl-2 = Cot (Wu and Wilmouth, 2008).

- snoRNP complexes, possibly through R2TP complex (Boulon et al., 2008; Zhao et al., 2008), and Hsp90 is required for accumulation of a series of small RNAs and ribosomal biogenesis.
- U5 snRNP during assembly through interaction with PRPF8, SNRNP200 and maybe other components (Malinová et al., 2017).
- Pink1 binds Hsp90 along with Cdc37; binding slightly affects isoform ratio and subcellular localization of Pink1 (Weihofen et al., 2008).
- polysomal ribonuclease 1 (PMR1) (Peng et al., 2008).
- Leucine-rich repeat kinase 2 (LRRK2) (Gloeckner et al., 2006; Wang et al., 2008); Hsp90 recruits CHIP to substrate (Ko et al., 2009).
- c-IAP1; only Hsp90β, complex moves from nucleus to cytoplasm upon differentiation (Didelot et al., 2008).
- Tyrosine hydroxylase: stabilizing interaction induced by ethanol via cAMP-PKA pathway and antagonized by GDNF (He and Ron, 2008).
- Ure2: Hsp82 interacts with globular Ure2 complexes and prevents formation of *{URE3}* prion fibrils (Savistchenko et al., 2008). Others find no genetic requirement (Kumar et al., 2015).
- Extracellular Hsp90α can interact with the receptor CD91 (=LRP1) (Basu et al., 2001; Cheng et al., 2008; Chen et al., 2010a); stabilized by Hsp90β binding to its cytosolic tail (Jayaprakash et al., 2015).
- SGK-1 (Belova et al., 2008; Ghani et al., 2022).
- p300 (Yang et al., 2008).
- TGFβ receptors I and II (Wrighton et al., 2008; Datta et al., 2015). Extracellular Hsp90 with TGFβRI (García et al., 2016).
- Uroporphyrinogen decarboxylase (HemE) in cyanobacteria (Watanabe et al., 2007; Saito et al., 2008).
- DNMT1 (Zhou et al., 2008).
- LAMP-2A associated with Hsp90 on the luminal side of lysosomes (Bandyopadhyay et al., 2008; see also Du et al., 2021).
- UCH-L1, along with LAMP-2A (Kabuta et al., 2008).
- Chronophin: Hsp90 inhibits phosphatase activity in presence of ATP (Huang et al., 2008).
- Transcription factor Sp1 (Hung et al., 2005; see also Chen et al., 2023a) for JNK-1-dependent maintenance (Wang et al., 2009a).
- Ricin catalytic A chain (Spooner et al., 2008).
- Trithorax and its mammalian ortholog "mixed-lineage leukemia" (MLL) (Tariq et al., 2009; see also Snir et al., 2024).
- SRPK1, most likely through Aha1, and released by stress and GA (Zhong et al., 2009).
- RIG-I (Matsumiya et al., 2009).
- Rab11a; involved in regulating recycling of extracellular α-synuclein (Liu et al., 2009b). Both Hsp90 isoforms interact and promote Rab11a-mediated inhibition of osteoclastogenesis (Tran et al., 2022).
- Cdc25c (Garcia-Morales et al., 2007) and Cdc25a (Giessrigl et al., 2012).
- Cup (Pisa et al., 2009).
- Mitochondrial Hsp60 (Liu et al., 2009c).
- Tyrosine kinase Fer (Hikri et al., 2009).
- Hepatitis C virus nonstructural protein NS3 (Ujino et al., 2009).
- Inositol 1,4,5-trisphosphate receptor 3 (IP_3R-3); Hsp90 inhibits activity and insulin further augments inhibition and interaction (Nguyen et al., 2009).
- Ryk, along with Cdc37 through kinase domain (Lyu et al., 2009).

- TOM40 (Anandatheerthavarada et al., 2009).
- Cdc13; Hsp82 promotes its dissociation from telomeric DNA (DeZwaan et al., 2009).
- Bcl-xL (Caldas-Lopes et al., 2009).
- HER3 (Caldas-Lopes et al., 2009).
- p90RSK (Caldas-Lopes et al., 2009).
- Tyk2 (Caldas-Lopes et al., 2009).
- Tab2/3 (Caldas-Lopes et al., 2009).
- BLM helicase in the context of alternative lengthening of telomere (ALT) pathway; Hsp90 colocalizes at ALT-associated PML bodies and represses BLM activity (Bhattacharyya et al., 2009).
- N-myc downstream-regulated gene 1 (NDRG1) (Tu et al., 2007; Banz et al., 2009). Promotes interaction of androgen receptor (AR) with Hsp90, correlating with reduced AR activity and better outcome of prostate cancer (Lim et al., 2021).
- Importin β1 (KPNB1) and Nup62, promoting the interaction of the latter with GR (Echeverría et al., 2009).
- Importin 4 (IPO4), along with Aha1 (Echeverría et al., 2011a).
- Importin-α6 (KPNA5), along with Aha1 (Echeverría et al., 2011a).
- EphA2 through kinase domain (Annamalai et al., 2009).
- Raptor (Ohji et al., 2006; Delgoffe et al., 2009).
- Cullin 5 (Ehrlich et al., 2009; Samant et al., 2014; Zhou et al., 2024a).
- DNA polymerase η; Hsp90 allows proper folding and interaction with monoubiquitinated PCNA, and thereby translesion repair of UV-damaged DNA (Sekimoto et al., 2010).
- BCL-6, including at BCL-6 target promoters (Cerchietti et al., 2009).
- DEDD (Kurabe et al., 2010).
- Type I lissencephaly gene product LIS1 (Yang et al., 2010; Zhu et al., 2010), stimulated by NudCL2 (Yang et al., 2010).
- PAMP receptor OsCERK1 in rice along with Hop/Sti1; interact at endoplasmic reticulum and required for transport to membrane (Chen et al., 2010b).
- AF9/MLLT3: Hsp90 required for nuclear localization and chromatin recruitment (Lin and Hemenway, 2010).
- p38 mitogen-activated protein kinase is inhibited by Hsp90-Cdc37 complex; interaction favored in presence of Cdc37 (Ota et al., 2010).
- Breast cancer metastasis suppressor 1 (BRMS1) along with HDACs (Hurst et al., 2006).
- Hepatitis E virus capsid protein (Zheng et al., 2010).
- SUR1 subunit of β-cell ATP-sensitive potassium channel (Yan et al., 2010a).
- K1 protein of Kaposi sarcoma-associated herpesvirus (KSHV) (Wen and Damania, 2010).
- Dsn1 and Nsl1 subunits of Mis12 complex involved in assembly of kinetochores; strongly stabilized by Sgt1 (Davies and Kaplan, 2010).
- Peptide-loaded extracellular Hsp90 binds Scavenger receptor expressed by endothelial cells-I (SREC-I) (Murshid et al., 2010; Murshid et al., 2014).
- Tissue plasminogen activator (tPA) interacts with Hsp90α secreted through exosomes (McCready et al., 2010).
- Latency-associated peptide (LAP) (Suzuki and Kulkarni, 2010).
- PKCε, interacts with and needs Hsp90 for its mitochondrial import (Budas et al., 2010).
- Unassembled RNA polymerase II subunit Rpb1 in the cytoplasm, possibly delivered to it by Spaghetti (Boulon et al., 2010; Villanyi et al., 2014).
- Cholera toxin A1 subunit (CTA1 = CtxA1); required for ratchet-like dislocation from endoplasmic reticulum to cytosol (Taylor et al., 2010), coupled to ATP hydrolysis-dependent refolding (Burress et al., 2014), following ATP-dependent binding to the N-

terminal sequence motif RPPDEI (Kellner et al., 2019). Also Pertussis toxin (Ptx) and *Salmonella enterica* serovar Typhimurium (ArtAB), which contain very similar motifs (Kellner et al., 2019). For CTA1, Hsc70 and Hsp90 independently play complementary roles, independently of Hop (Burress et al., 2019). Hsp90 may recognize these ADP-ribosylating toxins through their aforementioned motif following the proline *trans*-to-*cis* isomerization that is associated with their unfolding in the ER (Kellner et al., 2021).

- Prostanoid pathway proteins prostacyclin synthase and thromboxane synthase (Fike et al., 2010).
- Tel2 and Tel2-Tti1-Tti2 (TTT) complex; required with Hsp90 for maturation of ATM, ATR and mTOR complexes (Horejsi et al., 2010; Takai et al., 2010; Izumi et al., 2012; see also Pal et al., 2014), and SAGA (Elías-Villalobos et al., 2019).
- mTOR (Moulick et al., 2011).
- *E. coli* ribosomal protein L2 in its native unfolded state binds htpG and activates its ATPase (Motojima-Miyazaki et al., 2010).
- Triosephosphate isomerase (TPI) (Hrizo and Palladino, 2010).
- Wilms tumor 1 (WT1) (Bansal et al., 2010).
- LATS1 and LATS2 (Huntoon et al., 2010; see also Nokin et al., 2016); this promotes dephosphorylation by PP5 and degradation of LATS1/2, and activation of YAP/TAZ (Luo et al., 2020).
- Sentrin-specific protease 1 (= SENP1) with Hsp90β (Liu et al., 2024i).
- Sentrin-specific protease 3 (= sumo protease 3 = SENP3): in response to oxidative stress Hsp90 protects it from CHIP-mediated degradation but in a CHIP-dependent way and by blocking the CHIP E3 ligase activity (Yan et al., 2010b).
- Activation-induced deaminase (AID): Hsp90 inhibition reduces AID-induced antibody-diversification, class switching and off-target mutation (Orthwein et al., 2010).
- APOBEC-3B, -3C, and -3G (Chen et al., 2017c).
- Eml4-Alk (Chen et al., 2010c; Richards et al., 2014) and NPM-Alk (Kancha et al., 2013; see also Kuravi et al., 2019) fusion proteins.
- Piwi in *Drosophila* (Gangaraju et al., 2011). PIWI protein Ago3 colocalizes with Hsp83 to cytoplasmic foci and its RNA loading may be promoted by Hsp83 with the FKBP36 (=FKBP6) ortholog Shutdown (Olivieri et al., 2012). Alternatively, Hsp90-Shutdown may help to eject inhibitory RNAs from Ago3 (Xiol et al., 2012). Ago3 co-IPs with Hsp83 and Hop in *Drosophila* (Cappucci et al., 2019). Also promotes piRNA loading into PIWI proteins in silkworm (Izumi et al., 2013).
- PIWIL2 (= HILI) interacts and in doing so reduces stabilizing interactions of TGFβ receptors with Hsp90 (Zhang et al., 2012b).
- PIWIL4, as a complex with the piRNA piR-31115, interacts with Hsp90α and stabilizes it (Du et al., 2025).
- Cineole synthase 1 from sage (SfCinS1); co-overexpressed with Hsp90 in yeast leads to increased cineole production (Ignea et al., 2011).
- PIDD; interaction with Hsp90, along with p23, in the cytoplasm is required for autoproteolytic cleavage and PIDDosome function following Hsp90 release (Tinel et al., 2011).
- DNA-activated protein kinase (= DNA-PK=PRKDC) (Lees-Miller and Anderson, 1989a; Falsone et al., 2005; Quanz et al., 2012; Solier et al., 2012).
- α_{2C} adrenergic receptor: Hsp90 binds it and prevents surface expression at 37°C and less so at 30°C (Filipeanu et al., 2011).
- Rapsyn: interaction stabilizes it and through Rapsyn promotes acetylcholin receptor clustering; apparently only Hsp90β (Luo et al., 2008).
- Phosphatidylinositol 4-kinase type IIA (PI4K2A), stabilizing AXL by recruiting Hsp90 (Tan et al., 2023).

- Phosphatidylinositol 4-kinase type IIβ (PI4K2β): Hsp90 stabilizes cytosolic form and keeps it inactive until stimulus induces dissociation and recruitment to membranes (Jung et al., 2011).
- Pnck (Deb et al., 2011).
- NADPH oxidases 1, 2, 3, and 5 (Nox1-3, Nox5) through their C-termini for stability and superoxide formation (Chen et al., 2011; Chen et al., 2015a); Hsp90 inhibition prevents final activation of heme-bound and oligomeric state of Nox5 by calcium binding (Sweeny et al., 2020).
- F1F0-ATP synthase, suggested as co-chaperone (Papathanassiu et al., 2006); see also global proteome analysis (Krogan et al., 2006) and genetic analysis of assembly (Francis and Thorsness, 2011) for supporting evidence.
- FGFR3 and FGFR4 (Laederich et al., 2011). Influence of disease-relevant mutations on interaction with Cdc37 and Hsp90 (Bunney et al., 2018).
- FOP2-FGFR1 (Jin et al., 2011).
- BCR-FGFR1 (Peiris et al., 2020).
- FGFR3-TACC3 fusion protein; needs both Cdc37 and Hsp90 (Li et al., 2022b).
- Non-structural protein NS1 of influenza A virus (Zhang et al., 2011).
- PCNA (Wang et al., 2010).
- Kinase SSCMK1 of the fungus *Sporothrix schenckii*, possibly promoting thermotolerance through this interaction (Rodriguez-Caban et al., 2011).
- Beclin 1; required for TLR-mediated autophagy (Xu et al., 2011; see also Miao et al., 2021; Shi et al., 2024).
- Y-family polymerase REV1 for its folding and interaction with PCNA in translesion DNA synethis (Mayca Pozo et al., 2011).
- Ulk1 along with Cdc37 for regulation of mitophagy (Joo et al., 2011). Also yeast ortholog Atg1 (Backe et al., 2023b). Phosphorylation of Hsp90 S39/S25by Ulk1/Atg1, respectively, promotes dissociation of Ulk1/Atg1, their activation, and the initiation of autophagy (Backe et al., 2023b; discussed by Backe et al., 2024).
- Exportin-1 (XPO1=CRM1), with both Hsp90 isoforms and along with Aha1 (Echeverría et al., 2011a; see also Falsone et al., 2005).
- IRS-2 (Fukushima et al., 2011).
- Bruton agammaglobulinemia tyrosine kinase (BTK) (Moulick et al., 2011; Guo et al., 2017a).
- CARM1 (Moulick et al., 2011).
- PRKD2 (Moulick et al., 2011; see also Azoitei et al., 2014).
- PRKD3 (=PKD3) (Varga et al., 2023).
- Stat5, notably phosphorylated form (Moulick et al., 2011).
- Adhesin A from *Neisseria meningitidis* (NadA) (Cecchini et al., 2011; Montanari et al., 2012).
- Clostridium toxins CDT and iota, which need Hsp90 as membrane translocator (Kaiser et al., 2011).
- Campylobacter jejuni protein JlpA (Jin et al., 2003).
- F box protein ZEITLUPE (ZTL) of circadian clock in plants (Kim et al., 2011; see also Noren et al., 2016) in ternary complex with putative Hsp90 co-chaperone GIGANTEA (Cha et al., 2017).
- XPORT (Rosenbaum et al., 2011).
- TRIM8 with Hsp90β, α not looked at (Okumura et al., 2011).
- PARK7 (DJ-1) (Knobbe et al., 2011; see also Kim et al., 2021).

- E protein of Japanese encephalitis virus; specifically only with Hsp90β isoform, which gets co-secreted with viral particles (Hung et al., 2011); whole viral particles, too (Wang et al., 2017b).
- GTPase Bms1 in yeast (Franzosa et al., 2011).
- Phosphorylated β-catenin and axin 1 (Cooper et al., 2011).
- AMPK subunits α and γ (Zhang et al., 2012c; see also Park et al., 2017b).
- ALK1 and ALK5 (Antonov et al., 2012).
- Smyd2-methylated Hsp90 in complex with titin (Donlin et al., 2012).
- E3 ubiquitin ligase Hectd1 via a central domain (Sarkar and Zohn, 2012; see also Xing et al., 2024).
- Huntingtin (Baldo et al., 2012; He et al., 2017).
- BRCA1 (Stecklein et al., 2012); in particular BRCT domain mutants (Johnson et al., 2013; Gracia et al., 2024). The wild-type BRCT domain does not bind significantly, but many clinically relevant variants do, albeit most bind Hsp90 less than Hsp70 (Gracia et al., 2024).
- BRCA2 (Noguchi et al., 2006).
- WASF3 (Teng et al., 2012).
- NELF-E (= RDBP in human) (Sawarkar et al., 2012).
- DDR1 (Wu et al., 2012b).
- Adenylate cyclase Cyr1 in yeast (Flom et al., 2012).
- O-linked β-N-acetylglucosamine transferase (OGT) (Zhang et al., 2012a; Fierro-Monti et al., 2013a; Frank et al., 2014).
- Nanog (Bradley et al., 2012). Conversely, Hsp90α expression is regulated by Nanog (Song et al., 2020).
- Oct4 (Bradley et al., 2012; see also Ke et al., 2021).
- RNA-dependent RNA polymerase and 3'UTR of Bamboo mosaic virus (Huang et al., 2012).
- TDP-43 (Jinwal et al., 2012). Hsp90 prevents assembly and promotes disassembly of soluble TDP-43 filaments (Carlomagno et al., 2014). Hsp90 and notably Hop required for accumulation (Lin et al., 2021). Both Hsp90 isoforms promote phase separation of prion-like domain (Carrasco et al., 2023).
- PTK6 (Kang et al., 2012).
- p27 replicase component of Red clover necrotic mosaic virus (RCNMV) (Ahsan et al., 2012).
- Calmodulin methyltransferase (CAMKMT) (Magen et al., 2012).
- LANA of Kaposi sarcoma-associated HSV (Chen et al., 2012b).
- Adaptor protein Act1 (=TRAF3IP2); point-mutant variant linked to psoriasis-susceptibility fails to interact (Wang et al., 2013a; see also Wu et al., 2014).
- Transcription factors ATF3, BBX, C20orf194, CEBPE, CXXC1, DLX6, DMRTA1, FOXD4L6, FOXM1, FOXP2, GTF2IRD2, HMGA1, HP1BP3, IRF2, ISX, MAFG, MAX, MKX, NFIC, NFRKB, NR1H3 (see also Deng et al., 2025b, NR1I2, PCGF6, POGK, PRDM1, PREB, SETDB1, SIM2, SLFN11, SREBF1 (see also Kuan et al., 2017; Deng et al., 2025b), STAT2, TADA2A, TBX22, TCF25, TEAD2, TFDP3, THAP4, TRIM32, ZBED4, ZBTB17, ZBTB20, ZC3H7B, ZNF215, ZNF509, ZNF74 (Taipale et al., 2012).
- Kinases (Taipale et al., 2012) ACVR1B, ACVR1C, ACVR2B, AKT2, ALK, ALPK1, AMHR2, AURKC, AXL (see also Krishnamoorthy et al., 2013), BLK, BMPR1A, BMX, CAMK1G, CAMK2A, CAMK2B, CAMK2D, CAMK2G, CAMK4, CAMKK1, CAMKK2, CAMKV, CDK3, CDK11B, CDK14, CDK15, CDK18, CLK2, CLK3, CSF1R, CSNK1A1, DCLK2, DDR2, DMPK, DYRK1B (see also Miyata and Nishida, 2021), DYRK2, DYRK4 (see also Miyata and Nishida, 2021), EPHA1, EPHA4, EPHB1, EPHB6 (see also Allonby

et al., 2014), ERBB4, FASTK, FGFR1, FLT4, FRK, FYN, GRK4, GRK7, GSK3A, HCK, HIPK4, ICK, INSRR, IRAK2, IRAK3, ITK, LCK, LIMK1, LIMK2, LYN, MAP2K5, MAP2K7, MAP3K12, MAP3K15, MAP3K2, MAP3K6, MAP3K9, MAP4K1, MAP4K2, MAP4K4, MAPK15, MAPK4, MAPK7, MAST2, MATK, MERTK, MINK1, MUSK, MYLK2, MYLK3, MYLK4, NEK11, NEK8, NEK9, NPR2, NTRK1, NTRK2, NTRK3, NUAK2, PAK6, PASK, PDGFRB, PDIK1L, PIM2, PIM3, PKN1, PKN2, PRKAA2, PRKACB, PRKCA, PRKCB, PRKCG, PRKCH, PRKCI, PRKCQ, PRKCZ, PRKD1, PRKG2, PRKX, PRKY, PSKH1, PSKH2 (see also Byrne et al., 2023), PTK2, PTK2B, PTK6, ROR2, RPS6KA1, RPS6KA2, RPS6KA3, RPS6KA5, RPS6KA6, RPS6KB1, RPS6KC1, RPS6KL1, SGK2, SGK223, SGK3, SRPK3, STK32B, STK32C, STK38, STK38L, STYK1, TAOK3, TESK1, TESK2, TIE1, TNK1, TNK2 (see also Mahendrarajah et al., 2017), TNNI3K, TP53RK, TSSK1B , TSSK2, TSSK3, TYRO3, WNK4.

- Miscellaneous proteins: ARMC5, ASB17, ASB2, ASB3, ASB4, ASB6, DET1, ENC1, KAT5, KSR1, KSR2, LARP4B, MYO3B, RAG1, RGS11, RGS6, RGS7, RGS9 (Taipale et al., 2012), and CCDC117 (Taipale et al., 2014).
- E3 ligases and related proteins (Taipale et al., 2012) ANAPC2, BTRC, CUL1, CUL2, CUL3, CUL4A, CUL4B, DTX4, FBXL12, FBXL13, FBXL14, FBXL15, FBXL18, FBXL2, FBXL3, FBXL8, FBXO10 (see also Bhat et al., 2024), FBXO17, FBXO18, FBXO24, FBXO25, FBXO27, FBXO28, FBXO3, FBXO34, FBXO38, FBXO4, FBXO40, FBXO6 (see also Song et al., 2022), FBXO9, FBXW11, FBXW2, FBXW5, FBXW7, G2E3, GAN, HECTD3, HERC4, HERC6, KBTBD4, KBTBD7, KCNA5, KCNA6, KCNG1, KCNS3, KCTD8, KIAA0317, KLHL1, KLHL10, KLHL13, KLHL14, KLHL15, KLHL22, KLHL23, KLHL25, KLHL26, KLHL29, KLHL32, KLHL34, KLHL36, KLHL38, KLHL6, LGALS3BP, LNX1, LOC440248, LRSAM1, MARCH9, MDM4, NHLRC1, PARK2, PCGF1, PCGF3, PRPF19, RAB40A, RCBTB1, RCBTB2, RFWD3, RHOBTB1 (see also Prince et al., 2015), RNF10, RNF111, RNF19B, RNF40, SF3B3, SH3RF2, SKP2 (see also Lyapina et al., 2001), SOCS6, SPSB1, SPSB3, TNFAIP3 (=A20; see also Shen et al., 2021), TRIM10, TRIM17, TRIM2, TRIM36, TRIM37, TRIM41, TRIM49, TRIM56, TRIM7, TRIM73, TRIM74, VPS18, VPS41, WSB2, WWP1.
- E3 ligase KEAP1 (Prince et al., 2015).
- E3 ligase Hakai (Díaz-Díaz et al., 2020).
- E3 ligase SMURF1 (Qu et al., 2023).
- KCNQ4 potassium channel: Knock-down and overexpression of Hsp90β reduces and overexpression augments levels and the converse is true for Hsp90α indicating a particular case of isoform selectivity (Gao et al., 2013).
- Formylglycinamidine synthetase (FGAMS) and the entire purinosome (French et al., 2013; Pedley et al., 2018).
- Phosphoribosylpyrophosphate amidotransferase (PPAT) of the purinosome (Pedley et al., 2018).
- HAX-1 (Lam et al., 2013).
- PLN (Lam et al., 2013).
- SERCA2a (Lam et al., 2013).
- Sicily (fly ortholog of human NDUFAF6): cytoplasmic preprotein interacts in the cytoplasm to stabilize preprotein subunits of complex I (Zhang et al., 2013b).
- Flagellar motor protein FliN and FliI in *E. coli* (Li and Sourjik, 2011).
- p23 recruits PHD2 to Hsp90-HIF1α (Song et al., 2013).
- p53 family member TP73 (Zhang et al., 2013a).
- *Arabidopsis* transcription factors BES1 (Lachowiec et al., 2013; Shigeta et al., 2014) and BZR1 (Shigeta et al., 2015; Plitsi et al., 2022). BES1 complex is all over the cell, but accumulates in cytoplasm upon brassinosteroid signaling (Samakovli et al., 2020a).
- *Arabidopsis* brassinosteroid signaling factor BIN2 (Samakovli et al., 2014).

- Brassinosteroid receptor BRI1 and its co-receptor BAK1 at the plasma membrane; interaction of BAK1 with BRI1 depends on interaction of Hsp90 with kinase domain of BRI1 (Samakovli et al., 2022)
- Cla4: interacts genetically (McClellan et al., 2007) and biochemically (Hsieh et al., 2013) in yeast.
- Histone demethylases KDM4B/JMJD2B (Ipenberg et al., 2013) and KDM3A/JMJD1A (Kasioulis et al., 2014).
- thiazide-sensitive NaCl cotransporter NCC (=SLC12A3) (Donnelly et al., 2013).
- EBV DNA polymerase catalytic subunit BALF5, probably facilitating interaction with BMFR1 for nuclear transport (Kawashima et al., 2013).
- Flagellar motor protein FliN with htpG in *E. coli* (Press et al., 2013).
- Phosphatase CheZ with htpG in *E. coli* (Press et al., 2013).
- Chemoreceptor histidine kinase CheA with htpG in *E. coli (*Press et al., 2013).
- Chloroquine resistance transporter (PfCRT) of *Plasmodium* (Shahinas et al., 2013).
- USP1 and Met1 in insect cells in response to ecdysone and juvenile hormone, respectively, in a mutually exclusive way (Liu et al., 2013). Hsp83 promotes juvenile hormone-induced nuclear localization and chromatin binding of Met (He et al., 2014). Hsp83 activity required for ligand-binding competence of Met, but then juvenile hormone triggers Hsp83 dissociation and association of Met with coactivator Tai (Tumova and Jindra, 2023).
- EBAX-1 of *C. elegans* interacts genetically and by yeast 2-hybrid (Wang et al., 2013e).
- Adenosine A_{2A} receptor, but exclusively with Hsp90α (Bergmayr et al., 2013).
- Ura2 (Zuehlke et al., 2013).
- BRAT1 (Fierro-Monti et al., 2013a).
- vFLIP of KSHV (Nayar et al., 2013).
- Tax of HTLV-1 (Gao and Harhaj, 2013).
- Aldo-keto reductase 1B10 (AKR1B10); Hsp90α promotes its non-classical secretion through lysosomes (Luo et al., 2013).
- Wild-type and mutant glucocerebrosidase (GBA) (Lu et al., 2011; Yang et al., 2014a; Yang et al., 2015a); as part of a complex with Hop and Cdc37 that recruits Hsp27 for targeting GBA to degradation (Yang et al., 2015a).
- Fibronectin (Hunter et al., 2014; Chakraborty et al., 2020).
- DBC2/RhoBTB2; Hsp90 promotes GTP binding and assembly of DBC2-Cul3-COP9 complex (Manjarrez et al., 2014).
- Utp21 (Tenge et al., 2014).
- HSV-1 capsid protein ICP5 (Zhong et al., 2014) and VP16 (Wang et al., 2018).
- HSV-1 DNA polymerase UL42 (Qin et al., 2022).
- Precursor of Lysyl oxidase-like 2 protein (LOXL2) with extracellular Hsp90α (McCready et al., 2014).
- Legumain (= LGMN = asparaginyl endopeptidase) precursor associates with Hsp90α in a TRAF6-mediated ubiquitination-dependent way (Lin et al., 2014).
- nsP3 and nsP4 of Chikungonya virus (Rathore et al., 2014).
- Urokinase plasminogen activator (uPA) (Donet et al., 2014).
- ANKMY2 (Taipale et al., 2014).
- Broad-Complex-Tramtrack-Bric-a-brac (BTB) domain containing proteins BrZ7 and mod(mdg4) of insects (Cai et al., 2014).
- XRCC1, not bound to DNA Pol β, interacts with DNA-PK-phosphorylated Hsp90α (Fang et al., 2014).
- PGK1 (Chen et al., 2015b; Zhou et al., 2019b; Shen et al., 2025). Acts as "co-chaperone" for GSK3β (Tang et al., 2022b).

- Serotonin transporter (SERT), only with Hsp90β isoform, along with Hsp70, Hop, p23 and CHIP (El-Kasaby et al., 2014).
- Ribonucleotide reductase subunit Rnr4 (Truman et al., 2015).
- Macrophage migration inhibitory factor (MIF), but only with Hsp90α (Schulz et al., 2012).
- Calpain-1, even in its active state, but not calpain-2 (Averna et al., 2015).
- Hsp27 (Yang et al., 2015a).
- L protein (polymerase) of human respiratory syncytial virus (Munday et al., 2015).
- HPV splice isoform E6^E7 (Ajiro and Zheng, 2015).
- Human and mouse norovirus capsid proteins VP1 (Vashist et al., 2015).
- Rad51 and Rad52 (Suhane et al., 2015; see also Gavin et al., 2002; Zhao et al., 2005; Rani et al., 2024).
- VirE2 interacting protein 1 (VIP1) (Park et al., 2014).
- DNA polymerase λ of *Arabidopsis* (Roy et al., 2015).
- DYRK1A mutants, but not wt, in luciferase interaction assay (Sonamoto et al., 2015).
- SDF2 (Siragusa et al., 2015).
- Tup1 in *Candida* (Diezmann et al., 2015).
- ANP32C and ANP32D (Yuzefovych et al., 2015).
- BPIFB4, notably a longevity-associated variant, in a Perk and 14-3-3 dependent way (Villa et al., 2015).
- DnaA with overexpressed htpG (Grudniak et al., 2015).
- Auxin co-receptor TIR1 (Wang et al., 2016b; Watanabe et al., 2016), along with HOP proteins and SGT1b (Muñoz et al., 2022).
- HMGA2 (Kao et al., 2016).
- Pyruvate kinase M2 (PKM2) along with Hop and p23; as dimer stabilizes mutant EGFR (Yang et al., 2015b). Complex with Hsp90 promotes its stabilizing phosphorylation by GSK3β (Xu et al., 2017). See also Liu et al., 2024e; Shen et al., 2025.
- MLKL, promoting necroptosis (Bigenzahn et al., 2016; Zhao et al., 2016; see also Yang and He, 2016).
- Lectin-like oxidized LDL receptor-1 (LOX1=OLR1) as membrane receptor for membrane-bound Hsp90 (Zhu et al., 2016a).
- Hsp90α interacts with VP2 of IBDV (Hu et al., 2015).
- Kinase BGLF4 of EBV by split renilla assay (Wang et al., 2016a).
- Yeast cytochrome c peroxidase Ccp1 (Kathiresan and English, 2016).
- Multidrug resistance-associated protein 1 (MRP1) (Roundhill et al., 2016).
- Yeast galactokinase Gal1; when Hsp90 function is compromised, Gal1 and several other Gal proteins aggregate and galactose utilization is slightly less efficient (Gopinath and Leu, 2016; see also Gopinath and Leu, 2017).
- Hsp90 interacts with NMNAT2 to stimulate its ATPase and foldase activities (Ali et al., 2016).
- Phosphoprotein (P) of rabies virus, along with Cdc37 (Xu et al., 2016).
- Rab3GAP1 with Hsp90α, perhaps through Aha1, colocalized at secretory vesicles (Ghosh et al., 2015).
- BRD4 (Zhou et al., 2015).
- Integrin α2 and integrin αL (Ghosh et al., 2016).
- α4 integrin but not β2 integrin (Lin et al., 2019).
- αMβ2 integrin (Hoang and Kim, 2022).
- Integrin αVβ5: eHsp90α binds to push the integrin into an open high affinity binding state for irisin in an ATPase-independent fashion (A et al., 2023; and comment by Bourboulia et al., 2023).

- Checkpoint kinase Mps1 (=TTK); interaction stabilized by phosphorylation of Hsp90 by Mps1 itself and destabilized by dephosphorylation by Cdc14 (Woodford et al., 2016c; see also Woodford et al., 2021). Stability regulated by Hsp90 (Yao et al., 2022).
- Cdc14, preferentially with (T101) non-phosphorylated Hsp82 (Woodford et al., 2016c).
- Tumor suppressor folliculin (FLCN) (Woodford et al., 2016a).
- Proteins encoded by flowering genes Leafy (LFY), SOC1, AGL24, and SUP in *Arabidopsis* (Margaritopoulou et al., 2016).
- UHRF1; Hsp90 inhibitor-induced degradation is not mediated by CHIP or CUL5 (Ding et al., 2016).
- Tyrosine kinase receptor MET (= c-MET) (Prince et al., 2015).
- Transferrin receptor 1 (TFR1) (Shapiro et al., 2016).
- NHE1 (Amith et al., 2017; Odunewu-Aderibigbe and Fliegel, 2017).
- REB-ERBα; this interaction somehow antagonizes interaction of Hsp90 with GR (Okabe et al., 2016).
- N-acetyltransferase ARD1; not clear whether it is through androgen receptor (AR) (DePaolo et al., 2016).
- ATM phosphorylates nuclear Hsp90α (Elaimy et al., 2016).
- UCS protein and Unc45 relative She4 in yeast by 2-hybrid (Millson et al., 2004); heat increase affected by phosphorylation of She4 (Gomez-Escalante et al., 2017).
- p14ARF of *INK4a* gene; Hsp90 with CHIP induces lysosomal degradation of p14ARF, thereby preventing senescence of tumor cells (Han et al., 2017).
- Glutamate transporter 1 (GLT-1); Hsp90β promotes its degradation by the proteasome and epileptic seizures in mouse model, countered by GA (Sha et al., 2017).
- Spleen tyrosine kinase (SYK) (Guo et al., 2017a; Walter et al., 2017).
- SOD1 point mutant linked to severe ALS (Karras et al., 2017).
- FANCA, both wild-type (Oda et al., 2007) and mild disease mutants (Karras et al., 2017).
- Thioredoxin reductase (TrxR), thioredoxin (Trx1) and Rab3a on the cytosolic face of synaptic vesicles (Azarnia Tehran et al., 2017; see also Pirazzini et al., 2018).
- KAP1 (Hummel et al., 2017).
- EZH2 in complex with CDK1 to promote its phosphorylation and degradation (Göllner et al., 2017; see also Deng and Hu, 2023).
- Hsp90 is required for maturation of L protein of mumps virus (Katoh et al., 2017), together with R2TP complex and blocking RNA synthesis of mumps and measles viruses (Katoh et al., 2019).
- SREBP1 (= SREBF1), SREBP2, and SCAP (Kuan et al., 2017). Chlorogenic acid reduces interaction of SREBP2 through phosphorylation by AMPK (Meng et al., 2024).
- TilS in *Shewanella oneidensis* (Honoré et al., 2017).
- misfolded transthyretin (TTR) monomer, *in vitro* (Oroz et al., 2017).
- MTA1, Hsp90 required for hypoxia-induced nuclear-cytoplasmic translocation (Marzook et al., 2017).
- LYN (Taipale et al., 2012; see also Guo et al., 2017a).
- Intracellular domain (ICN1) of Notch1 (Wang et al., 2017d).
- Zyogen pro-Dcp1 in *Drosophila* (Choutka et al., 2017).
- Nibrin (NBN) (Pennisi et al., 2017).
- HNF4A (Jing et al., 2017).
- Tsc2 in a Tsc1-dependent way (Woodford et al., 2017).
- RanBP9 (Woo et al., 2017).
- STK33 (Azoitei et al., 2012; Liu et al., 2017).
- GREB1 (Savitski et al., 2018).
- Cholin acetyltransferase (ChAT), notably mutants (Morey et al., 2017).

- LSD1, stabilization also requires Hop (Tsai et al., 2018; see also Bennesch et al., 2016; Li et al., 2023b).
- PRDM14 (Moriya et al., 2018).
- mtHsp70/Grp75/mortalin (Rozenberg et al., 2018).
- Complement C9 (Rozenberg et al., 2018).
- Humanin (Gong et al., 2018).
- Tobamovirus resistance protein Tm-2^2 of tomato (Qian et al., 2018).
- Caspase-8, protecting it against degradation (Gupta et al., 2018).
- Lamin A/C; knock-down of Hsp90 reduces levels and affects morphology and migration of dermal papilla cells (Thanomkitti et al., 2018; see also Wang et al., 2021d).
- Chl1 component of sister chromatid cohesion complex in yeast (Khurana et al., 2018).
- HSV-1 protein Us11, disrupts Hsp90-TBK1 interaction (Liu et al., 2018).
- Mature interleukin-1β (IL-1β), promoting its secretion by translocation into a vesicle intermediate to formation of autophagosomes (Zhang et al., 2015b; see also Zhang et al., 2018b); stimulated by starvation (Zhang et al., 2015b) or infection by *Mycoplasma hyopneumoniae* (Zhang et al., 2018b). Hsp90 promotes unconventional protein secretion possibly by promoting ATP-dependent unfolding of cargo (Zhang et al., 2020a).
- SOX11, with Hsp90α (Elzakra et al., 2017).
- ER membrane complex component Emc2 in yeast in TPR-independent mode (Kudze et al., 2018).
- WTAP (Bansal et al., 2014; Kuai et al., 2018).
- Twist1 (Meng et al., 2019).
- Glutamine synthetase Gln1 in stressed yeast cells (O'Connell et al., 2014).
- Dual leucine zipper kinase (DLK), required for axon injury signaling (Karney-Grobe et al., 2018; see also Zheng et al., 2020a).
- Effectors NleH1 and NleH2 of type III secretion system of pathogenic bacteria upon injection into mammalian cells (Wu and Hardwidge, 2018).
- Capping enzyme RNGTT (Trotman et al., 2018).
- HMG-CoA reductase (HMGCR) (Dong et al., 2019).
- Clusterin, which appears to behave like a (intracellular) co-chaperone (Xiong et al., 2019a). See also interaction with eHsp90α (Tian et al., 2019).
- Neuraminidase of influenza virus A; Hsp90 overexpression further stabilizes it (Kumar et al., 2019).
- LRP5 with Hsp90β (Wang et al., 2019a).
- Cytosolic catalytic domain of type III CD38 (Wu et al., 2019d).
- Cwt1 in *C. albicans* (Guan et al., 2019).
- Nck-associated protein 1 (NAP1) (Xiong et al., 2019b).
- GluR1 subunit of AMPA receptors; association with FKBP51 promotes disposal of internalized receptors (Blair et al., 2019a).
- *E. coli* tubulin homolog FtsZ: holds it and prevents its polymerization in ATPase-independent manner (Balasubramanian et al., 2019).
- The metalloprotease toxin AIP56 from *Photobacterium damselae*, upon translocation from endosomes to cytosol (Rodrigues et al., 2019).
- Pellino protein Peli1, directly through its RING domain to regulate Ire1-Hsp90 interaction and Ire1 phosphorylation (Zhao et al., 2019).
- F-box protein COL1 in *Arabidopsis* (Zhang et al., 2015c).
- REST (Orozco-Díaz et al., 2019).
- TSG101 (Giordano et al., 2019).
- SLC6A14 interacts and depends on it for trafficking to cell surface (Rogala-Koziarska et al., 2019; Polosak et al., 2022).

- MAP1B (Wu et al., 2020b).
- Kinase Pbs2 of Hog1 pathway in *C. albicans* (O'Meara et al., 2019).
- Sumo deconjugating enzyme Ulp1 of *C. albicans*; Hsp90 impairment leads to hypersumoylation of Rvb1 (O'Meara et al., 2019).
- *S. aureus* protein Lpl1; interaction on cell surface triggers F-actin formation (Tribelli et al., 2019).
- HopBF1 family of bacterial effectors both as clients and Hsp90 kinases, independently of Cdc37 (Lopez et al., 2019).
- MAST1 (Pan et al., 2019).
- Bluetongue viral proteins (Mohl and Roy, 2019).
- Nuclear pool of HCFC1; Hsp90 inhibition affects its levels and function in regulating cell cycle genes (Antonova et al., 2019; see also Liu et al., 2024c).
- Rubella virus non-structural protein p150 (Sakata et al., 2019).
- Tumor suppressor NDRG2; in its absence PRMT5 methylation of Hsp90 is required to maintain Hsp90 activity (Ichikawa et al., 2020).
- *Bacillus thuringiensis* Cry1 prototoxins are protected from proteases in the insect gut and their interaction with the cadherin receptor is enhanced (García-Gómez et al., 2019), and Hsp90 and Hsp70 collaborate to enhance toxicity (García-Gómez et al., 2023).
- c-Myc (Lee et al., 2018); interaction with Hsp90 and stabilization of c-Myc stimulated by LSD1 overexpression (Li et al., 2023b).
- TCL1A (Song et al., 2020).
- Swr1 of SWR-C and Ino80 in yeast (Wang et al., 2020a).
- Cassava transcription factor MeWRKY20 and MeCatalase1 (Wei et al., 2020b), and transcription factor MeSRS1 (Wei et al., 2021b).
- *Arabidopsis thaliana* MAPKKK (MEKK) YODA (= YDA) (Samakovli et al., 2020c; Samakovli et al., 2021b).
- μ-opioid receptor (Zhang et al., 2020d).
- Splicesome complex component LSM8 in *Arabidopsis*, primarily mediated by putative co-chaperone prefoldin PFD4 (Esteve-Bruna et al., 2020).
- Bclaf1 (Zhou et al., 2019c).
- CD79a (Mahmud et al., 2020).
- BCAP (=PIK3AP1) (Mahmud et al., 2020).
- PLCγ2 (Mahmud et al., 2020).
- PTPN22 (Mahmud et al., 2020).
- FBXL6; the K63-mediated ubiquitination by FBXL6 stabilizes Hsp90α (Shi et al., 2020a).
- The components Tas3 and Arb1 of the complexes RITS and ARC, respectively, in *S. pombe* (Sun et al., 2020b).
- Clathrin heavy chain of Medaka and capsid protein of red-spotted grouper nervous necrosis virus (Zhang et al., 2020c).
- CPEB1-3 (Tsvetkov et al., 2020).
- LMTK3, possibly through Cdc37 (Ditsiou et al., 2020).
- STING (Sato et al., 2020).
- Components of *Aspergillus fumigatus* cell wall integrity pathway: PkcA, MpkA, RlmA (Rocha et al., 2020).
- MERS-CoV nucleoprotein (NP), with Hsp90β (Li et al., 2020b).
- Pseudorabies virus virion protein VP5 (Zhang et al., 2021b).
- Microtubule-associated protein 4 (MAP4) (Wu et al., 2020a).
- E2F1 and E2F2 (Kotwal et al., 2021).
- Argininosuccinate synthase (ASS1) (Erez et al., 2011; see also Wu et al., 2021a).
- Argininosuccinate lyase (ASL) (Wu et al., 2021a).

- Histone methyltransferase SUV39H1 (Lian et al., 2021).
- γ-secretase components anterior pharynx-defective-1 (APH-1) and nicastrin (NCT) (Noorani et al., 2020).
- IDH1, along with Aha1 (Zheng et al., 2021a).
- ROR1; specifically with Hsp90α (Khaledian et al., 2021).
- Newly synthesized adenovirus 5 protein E1A (Dalidowska et al., 2021).
- DYRK3 (Mediani et al., 2021).
- Guanylate-binding protein 1 (GBP1), possibly GBP2-5 as well; the binding to Hsp90 leads to the release and activation of Hsf1 (Li et al., 2021a).
- Rab-coupling protein (RCP = RAB11FIP1) with Hsp90α to promote its secretion through exosomes (Zhang et al., 2020b).
- C/EBPβ, along with Hop (Qi et al., 2021).
- RhoB; Hsp90 KD and overexpression reduce and increase levels, respectively (Miao et al., 2021).
- Pseudouridine synthase 7 (PUS7) (Song et al., 2021).
- HIPK2, whose nascent form is *destabilized* by Hsp90-Cdc37 (Müller and Klempnauer, 2021).
- L protein of snakehead vesiculovirus (Zhang et al., 2021d).
- Filamin A (=FLNA), along with NudC (Liu et al., 2021a).
- DDX5 (Zhang et al., 2021a).
- Nwd1 (Correa et al., 2014; Yamada et al., 2020).
- NBR1 with HSP90.1 in *Arabidopsis thaliana*, notably during recovery from heat-shock for ubiquitination-independent degradation of Hsp90 by targeting to autophagosomes (Thirumalaikumar et al., 2020).
- *Cassava* MeHSP90.9 interacts with autophagy proteins ATG8b, ATG8c, ATG8e, and ATG12 (Wei et al., 2021a).
- Senescence-associated beta-galactosidase (SA-β-galactosidase; from gene *GLB1*) (Chen et al., 2021a).
- Eukaryotic elongation factor 1α2 (EEF1A2), apparently only with Hsp90β, to promote TGFβ-SMAD signaling (Jia et al., 2021).
- The heme-containing indoleamine-2,3-dioxygenase (IDO1), but not tryptophan-2,3-dioxygenase requires Hsp90 for heme insertion (Biswas et al., 2022), and NO-stimulated heme allocation (Biswas and Stuehr, 2023; see also Biswas et al., 2024).
- COX-2 (Zhang et al., 2022d).
- Kinesin-like calmodulin binding protein (KCBP) of microalga *Dunaliella salina* (Shi et al., 2021).
- Avian reovirus non-structural protein p17 (Huang et al., 2022).
- CD147, protecting it from FBXO6-mediated proteasomal degradation (Song et al., 2022).
- STAT1, along with SGT1 (=SUGT1), interaction with Hsp90 further stimulated by IFNγ (Liu et al., 2022a).
- Acyl–coenzyme A (CoA) synthetase long-chain family member 4 (Acsl4) (Miao et al., 2022).
- Dynamin-related protein 1 (Drp1) (Miao et al., 2022).
- Human APEX2 and budding yeast ortholog Apn2 (Omkar et al., 2022).
- FHIT (Paduano et al., 2022).
- VP35 of grass carp reovirus type II (Jiang et al., 2022). VP5 and VP7 of GCRV (Hou et al., 2023).
- Upc2 bound to ergosterol in *Candida glabrata* and *S. cerevisiae*; ergosterol dissociation-induced Hsp90 release allows nuclear localization (Tan et al., 2022).

- Bifunctional glutamate/proline-tRNA ligase (EPRS) (Lu et al., 2022b).
- Ubiquitin-L40 fusion protein UBA52 (Tiwari et al., 2022).
- DELLA proteins GAI and RGA (Plitsi et al., 2022).
- Catenin α-like 1 (CTNNAL1) (Wu et al., 2023).
- Anillin is recruited to pharmacologically inhibited Hsp90 (Samant et al., 2022).
- CD80 (=B7-1) (Li et al., 2022a).
- Actin-4 of *Bombyx mori* (Chen et al., 2023b).
- Nrf2 (Ngo et al., 2022).
- CND1 of *Arabidopsis thaliana* (gene *At1g32730*); light induces interaction, which presumably facilitates chloroplast import of CND1 (Jin et al., 2023).
- HSP90.2 binds PsbO and 2Q2, and promotes their chloroplast import, possibly by binding actin microfilaments on the surface of chloroplasts (Yan et al., 2023a; Yan et al., 2023b).
- Glutathione peroxidase 4 (GPX4), induced by timosaponin AIII (Zhou et al., 2023).
- SARS-CoV-2 proteins N, M, Orf3, Orf7a, and Orf7b (Zhao et al., 2023).
- ZBTB7A (Choi et al., 2023).
- 14-3-3 protein GF14-4 in corn (Xu et al., 2023b).
- Adenosyl homocysteine hydrolase 1 (AHH1) in corn (Xu et al., 2023b).
- Connexin Cx43 (An et al., 2023).
- Phosphodiesterase 6 (PDE6), consisting of subunits α (PDE6C), β, γ, although it has not been established whether this is through the co-chaperone AIPL1 (Munezero et al., 2023). Hsp90, AIPL1, and PDE6γ are all required for efficient assembly to functional complex (Singh et al., 2024).
- Rsc3 of the chromatin remodeler RSC (Kolhe et al., 2023).
- RNA helicase Ded1 (Kolhe et al., 2023).
- CHMP4B interacts with Hsp90β in zebrafish lens epithelial cells (Fu et al., 2023).
- KAT8 (Zhang et al., 2022f; He et al., 2023).
- HDAC11 (He et al., 2023).
- SDCBP (He et al., 2023).
- PARP1 (Huang et al., 2023b).
- *Arabidopsis* ELF3 gets destabilized by its interaction with Hsp90 because this promotes interaction with the E3 ubiquitin ligase COP1 (Zeng et al., 2023).
- Deubiquitinase USP14, lengthens Hsp90 half life by reducing K48-linked ubiquitin (Wei et al., 2023). Same for USP21 (Xu et al., 2024b).
- Collagen-1 (Singh et al., 2023).
- Period-2 (Per2), through the PAS1 domain; Per2 competes with IKKα/β for Hsp90 binding (Zhang et al., 2023c).
- NME1 (Zhang et al., 2023b).
- APLP2 (=YWK-II), promotes degradation of TGFβ receptor II (TGFBR2) by interfering with its binding to Hsp90 (Tuersuntuoheti et al., 2023).
- TRIM21 (Xu et al., 2023a).
- Porcine deltacoronavirus proteins N, NS7, NSP10 (Zhao et al., 2024).
- *A. thaliana* WD40 repeat protein APRF1, with HSP90.1 in the nucleus and HSP90.2 in the cytoplasm (Isaioglou et al., 2024).
- PHOX2B: Hsp90 preferentially binds disordered conformation of polyAla segment preventing phase transition of PHOX2B into solid condensates (Antón et al., 2024).
- Non-structural proteins of SFTS virus (Wang et al., 2024b).
- VDAC1, interacts with Hsp90α on cytosolic side, and compromising Hsp90α C-terminus by truncation or with novobiocin reduces VDAC1 monoubiquitination and induces oligomerization (Zhang et al., 2023a).

- L protein of Rift Valley fever virus (Alem et al., 2024).
- Calmodulin-domain protein kinase 1 of Cassava (CPK1), interacts with HSP90.9 and phosphorylates it on S175 (Wei et al., 2024b).
- Outer protein C2 (XopC2) of bacterial pathogen *Xanthomonas phaseoli* interacts with Cassava HSP90.9 and inhibits the interaction of the latter with CPK1 (Wei et al., 2024b).
- α-enolase (= ENO1) (Liu et al., 2024e; Shen et al., 2025).
- Orf9b protein of SARS-CoV2 interacts with Hsp90α but not Hsp90β (Zhou et al., 2024a).
- MYG1, enhanced by EGF signaling (Chen et al., 2024a).
- Intracellular α-fetoprotein (AFP), possibly acting as Hsp90 co-chaperone to stabilize c-Myc and c-Met in cancer cells (Lin et al., 2024b).
- Capsid protein VP1 of feline calicivirus (FCV), possibly after cleavage of precursor protein (Pérez-Ibáñez et al., 2024).
- *Gingko* Hsp90 binds telomerase and structural maintenance of chromosomes protein 1 (SMC1) (Feng et al., 2024).
- Anti-apoptotic protein WSSV322 of white spot syndrome virus (Yingsunthonwattana et al., 2024).
- GLUT1 (= SLC2A1) (Yang et al., 2024).
- Regulator of chromosome condensation 2 (RCC2) with NudCL2 as co-chaperone (Xu et al., 2024c).
- RACK1B in plants, through SGT1 (Hu et al., 2024a).
- Calcium channel $Ca_v1.2$ of ER membrane (Tanaka et al., 2024).
- secreted frizzled-related protein 1 (sFRP1) (Yao et al., 2024).
- GLCCI1 (Liu et al., 2024b).
- GRP78 (= Bip) (Liu et al., 2024b).
- Xeroderma pigmentosum group B-complementing protein (XPB) (Chen et al., 2024b).
- βC1 of begomovirus betasatellites (Zhang et al., 2024a).
- Nonexpressor of pathogenesis-related genes 3 (NPR3) of *Nicotiana benthamiana* (Zhang et al., 2024a).
- NFκB subunit RelA/p65 (Zhan et al., 2024).
- TFEB, interaction with Hsp90α further stimulated by inducers of autophagy (Yang et al., 2023; see also Liu et al., 2024c).
- eHsp90α interacts with N-cadherin (Pan et al., 2025).
- RPAP2 (Cui et al., 2025).
- PGAM2, stimulated further by angiotensin II (Li et al., 2025b).
- E3 ubiquitin ligase SYVN1 (Li et al., 2025b).
- LDHA (Shen et al., 2025).
- Ptc2 (type 2C protein phosphatase) in *Candida albicans* (Zhang et al., 2025b).
- Retinol dehydrogenase 5 (RDH5) (Jia et al., 2025).
- Calnexin (CANX) (Jia et al., 2025).
- Fatty acid synthase (FASN) (Deng et al., 2025b).
- LXRα (=NR1H3) (Taipale et al., 2012; Deng et al., 2025b).

Other *in vivo* analyses (other than genetic in the narrow sense)**:** Top Refs

- For impacts of PTMs, see also chapter "Biochemistry".
- Subcellular localization: mostly cytoplasmic, some nuclear (see e.g. van Bergen en Henegouwen et al., 1987; Berbers et al., 1988; Akner et al., 1992; Perdew et al., 1993).

Slightly increased nuclear accumulation upon heat stress (van Bergen en Henegouwen et al., 1987; Berbers et al., 1988) and hypoxic shock (Katschinski et al., 2002). Associated with lysosomal membranes (Agarraberes and Dice, 2001; Bandyopadhyay et al., 2008; see also Luo et al., 2013; Gong et al., 2018). It binds the nuclear envelope of permeabilized cells (Schlatter et al., 2002). A GFP fusion gives same pattern and shows an increase in periplasmic and intranuclear staining after heat-shock (Langer et al., 2003). Evidence for Hsp90 at the cell surface (Ferrarini et al., 1992; see also below, paragraph "Unusual stuff"). Golgi targeting upon LPS stimulation (Triantafilou and Triantafilou, 2004). Shift to more nuclear localization is developmentally regulated in *Toxoplasma gondii* (Echeverría et al., 2005). Age- and estradiol-dependent shift to more cytoplasmic localization in fish (Rendell and Currie, 2005). Present in secreted exosomes (Hegmans et al., 2004; Clayton et al., 2005; Chen et al., 2006b; Yu et al., 2006; McCready et al., 2010; Lv et al., 2012; Takeuchi et al., 2015; Cruz et al., 2017; Ono et al., 2018; Saha et al., 2018), on exosome membranes (Yang et al., 2014b; Tang et al., 2019), and various other extracellular vesicles and membranes (Ono et al., 2018; Eguchi et al., 2020) (however, see below and Jeppesen et al., 2019). Hsp90 can be found in mitochondria (intermembrane space and matrix), notably of tumor cells (Kang et al., 2007; see also Barksdale and Bijur, 2009), and possibly in budding yeast (Francis and Thorsness, 2011). Stress and pulmonary arterial hypertension promotes mitochondrial localization of Hsp90 in pulmonary arterial smooth muscle cells, thereby preserving mitochondrial functions and promoting diseased state (Boucherat et al., 2018). PDGF stimulation recruits Hsp90 to membrane ruffles and macropinosomes (Gao et al., 2007). Recruited to stress granules along with several co-chaperones (Pare et al., 2009). Becomes nuclear in quiescent budding yeast along with Sba1 and Ydj1 (Tapia and Morano, 2010) and upon nitrogen starvation along with Cpr6 (Breker et al., 2013), and in *Aspergillus* after heat stress (Lamoth et al., 2012). *Helicobacter pylori* infection leads to membrane recruitment of Hsp90β and association with Rac1 (Cha et al., 2010). A Hsp90-FKBP52-p23 complex forms an intranuclear perinuclear ring in undifferentiated neurons that redistributes during differentiation (Quintá et al., 2010); both differentiation and disassembly are triggered by FK506 (Quintá and Galigniana, 2012). Relocalizes to nucleus in cells infected with influenza (Naito et al., 2007) and HSV-1 (Zhong et al., 2014). Concentrated at neuromuscular junctions (Luo et al., 2008). Ecdysone or juvenile hormone induce nuclear localization in insect cells (Liu et al., 2013). Overexpression of E3 SUMO ligase PIAS1 induces nuclear localization in astrocytes (Soares et al., 2013). HSP90.1 and HSP90.3 accumulate in nucleus in *Arabidopsis*, and geldanamycin or brassinosteroid signaling reversed that (Samakovli et al., 2014). Associated with and required for integrity of centrosome (Lange et al., 2000; see also Wigley et al., 1999), possibly through Polo (see there). Hsp90α phosphorylated on T5/7 appears to form a ring at the neck of the primary cilium (Wang et al., 2015). Associated with secretory vesicles along with Aha1 and survivin at the leading edge of migrating cells (Ghosh et al., 2016). Hsp90β along with Unc45a more nuclear in transformed breast epithelial cells (Eisa et al., 2019). Localizes to protein aggregate centers or cytoplasmic granules, which partially overlap with stress granules, and more to the nucleus upon heat shock in *S. pombe* (Cabrera et al., 2020; Takasaki et al., 2021). In contrast, arsenite induces Hsp90 aggregates in *S. pombe* that are different from conventional stress granules, but colocalize with the RNA-binding protein Nrd1; geldanamycin reduces both Hsp90 aggregates and arsenite tolerance (Tomimoto et al., 2024). Localizes to cytoplasmic granules (lysosomes) after heat shock in *Drosophila* ovaries and testes, along with Hsc70, Hop and Ago3 (Cappucci et al., 2019). Overexpression of DYRK1B induces nuclear accumulation in COS7 cells (Miyata and Nishida, 2021). Upon lamin A knockdown, Hsp90 becomes more nuclear (Wang et al., 2021d). Colocalizes to avian reoviral factories (Huang et al., 2022). DNA damage induces Aha1-dependent nuclear

accumulation of yeast Hs82 (Fangaria et al., 2022). In *Arabidopsis*, salt stress induces more nuclear accumulation of HOP1/2, and Hsp90 in a HOP1/2-dependent way (Zhang et al., 2022c). Transiently recruited to subcellular sites of heat-damaged proteins (Mistrik et al., 2021). Colocalizes with NudCL2 and RCC2 at midbody during cytokinesis (Xu et al., 2024c).

- by overexpression of mutants: interaction with ERα (Kang et al., 1994; Meng et al., 1996), GR (Cadepond et al., 1993; Kang et al., 1999).
- Antibody injections: reduces insulin-induced mitogenesis (Takata et al., 1997) and proteasome-mediated degradation of insulin receptor mutants (Imamura et al., 1998).
- Hsp90 added to medium stimulates neurite outgrowth (Ishimoto et al., 1998).
- Overexpressed Hsp90 with a NLS slightly inhibits GR function *in vivo* and DNA binding *in vitro* (Kang et al., 1999).
- Degradation of Hsp90 in budding yeast: both Hsp82 and Hsp90 from *C. albicans* are degraded to large C-terminal fragments upon shifting from fermentative to respiratory media (Panaretou et al., 1999).
- Hsp90 is cleaved upon treatment of cells with H_2O_2 (Pantano et al., 2003). Cleavage in tissue culture cells treated with mimosine or H_2O_2 (Panopoulos et al., 2005). Oxidative stress leads to cleavage of Hsp90β and degradation of Hsp90α, but only in tumor cells (Beck et al., 2009). Free radicals cleave Hsp90 isoforms at conserved site in ATPase domain in an ADP and ionic iron-dependent reaction (blocked by ATP and Hsp90 inhibitors) both *in vivo* and *in vitro* (Beck et al., 2012). Taxotere (docetaxel) induces ubiquitination and degradation (Murtagh et al., 2006). Hsp90 degradation accelerated in NOS-3/β-actin complex thus temporally limiting NOS-3 activity (Ji et al., 2007). Extracellular Hsp90α is a cleavage substrate of MMP-2 (Dean and Overall, 2007) and MMP-14 (Butler et al., 2008). UV induces Hsp90β cleavage by caspase-10, and cleavage mutants are protective (Chen et al., 2009a). Hsp90β is far more rapidly degraded by MMP-2 than Hsp90α (Song et al., 2010b). The diterpenoid andrographolide induces a ROS-dependent cleavage in the middle domain (Liu et al., 2014b). HDAC inhibitor SAHA also induces ROS and caspase-10 mediated cleavage (Park et al., 2015). The tricyclic pyrano-orthonaphthoquinone β-lapachone induces a NQO1- and ROS-dependent cleavage (Wu et al., 2016). Cleavage induced by proteasome inhibitors and HDAC inhibitor in leukemia cells through ROS and caspase 10 (Park et al., 2017a; Park et al., 2021). Cleavage of Hsp90β at D294 can be prevented with D294A mutation (Park et al., 2021). Oxidative stress-induced cleavage product promotes co-aggregation with accumulating oxidized actin (Castro et al., 2019). Cold physical plasma induces ROS-mediated cleavage (Bekeschus et al., 2019). Hsp90α is stabilized by the PIWIL4/piR-31115 complex (Du et al., 2025). SYVN1 is an E3 ligase for Hsp90 (Li et al., 2025b).
- Overexpression and antibody injections in Xenopus oocytes: anti-Hsp90 (and anti-p23) activates HSF1, and anti-Hsp90, -Hip, -Hop, -p23, or anti-FKBP delay attenuation; attenuation accelerated by Hsp90 (and Hsp70, Hip, or Hop; delayed by immunophilins) overexpression (Ali et al., 1998; Bharadwaj et al., 1999).
- Overexpression of Hsp90 in NIH 3T3 cells retards cell cycle, blocks Hsf1 (Zhao et al., 2002) and TNFα-induced apoptosis by preventing cleavage of Bid (Zhao and Wang, 2004). Opposite result to the latter in U937 cells (Galea-Lauri et al., 1996b). Also opposite effects of Hsp90α overexpression on survival in HC11 versus SkBr3 cells (Perotti et al., 2008).
- Antisense oligos and constructs: inhibits proliferation and TNFα-induced apoptosis, and affects macrophage phenotype of monoblastoid U937 cells (Galea-Lauri et al., 1996a; Galea-Lauri et al., 1996b). In contrast, another study says that Hsp90α knock-down sensitizes cells to TRAIL-induced apoptosis because of a failure to promote the

recruitment of FLIPs and RIP to DISC (Panner et al., 2007). Effect on oxidative protection of proteasome (Conconi et al., 1998) and telomerase activity (Chang et al., 2002).

- CHIP overexpression displaces Hop and p23 from Hsp90, promotes ubiquitination of substrate and targets it to proteasome for degradation (Connell et al., 2001).
- Hsp90 facilitates nuclear export of 60S ribosomal subunits in Xenopus oocytes (Schlatter et al., 2002).
- Role in disassembly of transcriptional complexes: Hsp90 and p23 are recruited to chromatin-bound glucocorticoid receptor (GR); promoter-tethered p23 and to varying extents Hsp90 inhibit adjacent GR, TR, NFκB, an AP-1 (Freeman and Yamamoto, 2002).
- Associates genome-wide with chromatin in *Drosophila*, notably with a large fraction of promoters containing paused RNA polymerases; helps to maintain the elongation factor NELF-E and to enable proper inducibility of genes in response to environmental and physiological stimuli (Sawarkar et al., 2012).
- Hsp90 ChIP-seq in BT474 cells shows strong overlap with NELF-A in promoters and gene bodies (Greer et al., 2015).
- Hsp90 is recruited to activated ERα complexes and can be found at ERα binding sites on chromatin; it is required for activation and possibly acts as a scaffold or chaperone for the assembly of transactivation complexes (Bennesch et al., 2016).
- Associates with hTERT promoter and required for its activity (Kim et al., 2008). Recruited to 12(*S*)-lipoxygenase promoter through Sp1 and required for activity (Hung et al., 2005). Recruited to a regulatory element of the MMP-13 promoter with inhibitory (Fan et al., 2009), or perhaps stimulatory (Boehm et al., 2007) effects. With BCL-6 at target promoters (Cerchietti et al., 2009). With AF9/MLLT3 at a target promoter (Lin and Hemenway, 2010). At HIV-1 LTR, possibly to regulate gene expression (Vozzolo et al., 2010). Heat further increases colocalization with actively transcribing HIV-1 provirus (Roesch et al., 2012). In *Drosophila*, associates genome-wide with chromatin (Sawarkar et al., 2012) and with Met at juvenile hormone response element (He et al., 2014).
- Found in polyglutamine aggregates; Hsp90 overexpression reduces rate of aggregate formation and improves cell survival (Mitsui et al., 2002). Multiple chaperones including Hsp90 associate with polyglutamine proteins during aggregation (Walter et al., 2011).
- Overexpression and underexpression (with siRNA) correlates with increased and decreased solubility and microtubule binding of tau protein (Dou et al., 2003; see also Dickey et al., 2007), respectively. Hsp90 complexes promoting folding (with p23) and degradation (in presence of Hsp90 inhibitor and/or with CHIP) compete with each other for phospho-tau folding versus degradation based on RNAi experiments (Dickey et al., 2007; see also Kundrat and Regan, 2010a). Knock-down of FKBP51 also dramatically reduces tau levels although FKBP51 can interact with tau in Hsp90-independent way and promote tau-Hsp90 interaction (Jinwal et al., 2010). See also pharmacological approach to tauopathies (Luo et al., 2007). Hsp90 and Hsp70 coordinately control tau clearance with Hsp90 promoting it (Thompson et al., 2012). FKBP51 with Hsp90 promotes accumulation of neurotoxic tau species and FKBP51 levels increase with AD progression (Blair et al., 2013). Decreasing Hsp90 levels or function impairs the foldase activity of NMNAT2 required to neutralize the proteotoxic burden of Tau (Ali et al., 2016; see comment by Shorter, 2017, and also Pinkerton et al., 2021). NMNAT functions as co-chaperone for the specific recognition of phospho-Tau (Ma et al., 2020). RanBP9 levels correlate with Hsp90 levels in Tau complexes and sensitivity of Tau to Hsp90 inhibitors (Woo et al., 2017). Gets sequestered to tau aggregates in cells (Yu et al., 2019).
- *Acanthamoeba* variants with lower levels of Hsp90 or wild-type treated with Hsp90 inhibitors are partially defective for phagocytosis of and killing pathogenic bacteria (Yan et al., 2004).

- ATP depletion, like geldanamycin, triggers rapid dissociation from ErbB2 and degradation -> Hsp90 may function as ATP sensor and thereby modulate growth factor responsiveness (Peng et al., 2005).
- Pharmacological and genetic (RNA interference) inhibition of Hsp90 in human tumor cells induces telomere shortening by promoting NOS-mediated production of oxygen radicals (Compton et al., 2006).
- Hsp90 knock-down or inhibition interferes with processing to antigenic peptides; Hsp90α but not Hsp90β is associated with large precursor peptides (Kunisawa and Shastri, 2006). Hsp90 associates with N-terminally extended antigenic peptides and loading into MHC-I depends on Hsp90 function (Callahan et al., 2008). Hsp90 required for generation of a pool of crosspriming viral peptide (Lev et al., 2008). Hsp90α/β associates with some MHC class II antigens and is required for their presentation (Houlihan et al., 2009; see also Tsuji et al., 2012). Hsp90α required for antigen cross-presentation, possibly by promoting antigen translocation from endosomes to cytosol (Ichiyanagi et al., 2010; Imai et al., 2011). Hsp90 interacts with ovalbumin added as extracellular antigen, presumably acting as cytosolic translocator (Imai et al., 2011).
- Hsp90 knock-down and glucocorticoids disrupt T-cell receptor signaling complex containing also Lck, Fyn, and glucocorticoid receptor (Löwenberg et al., 2006).
- Hsp90 associates with myosin folding intermediates but not mature myofibrils in differentiating muscle cells (Srikakulam and Winkelmann, 2004).
- FRAP analyses: intracellular mobility suggests bulk of Hsp90 is in a variety of complexes both with and without geldanamycin (Picard et al., 2006). Hsp90β overall mobility not affected by geldanamycin (Picard et al., 2006) whereas Hsp90α is slightly accelerated (Lev et al., 2008).
- Protects against amyloid β stress upon overexpression in cells (Veereshwarayya et al., 2006). Aβ reduces Hsp90 expression in cerebral endothelial cells and, possibly as a result, Hsp90 client levels (Chiu et al., 2011).
- Role in antigen presentation for extracellular Hsp90-peptide complexes: bind surface receptor, transit to early endosomes where precursor peptides can be processed and transferred to MHC class I (Kurotaki et al., 2007; Oura et al., 2011). Through an alternate route, proteins can be internalized and get to the cytosol through the ERAD pathway for refolding by Hsp90 (Giodini and Cresswell, 2008); inhibited by Hsp90 inhibitors (Lu et al., 2018).
- Hsp90α1 appears to be specifically required for myofibrillogenesis in zebra fish along with Unc-45b (Krone et al., 2003; Etard et al., 2007; Du et al., 2008; Hawkins et al., 2008; Bernick et al., 2010), and this involves Smyd1b (Li et al., 2013a), and exogenous Hsp90α2 can only partially rescue (Du et al., 2008; Hawkins et al., 2008). The Z line of striated muscle may serve as a highly dynamic reservoir for Hsp90 (and Unc-45b) (Etard et al., 2008). Hsp90 may be important for proteins other than myosin in myofibrillogenesis (Codina et al., 2010). Complementation of Hsp90α1 knock-down with point mutants abolishing ATP binding or affecting putative PTM sites interfere with thick filament organization (He et al., 2015). In *C. elegans*, Hsp90 associates dynamically with I and M-bands (Gaiser et al., 2011). Smyd2-methylated Hsp90 associates with and stabilizes the I-band in skeletal (Donlin et al., 2012) and cardiac muscle (Voelkel et al., 2013). Hsp90 translocates to titin springs in myofibrillar myopathy (Unger et al., 2017). Hsp90α1 KD in zebra fish impairs proper M-line localization of MURF1a (Li et al., 2020a).
- Inhibition of Hsp90 in cells by designed TPR modules that bind with higher affinity and specificity (Cortajarena et al., 2008).
- Hsp90β knock-down or inhibition compromises VDR signaling (Angelo et al., 2008).
- p23/Sba1 expression protects yeast and mammalian cells against Hsp90 inhibitors (Forafonov et al., 2008).

- Use of split Renilla luciferase assay to track p23/Hsp90 interaction in cells and mice, minus and plus Hsp90 inhibitors (Chan et al., 2008). Split firefly luciferase for Hsp90-RAR1/SGT1 interactions in plants (Chen et al., 2008a). Split Renilla for Hsp90-PP5 interaction (Connarn et al., 2014), and to screen for disruptors of Hsp90/Aha1-CTD interaction (Keegan and Blagg, 2023). Split NanoLuc to analyze interaction of insect Hsp83 with juvenile hormone receptor Met (Tumova and Jindra, 2023).
- Hsp90 knock-down relieves inhibition of FKBP38 (e.g. cataytic activity and inhibitory interaction with Bcl-2) and thus promotes apoptosis (Edlich et al., 2007; Erdmann et al., 2007). FKBP38's role in promoting CFTR folding is also inhibited by Hsp90 (Banasavadi-Siddegowda et al., 2011).
- Trafficking in Golgi is dependent on TPR1-mediated interaction with VAP-33 (Lotz et al., 2008).
- Knock-down of both Hsc70 and Hsp72 inhibits Hsp90 and renders cells GA hypersensitive (Powers et al., 2008). Similarly, knock-down of Cdc37 reduces client kinases, but not Cdc37-independent clients, and increases sensitivity of cells to Hsp90 inhibitors (Smith et al., 2009) and ATP-competitive kinase inhibitors (Polier et al., 2013).
- Knock down of Hsp90 inhibits HBV viral production (Liu et al., 2009c). Hsp90-dependent capsid assembly is promoted by ROS (Kim et al., 2015c).
- GA blocks intranuclear cyclical GR activation (Stavreva et al., 2009; Conway-Campbell et al., 2011).
- Hsp90α inhibits caspase-2 activation directly or indirectly, possibly by interacting with the PIDDosome (Bouchier-Hayes et al., 2009).
- Knock-down/inhibition of the Hsp90 kinase Wee1 sensitizes cancer cells to Hsp90 inhibitors (Mollapour et al., 2010).
- *Eimeria tenella* needs secreted Hsp90 for invasion and Hsp90 in general for growth (Péroval et al., 2006).
- Hsp90 mutants with higher ATPase activity render yeast and mammalian cells (expressed in addition to endogenous Hsp90) more resistant to Hsp90 inhibitors (Zurawska et al., 2010).
- Knock-down of Hsp90β impairs AP-1 activity and MAPK signaling as suggested by protein-protein interaction modules e.g. with MAPK6 (Bandyopadhyay et al., 2010).
- Hsp90 inhibition or Hsp90α knock-down induce contraction of CAG repeats in a model gene (Mittelman et al., 2010).
- Hsp90α expression levels correlate with freezability of boar semen (Casas et al., 2010).
- Overexpression in some cells favors switch from apoptosis to autophagocytosis (Jiang et al., 2011). Hsp90-Cdc37 is required for Ulk1-mediated mitophagy (Joo et al., 2011).
- KD in Wengchang chicken cells increases/decreases heat-stress induced pyroptosis/mitophagy and overexpression does the opposite (Shi et al., 2024).
- Analysis in yeast of effects of deleting p23 (Δ*sba1*) or inhibiting Hsp90 pharmacologically on gene expression patterns (Echeverría et al., 2011b).
- Knock-down or inhibition in *Arabidopsis* lenghtens circadian cycle (Kim et al., 2011) through defective entrainment via the morning loop (Davis et al., 2018).
- Hsp90α KD or inhibitor sensitizes cells to DNA damage, since Hsp90α accumulates in repair foci and is required for their maintenance (Quanz et al., 2012). Hsp90α KD but not Hsp90β KD or inhibitors decreases TRAIL-induced nuclear apoptotic effects, possibly in part by reducing DNA-PK (Solier et al., 2012). Accumulation at DSBs not seen by others (Pennisi et al., 2017). In yeast, in response to DNA damage, Hsp82 accumulates in nucleus and at DSB ends; nuclear accumulation depends on Aha1 and is essential for relative resistance to DNA damaging drugs (Fangaria et al., 2022).
- Hsp90 is required for embryonic stem cell pluripotency; the effect of a miRNA-mediated Hsp90 knock-down can be suppressed by Hsp90β overexpression (Bradley et al., 2012).

- KD and overexpression of Hsp90β destabilizes and stabilizes Akt, respectively, in Caco-2 cells (Zhang et al., 2013c).
- Colocalizes with and is required for the assembly of the purinosome (French et al., 2013). Required for purinosome condensates to maintain their liquid-like state (Pedley et al., 2022).
- Transduced nitrated Hsp90 kills neuronal cells (Franco et al., 2013; Jandy et al., 2022).
- Low levels of Hsp90 correlate with longer survival in non-small cell lung cancer patients (Gallegos Ruiz et al., 2008). High levels correlate with poor prognosis in acute myeloid leukemia cells (Flandrin et al., 2008), and gastric cancer (Wang et al., 2013b).
- KD and overexpression of Hsp90α in ovarian cancer cell line inhibit proliferation/viability and increase resistance to cisplatin, respectively (Chu et al., 2013). MAST1 is destabilized and cancer cells sensitized to cisplatin by Hsp90 KD or inhibition (Pan et al., 2019). KO of Hsp90α or Hsp90 inhibition sensitizes resistant ovarian cancer cell line to platinum-based treatments (Lombardi et al., 2021).
- 17-AAG or Aha1-targeted morpholinos partially correct severe phenotype of a Gata3 mutation (Sheehan-Rooney et al., 2013).
- Hsp90 inhibitors and proteotoxic stress impair PPARγ-mediated adipogenic differentiation in culture (Nguyen et al., 2013).
- Hsp90 protects Smad3 against CHIP-mediated degradation and thereby promotes TGFβ signaling (Shang et al., 2014). 17AAG or transfection of Hsp90 C-terminal truncation blocks nuclear localization and functions of Smads, possibly by affecting accumulation of importin-β1 (Lee et al., 2016a).
- Novobiocin blocks LPS-induced preconditioning of mice involving increase in Hsp90 and Hsp70 (Kaucsár et al., 2014).
- KD of Hsp90α impairs stability and secretion of precursor of asparaginyl endpopeptidase (Lin et al., 2014).
- Coexpression of Hsp90α and UNC45b improves yield of soluble and functional unconventional myosin 15 in baculovirus system (Bird et al., 2014).
- Knock-down of either Hsp90α or Hsp90β reduces VEGF-induced activation of eNOS (Natarajan et al., 2015).
- Knock-down of either Hsp90α or Hsp90β reduces leukocyte migration (Ye et al., 2015).
- Hsp90 is recruited to MG132-induced aggresomes and required for proteasome remodeling and aggresome clearance (Nanduri et al., 2015).
- γ-synuclein protects Hsp90 clients Akt and mTOR against Hsp90 inhibitor-induced degradation (Liang et al., 2015).
- Anticancer immune response induced by hyperthermic chemotherapy may be mediated by exposed Hsp90, since it can be blocked by antibodies and inhibitors (Zunino et al., 2015).
- Hsf1 KD leads to disruption of Hsp90 complex and hyperacetylation (Ganguly et al., 2015).
- Hsp90 siRNA or geldanamycin facilitate the liver metamorphosis of sea lamprey (Chung-Davidson et al., 2015).
- Hsp90α expression is reduced by ischemia/repefusion through direct targeting of its mRNA by miR-1 (Zhu et al., 2016c).
- In *C. albicans*, Hsp90 depletion leads to increased nucleosome density at Hsf1 targets, possibly by affecting the SAGA complex (Leach et al., 2016).
- Hsp90α is downregulated in differentiating mouse myoblasts and absence from adult muscle; maintaining expression interferes with differentiation (Echeverría et al., 2016).
- Cancers with "epichaperome" (integrated Hsp90-centered proteome hubs) are more sensitive to Hsp90α/β KD or inhibition (which disrupts epichaperome), but Aha1 KD

renders cells more resistant to Hsp90 inhibitors (Rodina et al., 2016; see also Wang et al., 2016c). Epichaperomes are maladaptive and sustain pathological traits by shifting to scaffolding functions in disease (Rodina et al., 2016; Rodina et al., 2023).

- Embryonic stem cells have epichaperomes and they are similarly composed to those of cancer cells; crosslinking-MS analysis shows that these cellular environments favor a closed-like Hsp90 conformation potentially more conducive to epichaperome formation; this is promoted by phosphorylation of S226 and S255 in charged linker, which enhances proliferation and stemness of embryonic stem cells(Roychowdhury et al., 2024).
- Hsp90 epichaperome ("oncogenic Hsp90") of lymphoma organizes non-membrane-bound metabolic compartments (Calvo-Vidal et al., 2021).
- Alzheimer's disease-related stressors switch chaperome into epichaperome, which leads to disturbed protein connectivity; this imbalance can be reverted with Hsp90-targeted epichaperome inhibitors (Inda et al., 2020).
- Hsp90α knock-down or knock-out sensitizes cells to ionizing radiation correlating with reduced γH2AX (Elaimy et al., 2016).
- Knock-down of Hsp90 in cardiomyocytes in the rat impairs signaling crosstalk to fibroblasts and reduces collagen synthesis (Datta et al., 2017).
- Hsp90 represses endogenous retroviruses and their gene regulatory effects in ESCs through the KAP1 complex (Hummel et al., 2017).
- Hsp90β overexpression or inhibition affect human endothelial cells by affecting expression of VEGFRs and CD31 (Meng et al., 2017).
- Hsp90β KD and overexpression indicate that Hsp90β promotes vascular mimicry and EMT through Twist1 in hepatocellular carcinoma (Meng et al., 2019); Hsp90 inhibitor impairs STAT3-promoted TWIST transcription and thereby EMT (Chong et al., 2019).
- Hsp90 KD or inhibition alleviates muscle wasting by reducing interaction with STAT3 (Niu et al., 2021).
- KD or inhibition leads to degradation of SREBP/SCAP and lower triglyceride and cholesterol levels; overexpression of Hsp90 has the opposite effects on lipid homeostasis (Kuan et al., 2017). Chlorogenic acid reduces nuclear localization of PXR and SREBP2 because of its opposite effects on Hsp90 binding and thereby leads to lower cholesterol (Meng et al., 2024).
- Hsp90 from the trematode parasite *Clonorchis sinesis* induces Th1 response (Chung et al., 2017).
- Inhibition or knockdown leads to CLL cell death (Guo et al., 2017a).
- *HSP90AB1* (Hsp90β) KO in iPS-derived endodermal progenitor cells prevents hepatic differentiation, possibly because of increased turnover of HNF4A (Jing et al., 2017).
- Conditional Tsc1 KO increases Hsp90 ATPase activity, overexpression reduces client levels (Woodford et al., 2017). Dual combinations of FNIP1/FNIP2 and Tsc1 in HEK293 cells augment ligand affinity of GR, AR, and ERα (Backe et al., 2022b).
- KD of either both Hsp90 isoforms or SGT1 prevents recognition of centromere-specific histone H3 variant CENP-A by CUL4A-COPS8 E3 ligase, and CENP-A centromere deposition (Niikura et al., 2017).
- KD of Hsp90α in head and neck cancer cells, which overexpress it, reduces proliferation (Elzakra et al., 2017).
- Overexpression of Hsp90α S164A mutant impairs ATM/ATR signaling and DNA repair by homologous recombination (Cheng et al., 2017).
- KD or inhibition reduces Runx2 levels in osteosarcoma cells (Liang et al., 2018).
- KD of Hsp90β in mice and in human skeletal muscle myoblasts increases glucose tolerance and metabolism, respectively (Jing et al., 2018).
- Hsf1-dependent cell-to-cell variations of Hsp90 levels affect cell-specific resistance to fluconazole in *S. cerevisiae* (Zheng et al., 2018).

- Involved in chaperone-mediated autophagy (CMA) (Majeski and Dice, 2004; Kaushik and Cuervo, 2012), in part for oligomerization and stability of LAMP2A (Bandyopadhyay et al., 2008; Kabuta et al., 2008). Humanin promotes interaction of Hsp90 with substrates of CMA on the cytosolic side of lysosomes (Gong et al., 2018). For some substrates such as IL-1β, it may be independent of LAMP2A (Zhang et al., 2015b). HDAC6 promotes association of Hsp90 with LAMP2A and CMA; overexpression of Hsp90 K489R mutant does that, too (Du et al., 2021).
- KD of Hsp90aa1.2 in zebra fish impairs cell cyle and migration of primordial germ cells (Pfeiffer et al., 2018).
- Macrophages are activated by recombinant Hsp90 or exosomes with Hsp90, as overrepresented in alcoholic liver disease (Saha et al., 2018).
- Hsp90 somehow stimulates myosin expression and thereby turnover in myofibrils (Ojima et al., 2018).
- KD and overexpression of Hsp90α correlates with increased drug sensitivity of osteosarcoma cells, and reduced sensitivity and increased autophagy, respectively (Xiao et al., 2018).
- Different proteotoxic stressors differentially compromise Hsp90 "availability" in yeast; there are distinct Hsp90- and Hsp70-dependent pathways for the activation of the heat-shock response (HSR) (Alford and Brandman, 2018).
- KD of both isoforms in HEK293T cells reduces adhesion of calcium oxalate crystals (Manissorn et al., 2018).
- KD of Hsp90α but not β blocks HSV-1 VP16-activated transcription (Wang et al., 2018).
- High fever promotes adhesion and transmigration of T-lymphocytes by stimulating expression and interaction of Hsp90 with cytoplasmic tail of α4 integrin; this Hsp90 ATPase- and dimerization-independent activity, which can be obtained by constitutive Hsp90 overexpression, promotes α4 clustering and activation; disruption of this interaction impairs fever-induced T-cell action (Lin et al., 2019).
- Knock-down inhibits necroptosis and ferroptosis (Wu et al., 2019e).
- KD of Hsp90β inhibits, and overexpression of Hsp90β promotes growth of gastric cancer cells through interaction with LRP5 (Wang et al., 2019a). Hsp90 overexpression in gastric cancer cells promotes proliferation, colony formation, invasion, and, in general stemness; it also enhances glucose consumption and lactate production, and cisplatin resistance, whereas KD does the opposite (Shen et al., 2025).
- KD of either Hsp90α or Hsp90β destabilizes type III CD38 (Wu et al., 2019d).
- Hsp90-stimulated MMP9 activation, invasion and metastasis of NSCLC cells requires NAP1 Xiong et al., 2019b).
- Hsp90 inhibitor or KD increase mitochondrial metabolism in iPSC-derived cardiomyocytes (Ebert et al., 2019).
- KD in *Arabidopsis* impairs jasmonate signaling (Zhang et al., 2015c).
- KD or inhibition aleviates effect of mutant huntingtin on REST resulting in a neuroprotective effect (Orozco-Díaz et al., 2019).
- KD of Hsp90β (not α) or inhibition and levels of wild-type p53 (and p53-mediated senescence) are anti-correlated in myoblasts and muscle, and Hsp90β promotes Mdm2-dependent degradation of wild-type p53 (He et al., 2019).
- Bacterial effectors of the HopBF1 family of kinases mimic a client to phosphorylate and to block Hsp90 in yeast, human cells and plants (Lopez et al., 2019).
- KD or inhibition impair accumulation of bluetongue viral proteins and viral replication (Mohl and Roy, 2019).
- KD or inhibition impair cAMP-induced differentiation of Schwann cells (Han et al., 2019).

- Hsp90α-specific inhibition or CRISPR/Cas9 KD of Hsp90α, p23 or Cdc37 in the brain blocks opioid anti-nociception by preventing MAPK activation through the mu (μ) opioid receptor (Lei et al., 2019). The effect is opposite for Hsp90 inhibition in the spinal cord (Duron et al., 2020), where intravenously given Hsp90β-selective inhibitor improves the opioid treatment (Duron et al., 2024). Hsp90-mediated inhibition also through β-arrestin pathway (Zhang et al., 2020d).
- Movement to nuclear periphery of induced gene locus in yeast is dependent on Hsp90 and p23 (Sba1) (Wang et al., 2020a).
- Genetic and pharmacological inhibition show that Hsp90 is required for stomatal development in *Arabidopsis thaliana* through the YODA-SPEECHLESS pathway (Samakovli et al., 2020c).
- KD of p23 or Hsp90 or inhibition of Hsp90 block necroptosis of pulmonary artery endothelial cells (Yu et al., 2020).
- Hsp90α, but not β, KO or inhibition with novobiocin, but not GA, affects Bclaf1 accumulation and function (Zhou et al., 2019c).
- KD or inhibition of Hsp90 reduce levels of BCR signalosome components in CLL (Mahmud et al., 2020).
- Hsp90 overexpression rescues destabilization of myosin-9 induced by NudCL2 depletion (Chen et al., 2020).
- Hsp90 as regulator of circadian clock (Yan et al., 2008; Hung et al., 2009; Kim et al., 2011; Schneider et al., 2014; Davis et al., 2018; Lu et al., 2020). Hsp90 inhibition or knock-down impairs accumulation of BMAL1 (Schneider et al., 2014); necdin may stabilize BMAL1 by promoting the recruitment of Hsp90-SGT1 to it (Lu et al., 2020).
- Hop KO in human cell lines reveals that Hop promotes shift of proteostasis from folding to degradation; KOs more sensitive to Hsp90 inhibitors; folding and anti-aggregation activities work even better, dependent on prokaryote-style direct interaction of Hsc70/Hsp70 with Hsp90; vast majority of clients not affected with GR, v-Src, and proteasome as notable exceptions; proteasome activity reduced, but not levels of components, possibly because docking of lid is impaired (Bhattacharya et al., 2020).
- KD of Hsp90β, but not Hsp90α, both of which interact with STING, affects DNA sensing responses (Sato et al., 2020).
- Triple KD of Cdc37/Hsp90α/Hsp90β in oral cancer reduces EMT phenotype and release of extracellular vesicles (Ono et al., 2020).
- KD or inhibition reduces HOS1 protein levels and HOS1-mediated thermotolerance in *Arabidopsis* (Han et al., 2020b).
- KD decreases client MAP4 levels, which results in microtubule deacetylation and destabilization, and fragmentation of Golgi (Wu et al., 2020a).
- Heat-shock increases association with LATS1/LATS2, which in turn promotes their dephosphorylation by PP5 and degradation, and activation of YAP/TAZ; impaired by KD or partial deletion of Hsp90 (Luo et al., 2020).
- KD prevents stimulation of Aβ production by increased body temperature (Noorani et al., 2020).
- KD reduces the stimulatoy effects of ES cell microvesicles on the retrodifferentiation of Müller cells into retinal progenitor cells (Ke et al., 2021).
- KD of Hsp90α, but not Hsp90β, or pharmacological inhibition of Hsp90 reduces levels of ROR1 (Khaledian et al., 2021).
- KD sensitizes multidrug-resistant ovarian cancer cells to drugs and reduces nuclear β-catenin whereas Hsp90 overexpression promotes β-catenin accumulation (Yin et al., 2021).
- KD or inhibition delays disassembly of stress granules (SGs) and restoration of translation because Hsp90 client DYRK3 is affected (Mediani et al., 2021).

- Hsp90 modulates TDP-43 misfolding, aggregation, and toxicity in yeast and mammalian cells (Lin et al., 2021).
- Hsp90-Beclin-1 interaction is enhanced by binding of RhoB to Beclin-1, promoting intracellular bacterial clearing through LC3 lipidation and autophagosome formation (Miao et al., 2021). Hsp90 overexpression protects chicken cardiomyocytes against heat stress and promotes mitophagy, possibly through interaction with Beclin 1 and increased mitochondrial translocation (Shi et al., 2024).
- Upon heat shock, induced Hsp70 in *Drosophila* ovaries/testes interacts with Hsp90 complex, which displaces Ago3, Hop, Hsp90 to lysosomes and results in the disruption of piRNA loading and increased steady-state levels of RNA from transposable elements (Cappucci et al., 2019).
- KD or inhibition increases or decreases PUS7 levels and migration (through effects on PUS7) of colorectal cancer cells, respectively (Song et al., 2021).
- HIPK2, and notably a kinase-defective mutant, is co-translationally targeted for UPS-mediated degradation by Hsp90-Cdc37; Cdc37 overexpression, Cdc37 KD and Hsp90 inhibition reduce and increase its levels, respectively (Müller and Klempnauer, 2021).
- FKBP4 (FKBP52) KD and overexpression decrease and promote Hsp90-IKK interaction, respectively (Zong et al., 2021). SKA2 promotes the incorporation of FKBP4 (FKBP52) into the GR-Hsp90 complex and thedissociation of FKBP5 (Hartmann et al., 2024).
- KD in *Drosophila* fat body impairs TORC1-stimulated production of insulinotropic hormones indicating that nutrient induction of Hsp90 expression mediates signaling to promote anabolic metabolism (Ohhara et al., 2021).
- Hsp90 overexpression suppresses defect of NudC mutation for client filamin A and cell migration (Liu et al., 2021a).
- The circular RNA circSHKBP1 binds Hsp90α/β blocking its interation with CHIP and thereby stabilizing it; both circSHKBP1 and Hsp90 are upregulated in gastric cancer (Xie et al., 2020).
- The circular RNA circSTK40 binds Hsp90, which competes with its client clusterin, thereby preventing the clusterin-dependent recruitment of the E3 ligase RBBP6 to Hsp90; this stabilizes Hsp90 and promotes activity of its client Akt (Ni et al., 2021).
- The circular RNA circSTK40 stabilizes Hsp90 and promotes activity of its client Akt (Ni et al., 2021). Circular RNA circHIPK2, through its target RNA miR-485-5p, promotes Hsp90 ubiquitination and tumor progression (Tong et al., 2022).
- circSLC4A7 interacts with Hsp90, and depends on it for promotion of stemness and progression of gastric cancer, and induction of Notch expression (Hui et al., 2023).
- circFOXK2 acts as scaffold for indirect TACO1-Hsp90 interaction, which promotes mitochondrial translocation of TACO1 and bladder cancer; Hsp90β Q279A mutant is defective for interaction with circFOXK2 and TACO1 (Deng et al., 2025a).
- Inhibitory impact of Hsp90 KD on HPV16^{+} cervical cancer cells is partially counteracted by heterologous expression of PD-L1 (Zeng et al., 2021).
- Even in the presence of Hsp90α, a minimum amount of Hsp90β is still required in cell lines to maintain client stability (Tang et al., 2022c).
- Hsp90α KD blocks IFNγ response through STAT1, which can be rescued by wt but not Hsp90α D88N (Liu et al., 2022a).
- KD inhibits ferroptosis by reducing the dephosphorylation of Drp1 by calcineurin and the Drp1-Ascl4 axis; overexpression does the opposite (Miao et al., 2022).
- Hsp90β functions as oncogene in head and neck squamous cell carcinoma (Zhang et al., 2022b).
- When only one Hsp90 allele is left (Hsp90α KO, Hsp90β heterozygous) in the mouse, or when Hsp90 mRNAs are reduced genetically and by knockdown in cell lines, only those

survive, which are able to increase Hsp90β mRNA translation through an IRES in the 5' UTR (Bhattacharya et al., 2022).

- Hsp90α KD reduces LPS-induced inflammatory response of human gingival fibroblasts (Zhang et al., 2022a).
- Knock-down interferes with differentiation of primary chicken adipocytes (Kang et al., 2022c).
- Hsp90 facilitates stemness and stimulates glycolysis in glioma cells (Kang et al., 2022b).
- Hsp90 KD induces glioma cell death through ER and oxidative stress (Önay Uçar et al., 2023).
- Hsp90β, but not Hsp90α, prevents SMURF1-mediated ubiquitination of LATS1; Hsp90 inhibition reverses this and allows YAP/TAZ-stimulated osteoblast differentiation (Qu et al., 2023).
- Hsp90β KD impairs activation by CD80 (B7-1) of LRP5/β-catenin signaling and reduces the resulting pdocyte injury and glomerulosclerosis (Li et al., 2022a).
- Induction of Hsp90 expression by aspirin (Zhang et al., 2016; Yao et al., 2023) may protect chicken primary myocardial cells from heat stress injury (Yao et al., 2023).
- Hsp90 promotes CRALBP expression through SP1 in retinal epithelial cells, and KO of either Hsp90α or Hsp90β or pharmacological inhibition impairs that (Chen et al., 2023a).
- Knockdown of Hsp90 of ciliate parasite *Ichthyophthirius multifiliis* reduces growth and infectivity in fish (Saleh et al., 2023).
- Knockdown exacerbates ER stress induced by arsenite/selenite by reducing eIF2α phosphorylation and destabilizing IRE1α (Chang et al., 2023b).
- Hop overexpression in rat cardiocytes promotes transition of connexin Cx43 from Hsp70 to Hsp90 and inhibits ubiquitination, and this is offset by Hsp90 KD (An et al., 2023).
- Human fibrosarcoma HT1080 Hsp90α and Hsp90β KO clones grow, and resist to heat and oxidative stress like wt, but Hsp90β show a migration defect (Petrenko et al., 2023).
- The proliferation and differentiation of hair follicle stem cells is stimulated (through c-Myc) and repressed by overexpression and knockdown of Hsp90, respectively (Li et al., 2023b).
- Hsp90 prevents targeting of IDR-containing clients to membrane-less compartments in yeast (Kolhe et al., 2023).
- Hsp90β KD in zebrafish promotes cataractogenesis by leading to the upregulation of the Hsp90β client protein CHMP4B; Hsp90β levels go down in human cataract patients and aging mouse (Fu et al., 2023).
- Hsp90β counteracts the inhibitory effect of PARP1, with which it interacts, on BLM promoter activity in prostate cancer cells (Huang et al., 2023b).
- Increased Hsp90 levels because of augmented expression of the deubiquitinase USP14 may promote non-alcoholic fatty acid liver disease (NAFLD) by stabilizing CYP2E1 (Wei et al., 2023).
- KD of Hsp90α or pharmacological inhibition causes chromosome segregation errors in diffuse large B cell lymphoma (Białopiotrowicz-Data et al., 2023).
- KD of Hsp90α inhibits proliferation, migration, invasion, and promotes cell apoptosis, and of hypopharyngeal squamous cell carcinoma cells (Tang et al., 2023).
- Human Hsp90α or Hsp90β KO cell lines largely maintain proteostasis under normal conditions. Under chronic mild stress, they fail to scale the increase in cell size to translation, which results in cytoplasmic dilution (translation as well as proteasome activity and autophagy are reduced). KO cells are defective in the "rewiring stress response" (RSR) to chronic stress, a translational reprogramming, which allows wild-type cells to turn translation back on after an initial reduction, to increase translation with

cell size. Adaptation to chronic stress requires a threshold level of Hsp90, not a specific Hsp90 isoform, as augmenting one or the other in KO cells can rescue (Maiti et al., 2023).

- KD or inhibition in the lepidoptera *Plutella xylostella*, or overexpression in insect cells reduce RNAi efficiency (Lin et al., 2023).
- Hsp90α and NME1 levels lower in breast cancer metastasis, while Hsp90α overexpression stabilizes NME1 and inhibits metastatic potential of breast cancer cells, and a 22 amino acid peptide of the Hsp90 middle domain is sufficient to interact and stabilize NME1 (Zhang et al., 2023b).
- KD or 17-AAG leads to degradation of TRIM21, which can be rescued by KD of CHIP (Xu et al., 2023a).
- Characterization of FKBP- and p23-containing GR-Hsp90 complexes *in vivo* by crosslinking of photoactivatable amino acid analogs provides structural insights, and shows rapid disruption of the GR-Hsp90 complex, and of the direct GR contacts with FKBP51 or FKBP52, or with p23 upon treatment with dexamethasone or the antagonist RU486 (Baischew et al., 2023b).
- Knock-out screen reveals Hsp90β, but not Hsp90α, and SGT1 as requirements for NLRP3 inflammosome; also affected by Hsp90β-specific pharmacological inhibitor (Spel et al., 2024).
- AAV-mediated overexpression of Hsp90 in the spinal cord inhibits microglial activation in a mouse model of neuropathic pain (Xing et al., 2024).
- KD and overexpression experiments show that Hsp90 promotes stemness and migration of gastric cancer cells, possibly by promoting spatially specific glycolysis through forming multienzyme complexes (Liu et al., 2024e).
- KD impairs the MYG1-stimulated phosphorylation of PKM2, and the nuclear actions of the latter, through the recruitment of Hsp90/GSK3β (Chen et al., 2024a).
- Overexpression of *Gingko* Hsp90 in human cells boosts cell growth and telomerase levels (Feng et al., 2024).
- KD in porcine jejunum epithelial cells (IPEC-J2) increases HIF1α mRNA levels (Liu et al., 2024f).
- KD of Hsp90α in lateral ventricle leads to reduced migration and differentiation of neural stem/progenitor cells induced by ischemia, and Hsp90α overexpression in astrocytes and microglial cells upregulates c-Jun protein levels, suggesting secreted Hsp90 may mediate communication between NSPCs and microglial cells (Hu et al., 2024b).
- Ago1, but not Ago2, promotes interaction of Hop-Hsp90 complex with clients, and, in a Hop-dependent fashion, reduces protein aggregation and maintains stemness of mouse embryonic stem cells (Liu et al., 2024d).
- Inhibition or knockdown of Hsp90 lead to increase of Aβ oligomers and p-Tau, whereas Hsp90 overexpression does the opposite, presumably through Hsf1, in a mouse APP/PS1 model (Wang et al., 2024a).
- Pharmacological inhibition or reduction of HSP90β down-regulates glycolysis through Glut1, and induces Foxp3 expression to enhance the shift of Th17 towards Treg cells, and reduces ulcerative colitis in a mouse model (Yang et al., 2024).
- Hsp90 is required for proper targeting of FXBO10 to outer mitochondrial membrane (Bhat et al., 2024).
- Kinesin KIF5B and Hsp90 colocalize to microdroplets on endoplasmic reticulum sheets, and kinesin is essential for Hsp70 to Hsp90 handover through Hop of calcium channel $Ca_v1.2$ (Tanaka et al., 2024).
- KD or inhibition in myotonic dystrophy type 1 myoblasts enhances *DMPK* mRNA levels and foci, and overexpression of Hsp90α or Hsp90β does the opposite; these effects are mediated by STAT3, but not in differentiated cells where the effect of Hsp90 inhibition is the opposite (Johnson et al., 2024).

- KD or deletion of one Hsp90α allele in mice with floxed allele impair inflammatory NFkB-mediated response of macrophages to sFRP1 secreted by Schwann cells (Yao et al., 2024).
- Interaction experiments, KD, and overexpression indicate that GLCCI1 alleviates apoptosis in retinopathy through a GLCCI1-Hsp90β-GRP78 axis (Liu et al., 2024b).
- Inhibition of translation prevents HSF1 activation, even upon Hsp90 inhibition, and, in line with HSF1 remaining bound to Hsp90 in response to proteotoxic stress, suggests that negative feedback of chaperones is indirect through restoration of proteostasis (Simoncik et al., 2024).
- Inhibition or KD of Hsp90α show that Hsp90α is required for induction of autophagy by starvation in a mouse neuronal progenitor cell line, and this correlates with reduced expression and nuclear accumulation of TFEB, and extended lifespan of *C. elegans* upon starvation (Yang et al., 2023).
- Hsp90 inhibition or overexpression of the Hsp90 M-C domains disrupts mitochondrial functions, and, mediated by reduced HCFC1-induced TFEB expression, induces the formation of mitochondria-derived vesicles and their derived extracellular vesicles, and promotes tumor metastasis in mouse model (Liu et al., 2024c).
- Hsp90 inhibition mitigates dysmenorrhea (menstrual cramps), and lentiviral overexpression of Hsp90β reverses the therapeutic effects of the androgen precursor DHEA on dysmenorrhea-associated symptoms (Wang et al., 2025).
- Inhibition or KD (of both isoforms) destabilizes RPAP2 (Cui et al., 2025).
- PGAM2 competes with E3 ligase SYVN1 for binding to Hsp90 and thereby stabilizes Hsp90, which in cardiomyocytes contributes to cardiac hypertrophy (Li et al., 2025b).
- Inhibition or KD of Hsp90 in colon cancer cells disrupts their survival through oxidative and endoplasmic reticulum stress (Abu-El-Rub et al., 2025).
- Inhibition or KO of either isoform leads to release of RDH5 from calnexin in the ER to the cytosol and its degradation by the autophagosome-lysosome pathway; this may explain the "night blindness" observed in clinical trials with Hsp90 inhibitors (Jia et al., 2025).
- Inhibition or KD/KO of either isoform in hepatocellular carcinoma cells reduce FASN levels and lipid accumulation, and overexpression of Hsp90α increases FASN and lipogenesis; Hsp90α augments FASN levels at the transcriptional level through LXRα and SREBP1 and posttranslationally by stabilizing the protein (Deng et al., 2025b).

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- *in vivo* analyses with geldanamycin (GA) and similar compounds, of Raf (Schulte et al., 1995; Schulte et al., 1996; Schulte et al., 1997; Stancato et al., 1997; Grammatikakis et al., 1999), glucocorticoid receptor (Whitesell and Cook, 1996; Czar et al., 1997), progesterone receptor (Smith et al., 1995), p53 mutants (Blagosklonny et al., 1995; Blagosklonny et al., 1996; see also Whitesell et al., 1998), pp60$^{v\text{-}src}$ (Whitesell et al., 1994), reverse transcriptase of duck hepatitis B virus (HBV) (Hu and Seeger, 1996; Hu et al., 1997), receptor tyrosine kinases (Sepp-Lorenzino et al., 1995). Reduction of hormone binding of androgen and estrogen (Segnitz and Gehring, 1997), glucocorticoid (Whitesell and Cook, 1996; Czar et al., 1997; Segnitz and Gehring, 1997), progesterone (Smith et al., 1995; Segnitz and Gehring, 1997) and mineralocorticoid (Bamberger et al., 1997) receptors, and Xenopus HSF (Ali et al., 1998). Glucocorticoid receptor levels reduced (Whitesell and Cook, 1996; Czar et al., 1997; Segnitz and Gehring, 1997). Glucocorticoid and progesterone receptors still in large complex with Hsp90 (Smith et al., 1995; Czar et al., 1997; Segnitz and Gehring, 1997). GA and herbimycin A induce degradation of Raf, receptor tyrosine kinases (Sepp-Lorenzino et al., 1995; Schulte et

al., 1997), CFTR (Loo et al., 1998) through proteasome, and transfected nNOS (Bender et al., 1999). Blocks "assembly" of active telomerase (Holt et al., 1999). Macbecin I, the most potent in budding yeast, inhibits v-src and steroid receptors (Bohen, 1998) or only slightly (Fang et al., 1998). Blocks induction of ecdysone receptor in fly cells (Arbeitman and Hogness, 2000). Inhibits accumulation of the Src family kinases c-Src, Lck, and Lyn indicating a requirement for Hsp90 very early during their synthesis, before membrane association (Bijlmakers and Marsh, 2000). Within a few minutes, GA transiently activates PKR and MAPK (Donzé et al., 2001), c-Src (Koga et al., 2006) and the ensuing osteoclast differentiation (Yano et al., 2008), PI4KIIβ (Jung et al., 2011), Ire1α (Ota and Wang, 2012), LKB1 (Gaude et al., 2012), and PKCδ (Lu et al., 2021). GA/radicicol induce the differentiation of *Leishmania* promastigotes into amastigotes (Wiesgigl and Clos, 2001). 17AAG promotes telomer shortening and disturbs growth of *Leishmania amazonensis* (de Oliveira et al., 2021). Drugs block morphogenetic movements during early development of ascidian and sea urchin embroys (Bishop et al., 2002). Induction of ER-stress response by GA is mediated by its effects on Grp94 (Marcu et al., 2002). GA transiently reduces translation (Marcu et al., 2002). GA and novobiocin inhibit Tom70-dependent import into mammalian mitochondria (Young et al., 2003; Fan et al., 2006; Barksdale and Bijur, 2009) and Toc64-dependent import into chloroplasts (Qbadou et al., 2006). GA blocks priming of HDAC3 by TRiC (Guenther et al., 2002) and its nuclear localization (Kotwal and Amere Subbarao, 2020). Induces complete loss of Processing Bodies (PBs) (Pare et al., 2009). Analyses of proteome- or kinome-wide changes in response to GA or other inhibitors (Haupt et al., 2012; Sharma et al., 2012; Wu et al., 2012b; Fierro-Monti et al., 2013a; Marrugal et al., 2019). GA induces a remodeling of the Hsp90 chaperone machine itself, in part by a combinatorial increase of both synthesis and degradation rates (Fierro-Monti et al., 2013a; Fierro-Monti et al., 2013b). GA also leads to increased levels of some oncogenes and decrease of some tumor suppressors (Fierro-Monti et al., 2013a). Hsp90 inhibitor induced changes partially resemble those due to aneuploidy (Donnelly et al., 2014). GA-induced ubiquitinome (Quadroni et al., 2015). Meta-analysis of multiple pharmacoproteomic studies shows specific signatures (Echeverría and Picard, 2014). Proteome-wide analysis of synthesis and degradation rates upon Hsp90 inhibition indicates that more stably associated clients have lower thermal stability and that most clients may only require Hsp90 during synthesis (Savitski et al., 2018). Slightly promotes (!) Dengue virus replication (Srisutthisamphan et al., 2018). Inhibits foot-and-mouth disease virus replication through blocking capsid precursor processing (Newman et al., 2018). Comparative proteomic analysis of impact of different Hsp90 inhibitors shows specific signatures (Echeverria et al., 2019). Inhibits replication of adenovirus 5 (Dalidowska et al., 2021). Global analysis of impact of Hsp90 inhibition on protein complexes combining size exclusion chromatography and mass spec (Samant et al., 2022). Global thermal profiling upon Hsp90 inhibition with three different inhibitors (Yin and Wu, 2023). And many more.....

- Hsp90 inhibitor induces dissociation of most Hsp90::kinase complexes, leading to degradation or aggregation dependent on client; interaction strength correlates poorly with subsequent degradation (Taipale et al., 2012). Inhibitor-specific effects on solubility of proteome (Sui et al., 2020).
- <u>Specificity of standard Hsp90 inhibitors ("off-target effects")</u>: the specificity of GA (Dikalov et al., 2002; McCollum et al., 2006; Clark et al., 2009; Samuni et al., 2010; Mlejnek and Dolezel, 2014) and radicicol (Ki et al., 2000; Tuganova et al., 2001; Besant et al., 2002a; Kato et al., 2007) may not be perfect, and some sources of GA contain a component with a different biological activity (Barzilay et al., 2004). At high concentrations, GA induces production of ROS and scavengers can prevent cytotoxicity (Clark et al., 2009; Samuni et al., 2010); it affects glutathione (GSH) levels (McCollum et al., 2006; Mlejnek and Dolezel, 2014). GA/17-AAG target VDAC (outer mitochondrial membrane) resulting

in membrane depolarization of mitochondria and increased intracellular Ca^{2+} (Xie et al., 2011). Radicicol but not GA inhibits the archaeal DNA topoisomerase type IIB (Gadelle et al., 2005) and binds its ATPase domain in equivalent manner (Corbett and Berger, 2006). Radicicol also inhibits mammalian branched-chain α-keto acid dehydrogenase kinase and at high concentrations yeast Sln1 histidine kinase (Besant et al., 2002b), and PDHKs (Tuganova et al., 2001; Kato et al., 2007). Dual inhibitors of Hsp90 and PDHK can be developed (Meng et al., 2014). Radicicol inhibits the GHKL ATPase Smchd1 (Chen et al., 2016). Assessment of kinase-targeted polypharmacology for a panel of Hsp90 inhibitors shows that some do and some don't target a representative set of kinases (Antolin et al., 2021).

- GA selectively targets tumor cells because of a 100-fold higher affinity of their Hsp90 complexes (Kamal et al., 2003). Contradicted in a more recent study that shows equal time-dependent binding of GA to Hsp90 from different sources; GA binding occurs in two steps with a µM Kd for the initial encounter complex to a nM Kd for the tight complex after 24 hours (Gooljarsingh et al., 2006). Along the same lines, though, as Kamal et al., Hsp90 in extract from Alzheimer disease brain has 1000-fold higher binding affinity for Hsp90 inhibitor (Dickey et al., 2007), but lower levels (Thompson et al., 2012). Systems biology analysis of such differences shows effects on critical clients (Vali et al., 2010). Normal blood cells have few-fold higher affinity for PU-H71 than leukemia cells and this correlates with killing potential of the inhibitor (Moulick et al., 2011). Increased sumoylation of Hsp90 in transformed cells may explain both increased ATPase and affinity for inhibitors (Mollapour et al., 2014). Hyperactivated signaling pathways in AML cells renders them more sensitive and vulnerable to Hsp90 inhibition; sensitivity correlates with gradual activation (and addiction) (Zong et al., 2015). Cancer types with epichaperome (integrated chaperome units) are more sensitive to Hsp90 inhibition than those with insular chaperomes (e.g. Hsp90 chaperome), and PU-H71 pulls out a different set of chaperome complexes; epichaperome, not Hsp90 abundance correlates with Hsp90 inhibitor sensitivity (Rodina et al., 2016; see also Wang et al., 2016c; Joshi et al., 2018; see also Pillarsetty et al., 2019). Hsp90 inhibitor sensitivity is determined by equilibrium between cellular quiescence and activity, and can be pushed towards less sensitivity in oncogenically transformed cells and more sensitivity in normal cells (Echeverria et al., 2019). Total Hsp90 levels of cell lines correlate with resistance, which can also be increased by overexpressing exogenous Hsp90α but not the D93N mutant (Tang et al., 2022c).
- Isoform-selective compounds: GA does not reach mitochondrial Hsp90 isoforms (Kang et al., 2007). GA derivative WX514 about 100-fold more specific for Hsp90 than Grp94 (Xu et al., 2001). Screen with split Renilla luciferase p23/Hsp90 interaction assay for new inhibitors, including isoform-selective compounds (Chan et al., 2012). Potentially Grp94-specific inhibitor (Duerfeldt et al., 2012). Probe for fluorescence polarization assay allowing comprehensive analysis of paralog- selectivity and affinity of inhibitors; several with poor affinity for Grp94 and Trap1 (Taldone et al., 2013). Several compounds with about 5-fold selectivity for Hsp90α over β, and selectivity for one or several Hsp90 paralogs (Patel et al., 2013). Compounds with over 1000x α/β-selectivity relative to Grp94 and Trap1 (Ernst et al., 2014). Vibsanin B may be an Hsp90β-selective inhibitor (Ye et al., 2015). TAS-116 is a highly Hsp90α/β-selective compound (Ohkubo et al., 2015; Yoshimura et al., 2021). Gambogic acid is Hsp90β-specific, not compatible with Hop and p23 binding, induces client degradation but not Hsp70 induction, and appears to bind middle domain (Yim et al., 2016). Only binds htpG in presence of ATP (Yue et al., 2018). Gambogic acid and gambogenic acid may not be isoform-selective and does induce heat-shock response (Pesonen et al., 2021). C-terminal inhibitor KU675 displays some Hsp90α-selectivity (Liu et al., 2015). Highly Hsp90β-selective inhibitor affects

certain clients more than others and does not induce Hsp90 expression (Khandelwal et al., 2018). New Hsp90β-selective N-terminal inhibitors specifically target Hsp90β-dependent clients such as CXCR4, B-Raf, and CDK4/6 (Mishra et al., 2021b). New Hsp90α-selective N-terminal inhibitor specifically target Hsp90α-dependent clients such as c-Src and survivin (Mishra et al., 2021a). Hsp90β inhibitor stimulates expression of endogenous retroviral sequences, interferon response, and immune checkpoint blocade therapy in cancer models (Rahmy et al., 2022).

- Blood-brain/testis barrier: 17-DMAG does not cross it (Glaze et al., 2005) whereas 17-AAG (Sha et al., 2017) and pochoxime (Grad et al., 2010) do.
- Budding yeast living on human Hsp90β is hypersensitive to Hsp90 inhibitors (Piper et al., 2003b).
- *C. elegans* Hsp90 does not bind GA, is not inhibited by it and does not confer GA resistance to mammalian cells (David et al., 2003). However, yeast with *C. elegans* Hsp90 is sensitive to high doses of GA (Piper et al., 2003b). Analysis of Hsp90s from other nematodes also suggest a complex mechanism of GA sensitivity (Him et al., 2009). *Humicola fuscoatra* produces radicicol and has an Hsp90 with low binding affinity for it (Prodromou et al., 2009). *Streptomyces hygroscopicus* produces GA and its htpG does not bind it at all (Millson et al., 2011).
- Reports on synergistic effects of adding both radicicol and GA (Rosenhagen et al., 2001; Ratts et al., 2003).
- Role of <u>CHIP or other E3 ligases</u> in degradation of Hsp90 clients induced by Hsp90 inhibitors: GA stimulates association of CHIP with client (erbB2) and facilitates degradation (Xu et al., 2002a; Zhou et al., 2003); U-box mutant of CHIP blocks GA effect (Zhou et al., 2003), but GA still works in CHIP-negative cells (Xu et al., 2002a; Morishima et al., 2008), and CHIP is replaced by other E3 ligases such as parkin at least for some substrates (Morishima et al., 2008). GA-induced degradation of ERα (Fan et al., 2005) and Akt (Dickey et al., 2008) depend on CHIP, and, conversely, Akt regulates Hsp90/CHIP-mediated degradation of phospho-tau (Dickey et al., 2008). Cullin5-RING E3 ubiquitin ligase complex is recruited to Hsp90 for CHIP-independent degradation of some substrates (Ehrlich et al., 2009; see also Samant et al., 2014). CHIP can also be required to stabilize the Hsp90 client SENP3 in response to oxidative stress (Yan et al., 2010b). In yeast, this involves the ubiquitin ligases Ubr1 and Ubr2 (Nillegoda et al., 2010); levels of Hsc82 itself are increased in Δ*ubr1* (Oh et al., 2017). In mammalian cells, Ubr1 contributes as well and its absence induces Hsp90 and renders cells more resistant to GA (Sultana et al., 2012). Inhibitor-induced OGT degradation is independent of CHIP (Zhang et al., 2012a). In addition to promoting the GA-induced degradation of kinases, Ubr1 promotes the degradation of GR and AR but not ERα (Sultana et al., 2013). KD of Cullin-5 or its partner RBX2 reduces inhibitor-induced degradation, delays co-chaperone release, and renders cells more resistant; moreover, Cullin-5 neddylation is required for client degradation, but not for loss of client activity (Samant et al., 2014). Global analysis shows that CHIP is primarily connected to Hsp70 system (Taipale et al., 2014). E3 ligase HECTD3 is recruited to Hsp90-Cdc37-kinase complexes (notably c-Raf) in the presence of Hsp90 inhibitors and contributes to client degradation (also: CUL5 but not CHIP) (Li et al., 2017c). CHIP mediates Hsp90 inhibitor-induced degradation of ICN1 (Notch1) (Wang et al., 2017d). Within a complex of cullin-5/Tom70/Hsp90α with SARS-CoV2 protein Orf9b, Hsp90α stabilizes Orf9b (Zhou et al., 2024a).
- *Plasmodium falciparum*: GA blocks primarily transition from Ring to trophozoite stages (Banumathy et al., 2003). Hsp90 inhibition effectively blocks growth of *P. berghei* and *Trypanosoma evansi* (Pallavi et al., 2010), *P. yoelii* (Mout et al., 2012) and *T. brucei* (Meyer and Shapiro, 2013) in a mouse model. The phenotype of the latter is mimicked by knock-down (Meyer and Shapiro, 2021). *P. falciparum*-selective Hsp90 inhibitor

Tropane 1 blocks liver, asexual blood, and early gametocyte life stages (Mansfield et al., 2024).

- GA induced degradation of Hsp90 clients suppressed by overexpression of CAIR-1/BAG-3 (Doong et al., 2003).
- Substrates that are NOT degraded in presence of Hsp90 inhibitors (or in Hsp90 mutants): list includes $P2X_7$ (Adinolfi et al., 2003; Migita et al., 2016), PPARα (Sumanasekera et al., 2003a), IRF3 (Yang et al., 2006a), αGDI (Chen and Balch, 2006), cyclin B and Msps (Basto et al., 2007), CB2 cannabinoid receptor (He et al., 2007), Cup (Pisa et al., 2009), NDRG1 (Banz et al., 2009), p38 (Ota et al., 2010), a mutant form of TPI {even stabilized} (Hrizo and Palladino, 2010), Piwi (Gangaraju et al., 2011), mutant glucocerebrosidase (Lu et al., 2011; Yang et al., 2014a; Yang et al., 2015a), CLC-1 (Peng et al., 2016b), GLT-1 (Sha et al., 2017), HIPK2 {stabilized} (Müller and Klempnauer, 2021).
- GA stabilizes Hsp90 degradation substrates (Gusarova et al., 2001; McClellan et al., 2005; Hrizo and Palladino, 2010; Hahn et al., 2011; Sha et al., 2017).
- Tissue-specific effects of GA on Zebra fish development (Lele et al., 1999). Selective sensitizing effects on mutant phenotypes of inhibition with GA or isoform-specific morpholinos (Pei et al., 2007; Yeyati et al., 2007; Pei and Feldman, 2009).
- Green tea contains polyphenol epigallocatechin gallate that appears to bind the C-terminal domain of Hsp90 and to block its release from AhR (Palermo et al., 2005).
- GA and RNAi against Hsp90 block replication of alphanodavirus Flock House virus (Kampmueller and Miller, 2005). GA blocks replication of HSV-1 and cytoplasmic relocalization of its DNA polymerase (Burch and Weller, 2005; see also Zhong et al., 2014; Wang et al., 2018; Qin et al., 2022). GA inhibits replication of hepatitis C virus, possibly by disrupting Hsp90-FKBP8-NS5A complex (Okamoto et al., 2006); Hsp90 KD also decreases HCV replication (Braga et al., 2017). Also destabilizes core protein and its toxic effects expressed in yeast (Kubota et al., 2012). GA blocks replication of RNA viruses of the picornavirus family (poliovirus, rhinovirus, coxsackievirus) by blocking folding and maturation of the capsid precursor protein P1 (Geller et al., 2007); see also impact of Hsp90 inhibition on balanced evolution of P1 protein stability and aggregation (Geller et al., 2018). GA blocks replication of hepatitis E virus, potentially by blocking the transport of capsid protein (Zheng et al., 2010). Also of HBV by affecting capsid formation (Shim et al., 2011; see also Seo et al., 2018). Inhibits infectivity but not replication of Japanese encephalitis virus (Hung et al., 2011; see also Wang et al., 2017b). GA and siRNA specifically against Hsp90β blocks cellular entry and replication of enterovirus 71 (Tsou et al., 2013). Inhibitors block paramyxoviruses such as mumps and measles (Katoh et al., 2017; see also Dalidowska et al., 2022).
- Peptidomimetic inhibitor shepherdin binds ATP pocket and when introduced into cells as fusion with carrier proteins inhibits Hsp90 functions (Plescia et al., 2005).
- GA or SGT1 knock-down blocks formation of inflammasome and NLR-mediated gene activation and gout (Mayor et al., 2007; see also Piippo et al., 2018; Spel et al., 2024). Polyphenol carnosol blocks NLRP3 inflammasome by inhibiting Hsp90 ATPase (Shi et al., 2020b). Impact of HDAC6 inhibitor and splenectomy on NLRP3 (Lin et al., 2024a).
- Small-cell lung cancer cells, unlike many other cancer types, go into apoptosis upon inhibition of Hsp90; protective effect of Hsp90 depends on Akt and blocking Apaf-1 (Rodina et al., 2007; see comments in Workman and Powers, 2007). See also effect of inhibitors on non-small cell lung cancer (NSCLC) cell lines (Gallegos Ruiz et al., 2008). KRAS mutations predict increased Hsp90 inhibitor sensitivity of NSCLC (Sos et al., 2009).
- Pharmacoproteomics with anaplastic large cell lymphoma cells (Schumacher et al., 2007).

- Hsp90 inhibitors reduce turnover of mitochondrial proteins pointing to a role of Hsp90 and the proteasome in degradation of mitochondrial proteins (Margineantu et al., 2007).
- Discovery of novel Hsp90 inhibitors, the natural triterpenoids celastrol and gedunin, by chemical genomics (Hieronymus et al., 2006; Lamb et al., 2006).
- Celastrol disrupts interaction with Cdc37 and function without blocking ATP binding (Zhang et al., 2008b; Zhang et al., 2009). Celastrol acts through C-terminal domain of Hsp90 to disrupt interaction with Cdc37 allosterically (Zhang et al., 2009). Also binds directly to p23 and disrupts complexes (Chadli et al., 2010). Effects on transcription factors (Zhang et al., 2010b). Gedunin and gamendazole may work similarly (Matts et al., 2011a) or not at all (Olesen et al., 2015). Celastrol induces oligomerization, possibly through C-terminal domain, and yet has no effect on anti-aggregation activity or interaction with TPR co-chaperone (Zanphorlin et al., 2014). Modelling and mutagenesis indicates that residues at dimer interface between middle and C-terminal domains may be involved (also required for Cdc37 binding) (Peng et al., 2016a).
- Small-molecule inhibitor disrupts Cdc37 binding and specifically affects Cdc37-Hsp90 substrates by binding to the interface next to ATP binding pocket (Wang et al., 2019b; Wang et al., 2020b).
- Male contraceptive agent gamendazole behaves like Hsp90 inhibitor but is not competed by GA or novobiocin (Tash et al., 2008). The specific Hsp90 inhibitor pochoxime A partially phenocopies an *hsp90α* mutation in the mouse resulting in reduced testis size (Grad et al., 2010).
- The withanolide Tubocapsenolide A leads to thiol oxidation and aggregation of Hsp90 (Chen et al., 2008b).
- Acute myeloid leukemia cells are more sensitive to 17-AAG than normal CD34-positive cells (Flandrin et al., 2008).
- Degradation of B-Raf mutant V600E upon treatment with Hsp90 inhibitors depends also on induction of oxidative stress (e.g. by 17-AAG) (Fukuyo et al., 2008).
- GA blocks development of *Dictyostelium* beyond mound stage (Sawarkar et al., 2008).
- Hsp90 inhibitors unveil a prodeath role of Hsp90 in ER stress induced death of calcineurin-defective yeast cells (Dudgeon et al., 2008).
- Inhibitors prevent γ-tubulin from being recruited to overduplicated centrosomes (Prosser et al., 2009).
- Potential of combination therapies for treating fungal diseases (Cowen et al., 2009; Singh et al., 2009) and preventing endocrine resistance in breast cancer (Whitesell et al., 2014); also in dermatophyte *Trichophyton rubrum* (Jacob et al., 2015).
- Induction of apoptosis by 17-DMAG in a variety of cell lines depends on p53 (Ayrault et al., 2009). Cancer cells with mutant p53 are more sensitive to Hsp90 inhibitors or HDAC inhibitors than cells with wt p53 (Li et al., 2011a; Li et al., 2011b). In irradiated T-cells, Hsp90 stabilizes induced p53 and inhibitors *protect* cells from apoptosis (Fukumoto and Kiang, 2011).
- Inhibitor screens to block interaction between Hop and Hsp90 (Yi et al., 2009). Small molecules (Yi and Regan, 2008) and modified TPR modules (Cortajarena et al., 2008) block it *in vitro* and *in vivo* leading to degradation of Hsp90 substrates. Compound that blocks interaction between Hop and Hsp90 but does not induce Hsp70 (Pimienta et al., 2011). Peptides that inhibit TPR2A-Hsp90 interaction *in vitro* (Vaaltyn et al., 2022).
- 4-hydroxy-tamoxifen (OHT) binds at or near the ATP binding pocket and stimulates ATPase (Zhao et al., 2010).
- GA disrupts P-bodies (Pare et al., 2009; Suzuki et al., 2009; Johnston et al., 2010) and delays disassembly of stress granules during recovery (Mediani et al., 2021).
- Hsp90 inhibition or Hsp90α knock-down induces contraction of CAG repeats in a model gene (Mittelman et al., 2010).

- Inhibitor occupancy is a better predictor of client protein degradation (pharmacodynamics) and tumor growth inhibition than plasma or tumor pharmacokinetics (Tillotson et al., 2010).
- Cell-permeable hybrid TPR peptide specifically inhibits interaction with Hop and affects Hsp90 clients and cell growth of cancer cells (Horibe et al., 2011; Horibe et al., 2012), in particular in the presence of an Hsp70-targeted peptide (Horibe et al., 2014). Short peptides which bind and block Hsp90 through MEEVD region (Buckton et al., 2016).
- Cyclic lipopeptide antibiotics block chaperone function but not ATPase of htpG, possibly by increasing surface hydrophobicity and oligomerization of the N-terminal domain (Minagawa et al., 2011).
- Peptides from Cdc37 to disrupt interaction (D'Annessa et al., 2020).
- Hsp90 or HDAC6 inhibition augments the activity of T-regulatory cells (Treg) (de Zoeten et al., 2011). It also protects islet cells against glucocorticoid toxicity (Zhu et al., 2020).
- Purine-based inhibitors block growth of filarial worm *Brugia pahangi* and can be selective for pathogen Hsp90 (Taldone et al., 2010). Other types of inhibitors work, too (Gillan et al., 2014).
- Gene expression profiling of mammalian cells (Maloney et al., 2007) and budding yeast (Echeverría et al., 2011b) treated with Hsp90 inhibitors. In yeast, radicicol induces a stress response through the Msn2/Msn4 pathway (Echeverría et al., 2011b). Network analysis of changes in lung cancer cells reveals ErbB as a key target pathway (Pham et al., 2011).
- Novel inhibitor that blocks FKBP52-stimulated AR function by preventing hormone-induced dissociation of the AR-Hsp90-FKBP52 complex (De Leon et al., 2011).
- *In silico* systems biology analysis of effects of Hsp90 inhibition on protein homeostasis (Proctor and Lorimer, 2011).
- Aneuploid cells are more sensitive to 17-AAG than euploid cells (Tang et al., 2011). And conversely, pharmacological, heat-induced or genetic inhibition of Hsp90 in yeast induces aneuploidy fueling rapid adaptation (Chen et al., 2012a).
- Hsp90 inhibition transiently releases paused RNA polymerases and thus results in gene activation (Sawarkar et al., 2012).
- A peptide matching the middle domain can block the interaction with LPS and its signaling, and in a cell-permeable form affects clients (Wu et al., 2012a).
- GA induces degradation of client PCNA and Hsp90 in extracts (Wang et al., 2010).
- Co-chaperones are usually not degraded upon treatment with Hsp90 inhibitors, but their may be exceptions, for example in endothelial cells (Zhang et al., 2012a).
- PU-H71 blocks *Plasmodium falciparum* and synergizes with chloroquine (Shahinas et al., 2013).
- <u>Species-selective inhibitors</u>: Differential sensitivities of *Plasmodium falciparum* and human Hsp90 to Hsp90 inhibitors in yeast system (Wider et al., 2009). The alkaloid harmine is selective for *Plasmodium* Hsp90 and this depends on the pathogen-specific Arg98 (Shahinas et al., 2010; Shahinas et al., 2012). Purine-based inhibitors block growth of filarial worm *Brugia pahangi* and can be selective for pathogen Hsp90 (Taldone et al., 2010). Selective inhibitors for *T. brucei* Hsp90 (Pizarro et al., 2013). Specific inhibitors against *E. histolytica* and *Giardia* (Debnath et al., 2014). 7-azaindole derivatives are selective for *Plasmodium* Hsp90 (Wang et al., 2014a); aminoalcohol-carbazoles that bind Hsp90 are more likely to inhibit *Plasmodium falciparum* proliferation (Wang et al., 2016d); see also Everson et al., 2021. *Plasmodium falciparum*-selectivity of inhibitor Tropane 1 may depend on species-specific pairing of D11 and R98 (Mansfield et al., 2024).
- Hsp90 inhibitors block BRCA1-dependent DSB repair, and BRCA1-deficient cells are hypersensitive (Stecklein et al., 2012).

- Protoporphyrin/hemin affects Hsp90 clients and may directly inhibit Hsp90 (Lee et al., 2012b; Lee et al., 2013).
- Dimer-monomer shift as assay to distinguish mode of action of Hsp90 inhibitors (Cruz et al., 2013).
- Inhibition affects the ILK-FAK pathway and impairs fibroblast migration and the fibrotic response (Radovanac et al., 2013).
- ATP acyl phosphate derivative as probe for paralog conformations and inhibitor binding (Nordin et al., 2015).
- Novel drug binding between N and M domains blocks interaction with TPR co-chaperones, induces degradation of GR, without inducing heat-shock response (McConnell et al., 2014).
- Acute Hsp90 inhibition can rescue some rhodopsin mutants (Aguilà et al., 2014).
- 17-AAG inhibits growth of *Entamoeba histolytica* (Singh et al., 2014), but promotes encystation (Singh et al., 2015). New specific inhibitors against *E. histolytica* and *Giardia* (Debnath et al., 2014).
- High-throughput screen based on luciferase refolding yields many new candidates (Davenport et al., 2014).
- mTOR inhibitors block Hsf1 activation and thereby potentiate inhibitory effects of Hsp90 inhibitors (Acquaviva et al., 2014).
- FITC-GA is *not* cell-permeable (Bozza et al., 2014).
- Compounds that accelerate Hsp90 ATPase, promote interaction with GR LBD but reduce its activity (Zierer et al., 2014).
- C-terminally targeted compounds such as novobiocin and silibilin induce the degradation of Cdc2 but not GR, which is released in mature form in the presence of glucocorticoids (Riebold et al., 2015). Novel compounds may block Hsp90 without inducing a heat-shock response (Wang and McAlpine, 2015c; Wang and McAlpine, 2015a; Wang and McAlpine, 2015b).
- Overexpression in tomato protoplasts reduces cytosolic accumulation of some chloroplast precursor proteins suggesting a role in quality control (Tillmann et al., 2015).
- Computational modeling and *in silico* screen for inhibitors against specific Hsp90-target combinations (Anighoro et al., 2015).
- Goniothalamin enhances ATPase but inhibits chaperone activity in collaboration with Hsp70 system (Yokoyama et al., 2015).
- Mild heat-shock and isothermal geldanamycin yield similar proteomic changes (Finka et al., 2015).
- Capsaicin inhibits PR assembly *in vitro* and may be an inhibitor of the Hsp90 machine (at high concentrations) (Patwardhan et al., 2015). It binds N-terminus of Hsp90, inhibits ATPase, and yet synergizes with 17-AAG and does not induce an HSR (Patwardhan et al., 2023).
- Inhibition of c-Abl sensitizes cancer cells to Hsp90 inhibitors because of its impact on Aha1 (Dunn et al., 2015).
- Allosteric activators of ATPase and their impact on co-chaperone and client interactions (Sattin et al., 2015), and on dynamic properties of the closed state (Vettoretti et al., 2016).
- Repression of transcription elongation by HDAC inhibitors requires Hsp90, presumably through NELF; both HDAC inhibitors and geldanamycin inhibit the production of eRNAs. (Greer et al., 2015).
- Hsp90 inhibition compromises temperature-dependent and auxin-stimulated growth in *Arabidopsis*, most likely by affecting TIR1 (Wang et al., 2016b); see also more direct evidence for interaction with TIR1 (Watanabe et al., 2016), and HOP and SGT1b (Muñoz et al., 2022).

- Hsp90 inhibition (and Cdc37 knock-down) reduces MLKL, its membrane targeting and the ensuing necroptosis (Jacobsen et al., 2016; Zhao et al., 2016; see also Li et al., 2016; Yang and He, 2016).
- Kongensin A inhibits Hsp90 by a covalent attachment to C420, resulting in the release of Cdc37, downregulation of client kinases and inhibition of necroptosis (Li et al., 2016).
- Hsp90 and HDAC inhibitors protect endothelial cells against LPS-induced barrier dysfunction (Antonov et al., 2008; Chatterjee et al., 2008; Joshi et al., 2014; Joshi et al., 2015).
- Geldanamycin blocks the differentiation of myoblasts (Wagatsuma et al., 2011; Echeverría et al., 2016) and affects a large number of proteins that are regulated during myoblast differentiation (Echeverría et al., 2016).
- Geldanamycin can sensitize tamoxifen-resistant breast cancer cells to tamoxifen (Bennesch et al., 2016).
- Consider combination therapies with Hsp90 inhibitors to target oncogene addiction (Mandato et al., 2016).
- Renal cell carcinoma overexpress the Hsp90 regulatory kinase Mps1 resulting in higher affinity and intracellular accumulation of Hsp90 inhibitors (Woodford et al., 2016c).
- High levels of FNIP1/2 increase Hsp90 drug binding and sensitize cancer cells to Hsp90 inhibitors (Woodford et al., 2016a).
- PP5 overexpression or knock-down increases inhibitor binding to Hsp90 (Oberoi et al., 2016).
- HER2 expression may be a biomarker for sensitivity to Hsp90 inhibitors in treated breast cancer patients (Jhaveri et al., 2016).
- Calpain KD sensitizes cells to geldanamycins by affecting the levels of ABC transporters (Grieve et al., 2016).
- Geldanymcins are both inhibitors and substrates of some ABC transporters such as Pgp and MRP1 (Huang et al., 2007; Pham et al., 2009).
- Gyrase B inhibitors such as coumermycin A1 inhibit dimer formation through C-terminus (Vozzolo et al., 2010; Cele et al., 2016).
- Hsp90 inhibitors block Sendai virus-induced prion-like aggregation of MAVS (Hou et al., 2011) and of prion-like luminidependens in *Arabidopsis* (Chakrabortee et al., 2016b).
- Some prion-like heritable traits induced by overexpression of intrinsically disordered proteins in yeast are lost upon inhibition of Hsp90 (Chakrabortee et al., 2016a; see comment by Tuite, 2016).
- Some disparities between *in vivo* effects, IC50s, and *in vitro* affinities between N- and C-terminal inhibitors and effects of Hsp90α knock-down (Wang et al., 2017a).
- 1,4-naphthoquinone forms adducts on C412 and C564 of Hsp90 and disrupts complexes with Hsf1 (Abiko et al., 2017).
- The kinase Ulk1, by phosphorylating Cdc37 on S339, compromises client recruitment, a Cdc37 C339E mutant sensitizes cells to Hsp90 inhibitors, and an Ulk1 knock-down renders them more resistant (Li et al., 2017a).
- Single-cell proteomics with some GFP fusion proteins show bimodal effects of an Hsp90 inhibitor (Zimmer et al., 2017).
- Toxicity of single-walled carbon nanotubes may in part be mediated by inhibiting Hsp90 function and can be suppressed by overexpression of Hsp90β (Ong et al., 2017).
- DYRK1B mutants are more vulnerable to Hsp90 inhibition and display increased interaction with Cdc37 (Abu Jhaisha et al., 2017).
- Pathogenic fungus *Cryptococcus neoformans* is hypersensitive to Hsp90 inhibitors at elevated temperature (Chatterjee and Tatu, 2017).

- Hsp90 inhibitors have senolytic activity, i.e. preferentially kill senescent cells, possibly by inhibiting the PI3K/Akt pathway, and could be repurposed as anti-aging drugs (Fuhrmann-Stroissnigg et al., 2017). Opposite effects (cytotoxicity and impact on senescence) in retinal pigment epithelial cells (Chen et al., 2021a). Hsp90 inhibitor as senolytic agent preferentially targets lung fibroblasts with high expression of $p16^{INK4a}$ from idopathic pulmonary fibrosis patients (Lee et al., 2024; see comment by Khosla, 2024).
- Hsp90 inhibitor restricts influenza virus evolution (Phillips et al., 2017).
- Compound that binds N-terminal domain at a transient interaction site with Aha1 and prevents stimulation by Aha1 (Stiegler et al., 2017).
- Inhibitor of Aha1-stimulated Hsp90 ATPase binds Aha1 CTD, blocks its interaction with Hsp90, and reduces activity (and/or accumulation) of Hsp90 clients, notably luciferase, GR and AR, and tau (Singh et al., 2020a).
- The tetrapeptide NFGK from bovine hemoglobin may affect eHsp90α levels by binding N-terminal domain (Wang et al., 2017c).
- High levels of miR-21 correlate with resistance to Hsp90 inhibitors of cholangiocarcinoma, possibly mediated by targeting DnaJB5 expression (Lampis et al., 2018).
- Hsp90 inhibition impairs chromosome segregation in budding yeast (Khurana et al., 2018).
- Parkinson's disease-related cellular phenotypes can be reverted with PU-H71 (Kishinevsky et al., 2018).
- Hsp90 inhibitor sensitivity correlates with basal Hsf1 activity and inversely with magnitude of activation of Hsf1 (Pastorek et al., 2018).
- The cyclic sesquiterpene zerumbone stimulates ATPase and inhibits Hsp90 function by covalently coupling to several cysteine residues (Nakamoto et al., 2018). Several electrophiles such as cadmium, 1,4-naphthoquinone, and the morphine metabolite morphinone can covalently couple to various cysteines on Hsp90, and thereby trigger Hsf1 activity (Shinkai et al., 2017; Matsuo et al., 2023).
- Hsp90 inhibitor that covalently binds Cys598 of Hsp90α, disrupts Cdc37 binding, but does not affect ATPase activity (Li et al., 2021c).
- Hsp90 inhibitors block axon injury signaling (Karney-Grobe et al., 2018).
- Bentropine mesylate removes inhibitory FKBP51 from GR-Hsp90 complex (Sabbagh et al., 2018).
- GA destabilizes the capping enzyme and reduces levels of cytoplasmic capped RNAs (Trotman et al., 2018).
- Hsp90 inhibition or heat shock induce the expression of LINE-1 and ALU transposable elements in samples of systemic lupus erythematosus patients (Kelly et al., 2018).
- Transformation of NIH-3T3 cells with the oncogene Ras renders them hypersensitive to Hsp90 inhibitors; inhibitors affect a substantial portion of oncogenic program (Echeverria et al., 2019). Hsp90 inhibitor sensitivity is determined by equilibrium between cellular quiescence and activity, and can be pushed towards less sensitivity in oncogenically transformed cells and more sensitivity in normal cells (Echeverria et al., 2019).
- Selection for Hsp90 inhibitor resistance yields cell clones with activated JAK-STAT pathway and sensitivity to combined inhibition of this pathway and Hsp90 (Mumin et al., 2019). In non-small cell lung cancer, integrins $\alpha v\beta 3$ promote resistance to AUY922 (Yoon et al., 2022).
- GA treatment leads to reduced levels of cohesin subunits and defective sister chromatid cohesion (Yang et al., 2018).
- Similarly to heat shock, Hsp90 inhibition induces transient high SUMO2/3 conjugation (Liebelt et al., 2019).

- Radicicol derivatives with high selectivity for *C. albicans* Hsp90 over human Hsp90 (Whitesell et al., 2019).
- Hsp90 inhibitors extend lifespan in *C. elegans* through activation of Hsf1 (Janssens et al., 2019).
- Induction of nuclear localization of HSFA1 proteins in *Arabidopsis* is insufficient to induce robust transcriptional response (Yoshida et al., 2011).
- Novobiocin analog KU-32 stimulates partial N-terminal closure and ATPase activity, and antagonizes GA binding and effects (Chatterjee et al., 2019).
- Binds artemisinin at high concentrations, possibly through K58 (Hsp90β), resulting in disruption of Hsp90-iNOS complex (Wu et al., 2019a).
- Loss of tumor suppressor Tsc1, as in bladder cancer, reduces sensitivity and binding to Hsp90 inhibitors (Woodford et al., 2019).
- Chronic low dose Hsp90 inhibition increases MHC I expression and antigenicity of cancer cells whereas high dose treatment reduces it (Jaeger et al., 2019; see also comments in Srivastava and Callahan, 2019).
- Destabilizing effects of Hsp90 inhibitors can be counteracted for some clients by specific ligands, which can be exploited as a drug screening tool (Taipale et al., 2013; see also Cho et al., 2020).
- Hsp90 inhibitors promote T-cell-mediated anti-tumor responses (immunotherapy) (Mbofung et al., 2017), and sensitize cancer cells to killing by CTLs (Song et al., 2020).
- C-terminal but not N-terminal inhibitors reduce incorporation of fibronectin into matrix and cell migration (Chakraborty et al., 2020). Cancer immunotherapy promoted by reducing expression of PD-L1, possibly through STAT3 and c-Myc, and several other checkpoint proteins (Zavareh et al., 2021).
- Derivative of ATP-competitive inhibitor that covalently links to surface lysine (Cuesta et al., 2020).
- Allosteric regulator binding to middle domain (Zhou et al., 2020).
- Inhibitor attentuates formation of abdominal aortic aneurysm (Qi et al., 2015) and angiotensin II-induced remodelling of adventitial fibroblasts (Huang et al., 2020).
- Client-mimic peptides representing regions with high probability of local unfolding bind Hsp90 complex and disrupt Hsp90-client interaction (Paladino et al., 2020).
- 17-AAG inhibits replication and spreading of human coronaviruses, including SARS-CoV-2 (Li et al., 2020b). Hsp90α expression is induced by SARS-CoV-2 and inhibition blocks replication and inflammatory response (Wyler et al., 2021); Hsp90β also induced and Hsp90 inhibition blocks protein production (Kamel et al., 2021). 17-DMAG inhibits viral assembly and alleviates virally induced pyroptosis and lung injury in syrian hamster model (Zhao et al., 2023).
- Hsp90β is a host factor for the swine coronavirus "transmissible gastroenteritis virus"; KD of Hsp90β, but not Hsp90α, or inhibition affect M gene mRNA and N protein levels (Song et al., 2023).
- More effective treatment using the order docetaxel > radicicol of triple-negative breast cancer cells and priming of natural killer cells informs engineering of nanoparticles with docetaxel and cholesterol-tethered radicicol (Smalley et al., 2020).
- Transient inhibition of zebra fish embryos promotes cold tolerance of adults (Han et al., 2020a).
- Chaetocin is a C-terminal Hsp90 inhibitor (Lian et al., 2021).
- Activated NRF2 is synthetically lethal with geldanamycin-type inhibitors because of upregulation of NQO1 (Baird et al., 2020).
- 17AAG inhibits capacitation of human sperm (Sun et al., 2021).

- Development of new PUH71-derived probes for selective detection of presence of epichaperome (e.g. in brain tumors) in living organisms; presence correlates with sensitivity to epichaperome-selective Hsp90 inhibitors (Bolaender et al., 2021). Flow-cytometric detection of epichaperome in leukemic patients and treatment of highly epichaperome-positive case (Sugita et al., 2021).
- Sensitivity of cancer cell lines to Cdk4/6 inhibitors depends on cellular context and correlates with thermal instability of Cdk6 and strong association with (i.e. dependence on) Hsp90/Cdc37 (Wu et al., 2021b).
- Saturable binding and imaging with an Hsp90 PET (positron emission tomography) probe to brain and tumors (Vermeulen et al., 2021).
- New Trap1 inhibitor also inhibits cytosolic Hsp90 upon prolonged exposure by interacting with and blocking client binding site (Yoon et al., 2021).
- Inhibitor of C-terminal dimerization based on tripyrimidonamide scaffold, does not induce HSR (Bhatia et al., 2022).
- Cordycepin (3'-deoxyadenosine) inhibits Hsp90 by competing with ATP (Lee et al., 2022).
- Pimitespib (TAS-116) approved in Japan (June 2022) for gastrointestinal stromal tumor (GIST) after chemotherapy (see Hoy, 2022).
- Machine learning models for Hsp90 inhibitor screens (Khan et al., 2022).
- Bringing Hsp90 to Cdk4/6 with a chimeric ligand promotes more efficient client degradation (Li et al., 2023c).
- The steroid saponin timosaponin AIII binds Hsp90, increases its levels, promotes the interaction of Hsp90 with GPX4, and through the degradation of GPX4 ferroptosis, all antagonized by tanespimycin and/or Hsp90 knockdown (Zhou et al., 2023).
- Ganetespib does not sufficiently improve chemotherapy to warrant further development for HER-negative breast cancer (Lang et al., 2022).
- Hsp90-targeting PROTAC: Chimeric molecule with Hsp90 inhibitor moiety efficient against breast cancer cells (Liu et al., 2022b); geldanamycin linked to a cereblon-recruiting compound reduces both Hsp90α and Hsp90β (Wurnig et al., 2023); targeting of glutathione peroxidase 4 can trigger ferroptosis (Dong et al., 2024); and others (Liang et al., 2024a).
- Dual/chimeric inhibitor for CYP15 and Hsp90 may be a potent compound against invasive candidiasis (Zhang et al., 2025a).
- The heat-shock response to compromising Hsp90 function by heat or pharmacologically depends on ongoing translation (Kolhe et al., 2023).
- Pharmacological blockade of SDCBP mitigates stabilizing butyrylation of Hsp90, thereby reducing chemoresistance of cancer cells (He et al., 2023).
- Cell-impermeable Hsp90α-selective inhibitors (Reynolds and Blagg, 2023).
- MD simulations to explore the species-selective binding of an N-terminal inhibitor with preference for fungal Hsp90 (Cheng et al., 2023).
- Survey of effectiveness of Hsp90 inhibitors against a panel of *Candida* species and isolates reveals complex pharmacology, and that, of the C-terminal inhibitors, only the green tea catechin epigallocatechin-3-gallate is inhibitory (Rouges et al., 2023).
- Small molecule inhibitor of FKBP51-Hsp90 interaction with specificity for FKBP51 (Wang et al., 2024d).
- Arenobufagin, a component of toad venom, most likely binding middle domain of Hsp90β, reduces interaction with the phosphorylated form of STAT3, thereby reducing PD-L1 expression (Shang et al., 2024).
- Characterization of new type of C-terminal inhibitor with anti-tumor activity against TNBC cell line (Zajec et al., 2024).

- Repurposing and optimizing toposimerase IIα inhibitors as Hsp90β-selective inhibitors (Dernovšek et al., 2024).
- The terpenoid saponin astragaloside IV inhibits Aβ-induced astrocyte senescence by downregulation of Hsp90α, a potential direct target, and Hsp90α overexpression suppresses these effects (Yan et al., 2024).
- EGFR inhibitor gefitinib targeted to cells with a silicon-based hydrophobic tag dissociates Hsp90 from EGFR and induces degradation of the latter (Ma et al., 2024).

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- Dimers: homodimers α/α and β/β (Radanyi et al., 1989; Minami et al., 1991), some β monomer (Minami et al., 1991; see also Cortés-González et al., 2010). Evidence that some heterodimers exist as well (Perdew et al., 1993; Miao et al., 2008), but mass spec analysis revealed no α-β heterodimers (Garnier et al., 2001) and sepharose-immobilized Hsp90β pulls out only β (Tsaytler et al., 2009). Dimerization constant for wild-type yeast Hsp90 is 60 nM (Richter et al., 2001). Poor dimer formation of human Hsp90β can be mapped to two amino acid differences compared to α (Kobayakawa et al., 2008). Yeast Hsp90 isoforms readily form heterodimers both *in vitro* and *in vivo* (Girstmair et al., 2019), but this is disfavored in humans (Richter et al., 2008). Dimerization is through C-terminal domain and high temperature or ATP induce transition to O-ring shaped structure (Maruya et al., 1999). Evidence for heterodimers from co-IP experiments with retinal pigment epithelial cells (Jia et al., 2025).
- Oligomers: forms higher oligomers at elevated temperature (Lanks, 1989; Minami et al., 1993; Yonehara et al., 1996); cut-off temperature is 50°C and oligomerization is primarily due to self-association of dimers; it is inhibited by ATP and GA and promoted by molybdate, vanadate and NP-40 (Chadli et al., 1999). Also evidence for higher oligomers of both isoforms (Nemoto and Sato, 1998). Oligomerization correlates with activity in aggregation assay (Nemoto et al., 2001b). Also promoted by divalent cations, not inhibitable by GA (Garnier et al., 2002a). Oligomerization inhibited by ATP binding to C-terminal site (Garnier et al., 2002b). ATP, ADP, CTP and NAD inhibit oligomerization of Neurospora Hsp90 (Ouimet and Kapoor, 1999). Mg^{2+} and heat induce similar oligomers, notably tetramers, hexamers and double hexamers, with the circular hexamer containing a 50 Å central chamber (Moullintraffort et al., 2010). N-terminally truncated human Hsp90α exists as dimers, tetramers and hexamers (Lee et al., 2011), with residue W320 playing a key role for the oligomerization (Peng et al., 2022b). Biochemical characterization of *Arabidopsis* Hsp90 isoforms 1 and 3 shows that higher oligomeric state of isoform 3 correlates with higher holdase and ATPase activities (Cha et al., 2013). Maximum stoichiometry of Aha1-Hsp90 interaction is 4 Aha1 per Hsp90 dimer, including in higher order oligomers, which have higher Aha1 affinity than Hsp90 dimer (Lepvrier et al., 2015a). In contrast, p23 has higher affinity for dimer and promotes a shift of the oligomer-dimer equilibrium towards dimer (Lepvrier et al., 2015b).
- Oxidative stress can lead to disulfide bond formation (Cumming et al., 2004).
- Phosphorylation: P-Ser (Lees-Miller and Anderson, 1989b), *in vitro* by CKII (Lees-Miller and Anderson, 1989b; Shi et al., 1994), and Hsp90α but not β by dsDNA-activated protein kinase (DNA-PK) on T5/T7 (Lees-Miller and Anderson, 1989a; see also Quanz et al., 2012; Solier et al., 2012; Park et al., 2017b). Hsp90 phosphorylation, restored by CKII, is essential for stimulation of HRI (Szyszka et al., 1989), and correlates with release from the substrate protein σ1 (Zhao et al., 2001). In cells, phosphorylation of Hsp90 may trigger release of $pp60^{v\text{-}src}$ (Mimnaugh et al., 1995). Statins induce tyrosine phosphorylation of Hsp90 in endothelial cells (Brouet et al., 2001). Hsp90 is tyrosine

phosphorylated in an inhibitory complex with the purinergic receptor $P2X_7$, and GA reduces it and increases $P2X_7$ activity (Adinolfi et al., 2003). Di-phosphorylated form is the most abundant (in pig brain) (Garnier et al., 2001). Capacitation of sperm induces tyrosine phosphorylation (Ecroyd et al., 2003; see also Li et al., 2021b). Hsp90α/β in AhR complexes have inhibitory (for assembly and AhR function) phosphorylations in charged domain (Ogiso et al., 2004). Ppt1 binds, specifically dephosphorylates Hsp90 and ameliorates function of several Hsp90 substrates in yeast (Wandinger et al., 2006). Substrate of Akt (Barati et al., 2006). Phosphorylation of Hsp90α T90 by PKA promotes secretion (Lei et al., 2007; Wang et al., 2009b) and this may be directly reversed by PP5 (Wang et al., 2009b). T90 phosphorylation decreases ATP and client binding, and differentially affects co-chaperone binding (Wang et al., 2012). 5-fluorocytosine treatment of cells induces phosphorylation on S254 (Negroni et al., 2007). VEGF signaling leads to Y300 phosphorylation of VEGFR-2 associated Hsp90β by Src and this is essential for eNOS association with Hsp90 and activity (Duval et al., 2007) and stimulates association with Aha1 (Desjardins et al., 2012). Phosphorylation of S226 and S255 of human Hsp90β reduces interaction with Apaf-1, as in transformed cells; not controlled by PP5 in this case (Kurokawa et al., 2008). p23, C-terminally truncated by caspases, reduces Hsp90 phosphorylation (at S231 and S263 of Hsp90α) and activity, for example for telomerase, possibly by recruiting more PP5 and thus reducing Hsp90 phosphorylation (Woo et al., 2009). Swe1/Wee1 modulates Hsp90 activity by phosphorylation of Y24 of yeast Hsp82 (Y38 of human); this constitutes a signal for ubiquitination and nuclear export, and non-phosphorylatable mutants are defective for supporting some client proteins and for interaction with some co-chaperones (notably Aha1 and p23) (Mollapour et al., 2010, commented on by Mayer, 2010). Phosphorylation sites identified in phosphoproteome analysis of *Leishmania* (Morales et al., 2010). Casein kinase II (CK2) phosphorylates Hsp90 on T22 (in yeast), altering ATPase and chaperone function, reducing interaction with Aha1 and Cdc37, and affecting inhibitor sensitivity (Mollapour et al., 2011a; Mollapour et al., 2011b). Pnck overexpression leads to hyperphosphorylation of T89 (T90) and T616 of both Hsp90α and β and S391 of α (Deb et al., 2011). Ten sites identified in yeast Hsp90, two of which are Ppt1-regulated and some affect chaperone function (Soroka et al., 2012). Hsp82 S485 hyperphosphorylation upon (glucose) starvation, which downregulates Ppt1, leads to nuclear accumulation of Hsp82 and improved survival (Shang et al., 2020). Hsp90α is phosphorylated by DNA-dependent protein kinase (DNA-PK) (and other PIKKs) on T7 upon induction of DNA stress (Quanz et al., 2012). DNA-PK also phosphorylates Hsp90α in response to apoptotic signals and recruits it to nuclear apoptotic rings (Solier et al., 2012). Yes promotes phosphorylation of Y197, Y313 and Y627 (human Hsp90α) (Xu et al., 2012a; see also Desjardins et al., 2012). In humans, Y627 phosphorylation, instead of Hch1 interaction in yeast, impairs interaction with clients, impairs formation of closed state and corresponding co-chaperone interactions (Zuehlke et al., 2017). c-Src mediates LPS-induced phosphorylation of Y309/Y300 (Hsp90α/β) and increased function towards Hsp90 clients (Barabutis et al., 2013). Phosphorylation of serine just N-terminal of MEEVD reduces and favors binding to CHIP and HOP, respectively, tilting the balance between degradation and chaperoning; mimicked by point mutations (Muller et al., 2013). Chemically introducing phosphorylation on T725 and/or S726 within CTD only slightly affects thermal stability and not anti-aggregation activity (Gajsek et al., 2024). PKCγ phosphorylates T115 (would be T101 in yeast Hsp82), T425 and T603 of human Hsp90α; phosphorylation of the first two sites affects ATPase activity and of all three differentially affects co-chaperone binding, triggering the release of PKCγ itself (Lu et al., 2014). CK2-phosphorylated Hsp90-Cdc37 complexes are exquisitly sensitive to disruption by ADP (Olesen et al., 2015). CK2 phosphorylates Hsp90β on Ser 225/254

and promotes interaction with PXR (Kim et al., 2015b). Phosphorylation of Aha1 by c-Abl is essential to promote interaction with Hsp90 and chaperoning (Dunn et al., 2015). Yeast checkpoint kinase Mps1 phosphorylates T101, with T22 the only other P-site in the N-terminal domain, inhibiting ATPase activity, p23 binding, activating and repressing kinase and non-kinase clients, respectively; human Mps1 phosphorylates Hsp90α at T115 (Woodford et al., 2016c). Cdc14 dephosphorylates T101 promoting inactivation of Mps1 and mitotic exit (Woodford et al., 2016c; see also Woodford et al., 2021). PP5 overexpression or knock-down increases inhibitor binding to Hsp90 (Oberoi et al., 2016). ATM phosphorylates Hsp90α on T5/T7 in response to ionizing radiation (Elaimy et al., 2016). Phosphorylation of Y197 by BCR signaling in Burkitt lymphoma cells is specifically essential for interaction with SYK (Walter et al., 2017). S365 is an Hsp90β-selective phosphorylation site; can be phosphorylated *in vitro* by CK2; mutants have some effects on growth and client activity in yeast, and affect conformational dynamics and interaction with Cdc37 (Nguyen et al., 2017). T5/T7 phosphorylation of Hsp90α by DNA-PK increases with age in some tissues, notably muscle, and triggers release of clients (Park et al., 2017b). MAPK1 of *Leishmania donovani* phosphorylates Hsp90 and regulates its protein levels (Kaur et al., 2017). Hsp90α S164 is a key target of Cdc7-Dbf4 for recovery from DNA replication stress and DNA repair by homologous recombination (Cheng et al., 2017). T5/T7 phosphorylation stimulated by low electric treatment of cells (Hasan et al., 2019). Testosterone stimulates T89 phosphorylation by PKA in AR-positive cells and promotes release of Hsp90 from AR (Dagar et al., 2019). Y313 phosphorylation (of human Hsp90α) promotes asymmetric association with Aha1, and reduced Hop binding, through long-range conformational effects throughout Hsp90 (Xu et al., 2019). Bacterial HopBF1 specifically phosphorylates eukaryotic Hsp90 on the serine of the lid (e.g. S108 of human Hsp90β) that contacts the β-phosphate of ATP, resulting in ATPase inhibition (Lopez et al., 2019). In *Candida albicans*, S530 is the main, but low stoichimetry phosphorylation site and a phosphomimic mutant has compromised virulence traits, (Alaalm et al., 2021). More than 90% of intracellular human Hsp90β is phosphorylated at S226 and S255; this is not affected by stresses, but S226A/S255A globally increases the amount of interacting proteins and promotes secretion (Weidenauer and Quadroni, 2021). TSSK4 phosphorylates S255 of Hsp90β, inhibiting its ATPase activity and TNFα-stimulated interaction with AKT (Chen et al., 2021b). Atg1/Ulk1 phosphorylates conserved S25 of yeast Hsp82 and S39 of human Hsp90α leading to altered co-chaperone dynamics and client processing (Backe et al., 2023b; discussed by Backe et al., 2024). Impact of mutants of phosphorylation sites Y38, 61, 197 of human Hsp90α shows differential impact on conformation and cochaperone interactions, growth in yeast, and on client maturation in both yeast and human Hsp90α KO cells (Huo et al., 2024). Phosphorylation of S226 and S255 (Hsp90β numbering) in charged linker enhances epichaperome formation, and proliferation and stemness of embryonic stem cells (Roychowdhury et al., 2024). Phosphorylation of Hsp90α S252 and S263 by PLK2 is essential for its activation of the NFκB pathway (Cheng et al., 2024). CDK5 phosphorylates Hsp90α on S595 within a highly conserved sequence; the mutant S595D displays reduced dimer formation, and interaction with Hsp70 and TFEB (Yang et al., 2023). *C. albicans* Hsp90 is dephosphorylated by the CO_2 sensor Ptc2 at S376 in response to 5% CO_2 (concentration in host); Hsp90 promotes and is recruited into Ptc2 condensates, which form by phase transition, for efficient dephosphorylation (Zhang et al., 2025b).

- <u>Acetylation</u>: Acetylation sites mapped to K294 and K287 in Hsp90α and β, respectively (Scroggins et al., 2007). Seven different sites mapped in Hsp90α by Bhalla and colleagues (Yang et al., 2008); and there are a number of other ones (Krämer et al., 2014; see also Du et al., 2021). HDAC inhibitors induce hyperacetylation of Hsp90 and

block binding to substrates (Yu et al., 2002; Nimmanapalli et al., 2003). HDAC inhibitor reduces binding to ATP sepharose (Nimmanapalli et al., 2003; Murphy et al., 2005). HDAC6 is the regulator (Bali et al., 2005; Kovacs et al., 2005) and its inhibition leads to substrate degradation (Bali et al., 2005; Fiskus et al., 2007), dissociation of p23, and compromised GR (Kovacs et al., 2005; see also Zhu et al., 2020) and ERα (Fiskus et al., 2007) functions and assembly (Murphy et al., 2005) (reviewed in Krämer et al., 2014). Δ*hdac6* MEFs have hyperacetylated Hsp90 and compromised GR function (Zhang et al., 2008c). Mutants mimicking acetylation have reduced interactions with co-chaperones and clients but still support viability and src function in yeast (Scroggins et al., 2007). Inhibition of HDAC6 or HDAC10 leads to degradation of Hsp90 substrates VEGFR1 and VEGFR2 (Park et al., 2008). Acetylation-resistant mutant (Hsp90α K294R) stimulates membrane ruffling (Gao et al., 2007), and eNOS interaction and NO production (Yang et al., 2021). p300 is one of the acetylases (Yang et al., 2008). Different set of single acetylation-deficient mutants (K to R) show hardly any effects on ATP, co-chaperone and substrate binding whereas some of the acetylation-mimetics (K to Q) are modified (Yang et al., 2008). Acetylation correlates with GA binding, promotes secretion of Hsp90α, interaction with MMP2 and cell invasion (mimicked by some acetylation mutants) (Yang et al., 2008). HDAC1 can deacetylate Hsp90 in the nucleus (Zhou et al., 2008; see also Zhang et al., 2013a). 17-AAG reduces HDAC6 binding and leads to hyperacetylation, and conversely, hyperacetylation increases 17-AAG binding (Rao et al., 2008). Response of androgen receptor is regulated by HDAC6-regulated Hsp90 acetylation (Ai et al., 2009). Dramatically reduced HDAC6 expression in JNK1-negative cells leads to lower Hsp90 levels and defective HIF-1α stabilization (Zhang et al., 2010a). Sites in *Plasmodium falciparum* Hsp90 are different from those in human but may also interfere with Aha1 and p23 binding (Pallavi et al., 2010). Yeast Hsc82 is acetylated on K27 and K270, and acetylation is regulated by Hda1 and Rpd3 (Robbins et al., 2012, see also Rani et al., 2024); deacetylation of K27 promotes the interaction of the Hsp82-Aha1 complex with Hsp82 and DNA repair (Rani et al., 2024).. Human Hsp90α on K191 (Mollapour et al., 2014). Acetylation of K27 and K271 (equivalent to human K294) of *A. fumigatus* Hsp90 compromises function (Lamoth et al., 2014). Promoted by Hsf1 knock-down (Ganguly et al., 2015). HDAC6-reversible Hsp90 acetylation affects interaction with MR and subcellular localization of apo-MR but not transcriptional response (unlike GR) (Jiménez-Canino et al., 2016). Deacetylation by SIRT2 triggers Hsp90 ubiquitination and degradation leading to reduced actin polymerization (Min et al., 2018). Tsc1 promotes acetylation of Hsp90α on K407/K419, which is essential for drug sensitivity (Woodford et al., 2019). SIRT2-mediated deacetylation of K294 promotes anti-inflammatory activity of GR (Sun et al., 2020a). HDAC3 inhibitor increases nuclear acetylated Hsp90 (Kotwal and Amere Subbarao, 2020). HDAC6 reverses acetylation of K489 (Du et al., 2021). Alcohol metabolism via CYP2E1 promotes Hsp90 acetylation resulting in reduced eNOS activity (Yang et al., 2021). MOF (=KAT8) promotes K294 acetylation, which disrupts interaction with ERα and promotes interaction with CUL4B (Zhang et al., 2022f). Nuclear polyhedrosis virus infection of *Bombyx mori* cells reduces acetylation of K64 of *B. mori* Hsp90 (also corresponds to K64 in human Hsp90β), and acetylation mimic K64Q reduces ATPase, chaperone activity, and viral replication (Zhang et al., 2024b). Impact of HDAC6 inhibitor and splenectomy on NLRP3 (Lin et al., 2024a). Splenectomy promotes HDAC6-mediated deacetylation of Hsp90 and functional GR association in the hippocampus (Liu et al., 2024h). A ischemia-reperfusion model increases acetylation of Hsp90α on K284, and reduces its ATPase activity in mouse cardiomyocytes; the K284R mutant displays increased interaction with NFκB p65, which is associated with reduced activity of this pathway (Zhan et al., 2024).

- Nitrosylation: Hsp90 becomes S-nitrosylated (Gao et al., 2005; Martínez-Ruiz et al., 2005; Zhang et al., 2005c), including htpG in *M. tuberculosis* exposed to NO (Rhee et al., 2005). S-nitrosylation on C597 (human Hsp90α) results in reduced ATPase and NOS stimulation (Martínez-Ruiz et al., 2005). This conserved cysteine acts as a switch point affecting N- and C-terminal association and therefore ATPase activity (Retzlaff et al., 2009; discussed in Scroggins and Neckers, 2009). S-nitrosylated Hsp90β (on C589) is a fibrosis marker and Cys589 mutant reduces binding to TGFβR2 and cardiac fibrosis (Zhang et al., 2021c). S-nitrosylation of Cys521 of Hsp90β is elevated in oxLDL-stimulated endothelial cells and in atherosclerotic samples; this shifts the balance from Aha1 to Cdc37 association towards atherosclerosis (Zhao et al., 2022).
- Nitration of tyrosines: several tyrosine residues can be nitrated of which Y33 or Y56 in Hsp90β are sufficient to inhibit ATPase and to display a dominant toxic gain-of-function; nitrated Hsp90 binds and activates P2X7 thereby eliciting apoptosis, for example in motoneurons (Franco et al., 2013). A fraction of Hsp90β with nitrated Y33 localizes to outer mitochondrial membrane and down-regulates mitochondrial membrane potential and therefore metabolic activity in a manner dependent on non-nitrated Hsp90 (Franco et al., 2015). In the case of PC12 cells, nitration of Y56 is necessary and sufficient to induce apoptosis through activation of P2X7 and PTEN (Jandy et al., 2022). Site-specifically nitrated Hsp90 (either Y33 or Y56), introduced into cells as proteins, promotes the proliferation of normal schwann and schwannoma cells, and differentially reprograms cellular metabolism (Logan et al., 2024).
- Methylation: Human Hsp90α is methylated by SMYD2 on K209 and K615 (616 in mouse), which is inhibited by Hop, and K615 is demethylated by LSD1 (Abu-Farha et al., 2011). K616 methylation is *not* affected by KDM3A (Kasioulis et al., 2014). Hsp90β also methylated by Smyd2, on lysine equivalent to K607 in human (Donlin et al., 2012). Smyd2 may methylate human Hsp90β on K531 and K574 thereby promoting dimerization and interaction with Hop and Cdc37 (Hamamoto et al., 2014). Methylation of R345 and R386 of Hsp90α required to maintain Hsp90 activity in tumors with low NDRG2 (Ichikawa et al., 2020). Methylation of K615 of human Hsp90α and its equivalents in Hsp90β and in yeast Hsp82 act as a conformational switch point affecting N-terminal closure, co-chaperone interaction, complementation of yeast, and client maturation (Rehn et al., 2020).
- O-glycosylation (O-GlcNAc) sites in middle domain (Overath et al., 2012; see also Frank et al., 2014).
- Sumoylation: K178 and K191 of yeast Hsp82 and human Hsp90α, respectively, promoting the asymmetric interaction with Aha1; sumoylated Hsp90 has higher affinity for inhibitors, which increase sumoylation, compete with Aha1, and displace ATP prior to lid closure (Mollapour et al., 2014). K559-sumoylated Hsp90 present in blood, and antibodies against it, correlates with certain BCR-driven diseases (Preuss et al., 2015). Sumoylation of K178C *in vitro* does not affect ATPase (Wolmarans et al., 2019). Primary sumoylated site of Hsp90β in mouse cardiomyocytes is K72, and overexpression of SENP1 or the Hsp90β mutant K72R ameliorate poor ventricular remodeling response after myocardial infarction through reduced interaction with STAT3 and downstream signaling (Liu et al., 2024i).
- Ubiquitination: Long-term treatment of cells with the pH lowering drug hypericin induces monoubiquitination (primarily) (but not degradation) of Hsp90, release of Cdc37, and degradation of clients (Blank et al., 2003). Taxotere (docetaxel) induces ubiquitination and degradation (Murtagh et al., 2006). CHIP can mediate polyubiquitination of Hsp90 *in vitro* (Morales and Perdew, 2007; Kundrat and Regan, 2010b; Kundrat and Regan, 2010a). Hectd1 polyubiquitinates Hsp90α via K63 linkages, which prevents its secretion (Sarkar and Zohn, 2012), and reduces its levels in microglia (Xing et al., 2024). Human

Hsp90α on K191 (Mollapour et al., 2014). Deacetylation by SIRT2 triggers its ubiquitination and degradation (Min et al., 2018). Half life is long and degradation, if any, through proteasome (Xie et al., 2020). FBXL6 polyubiquitinates Hsp90α via K63 linkages, which stabilizes it; Hsp90α half life in FBXL6 KO cells drops to about 4 hours from much longer than 8 hours (Shi et al., 2020a). CHIP-mediated ubiquitination of Hsp90 depends on UBA52 (Tiwari et al., 2022). Lysosome-dependent degradation of Hsp90 triggered by the CUL-6 (cullin 6) in the intestine of *C. elegans* promotes thermotolerance (Bardan Sarmiento et al., 2024).

- Glycation: by methylglyoxal on many residues across protein resulting in inhibition of activity (Nokin et al., 2016).
- Fucosylation: stimulated by FUT8 (Guo et al., 2023).
- S-glutathionylation: Redox-dependent modification of C366/C412 (of Hsp90β, but also Hsp90α) induces conformational change, loss of ATPase, reduced C-terminal CK2-mediated phosphorylation and therefore increased CHIP-binding, and reduction of Hsp90 levels (Shih et al., 2022).
- Butyrylation: K754 of Hsp90α is a major lysine butyrylation site in chemoresistant cancer cells, with KAT8 and HDAC11 as writer and eraser; the non-modifiable K754R mutant is destabilized and reduces chemoresistance, and SDCBP competes with HDAC11 for binding and thereby stabilizes Hsp90 as well (He et al., 2023).
- N-terminal ATP binding domain, ATPase cycle (see also Hsp90 cycle):
  - binds ATP in presence of Ca^{2+} or Mn^{2+} (Csermely and Kahn, 1991).
  - ATPase activity in some species (e.g. Trypanosomes) (Nadeau et al., 1992; Nadeau et al., 1993; Nardai et al., 1996), maybe even GTPase (Nardai et al., 1996). Yeast Hsp82 and *E. coli* HtpG have ATPase activity, roughly like Hsp70; mutations in pocket destroy selectively ATP binding or hydrolysis, and abolish complementation *in vivo* (Obermann et al., 1998; Panaretou et al., 1998). A hydrolysis mutant can still bind p23 and has reduced affinity for Hop, but both binding and hydrolysis required for full luciferase refolding and assembly of mature PR complex (Grenert et al., 1999). ATP binding by both subunits but only ATP hydrolysis by one protomer are required for complementation in yeast (Mishra and Bolon, 2014).
  - low autophosphorylation activity (Csermely and Kahn, 1991; see also Park et al., 1998), blocked by novobiocin (Langer et al., 2002).
  - ATP induces conformational change (Csermely et al., 1993); contradicted by other authors (Shi et al., 1994; Jakob et al., 1996).
  - ATP binds with adenosine toward bottom of pocket (Grenert et al., 1997; Prodromou et al., 1997a).
  - higher affinity for ADP than ATP (Grenert et al., 1997; Prodromou et al., 1997a), but note that there is much more ATP in the cell than ADP (about 100x).
  - ATP and GA-binding domain (N-terminal 200 AA) (Grenert et al., 1997; Prodromou et al., 1997a; Stebbins et al., 1997). N-terminal domain alone only binds ATP but has low ATPase activity (Obermann et al., 1998; Weikl et al., 2000). "Lid" closure upon ATP binding promotes N-terminal dimerization and closure of a molecular clamp which in turn stimulates ATPase activity (Prodromou et al., 2000; Vaughan et al., 2009). More C-terminal sequences (N451) are required for commitment to ATP hydrolysis and even more for high level ATP hydrolysis (Weikl et al., 2000; see also Owen et al., 2002; Ratzke et al., 2012a). N-terminal dimerization required for ATPase allowing coupling of hydrolysis and opening-closing movements of Hsp90 (Richter et al., 2001). AA 8-24 of yeast Hsp82 are necessary for ATP hydrolysis, not binding; Δ16 can still stimulate ATPase of a wild-type subunit (Richter et al., 2002). γ-phosphate may "touch" middle domain

(Sóti et al., 2002). Crystal structure and mutagenesis reveal a loop around AA 380 (yeast) that may contact the γ-phosphate (Meyer et al., 2003), and is released by interaction with Aha1 (Meyer et al., 2004). Middle domain required for trapping ATP and efficient ATPase, and N-terminal dimerization per se is not sufficient (Wegele et al., 2003). Conformationally coupled ATPase mechanism is common to yeast and human (Vaughan et al., 2009). R380 does not directly participate in catalysis, but helps to stabilize the proper conformation (Cunningham et al., 2012).

- McLaughlin et al. find no evidence of N-terminal coupling or of a requirement for N-terminal dimerization for ATPase for human Hsp90 -> open ring model (McLaughlin et al., 2004).
- Sti1 (yeast Hop) binds N-terminal domain, blocks access to ATP (but see also below), and displaces GA; antagonized by Cpr6 (Prodromou et al., 1999), which binds preferentially in presence of AMP-PNP (Johnson et al., 2007). If Hop is also bound to Hsp70, it does not inhibit ATP binding (Hernández et al., 2002b). Cdc37 also blocks ATPase without displacing GA or nucleotides (Siligardi et al., 2002; Roe et al., 2004; Gaiser et al., 2010), but does not bind ATP-bound Hsp90 (Zhang et al., 2009; however, also see Olesen et al., 2015). TPR domain of Cpr6 can stimulate ATPase activity 2-fold (Panaretou et al., 2002). Sti1 blocks ATPase of yeast Hsp90 but not nucleotide binding, probably by blocking N-terminal dimerization of Hsp90 (Richter et al., 2003). Sti1 blocks early conformational changes (incuding lid closure) in ATPase cycle (Hessling et al., 2009). ATPase activity of human Hsp90 not blocked by Hop (McLaughlin et al., 2002). Sba1 inhibits ATPase (Panaretou et al., 2002; Cox and Miller III, 2004). p23 increases apparent affinity of human Hsp90 for AMP-PNP and blocks ATPase (McLaughlin et al., 2006).
- Stimulation by substrates (McLaughlin et al., 2002; Falsone et al., 2009; Motojima-Miyazaki et al., 2010; Hagn et al., 2011; Street et al., 2011). Opposite effect seen with the GR HBD under slightly different conditions (Lorenz et al., 2014).
- The even stronger stimulation by Aha1 and Hch1 (without an increase in affinity for ATP) is inhibitable by Sti1 and Sba1, but slightly stimulated by Cpr6 (Panaretou et al., 2002). At lower ratios, only Aha1 not Hch1 stimulates (Lotz et al., 2003; see also Horvat et al., 2014; Wolmarans et al., 2016). ATPase and stimulation by Aha1 inhibited by GCUNC-45 (Chadli et al., 2006). Aha1 remodels Hsp90 even in absence of nucleotide to promote N-terminal dimerization (Hessling et al., 2009). One Aha1 molecule can bridge the two Hsp90 subunits and stimulate the ATPase (Koulov et al., 2010; Retzlaff et al., 2010) either in *cis* or *trans*, potentially allowing a substrate molecule to be bound to the other subunit; although affinities are low, p23 and Sti1/Hop can form ternary complexes with Hsp90 and Aha1 (Retzlaff et al., 2010). See also detailed analysis of Hsp90-cochaperone complexes in the *C. elegans* system (Gaiser et al., 2010). *E. histolytica* contains only the C-terminal domain and yet it can stimulate Hsp90 from various species (Singh et al., 2014). Aha1 and Hch1 regulate Hsp90 function through catalytic loop but *in vivo* functions of Hch1 may not be linked to its ability to stimulate the ATPase (Horvat et al., 2014).
- NASP stimulates ATPase (Alekseev et al., 2005).
- ATP hydrolysis required for substrate release and its stimulation by p23 (Young and Hartl, 2000; see also Kaziales et al., 2020).
- nucleotide binding specificity: prefers adenosine nucleotides; NAD and diadenosine polyphosphate alarmones are specific for N-terminal ATP binding domain (Söti et al., 2003).

- Hsp90 multichaperone complexes from tumor cells have higher ATPase activity (Kamal et al., 2003). Systems biology analysis of such differences shows effects on critical clients (Vali et al., 2010).
- The lid both inhibits dimerization in the absence of ATP and promotes the ATPase together with N-terminus of other subunit after closure (Richter et al., 2006).
- weakly stimulated by a large excess of Tah1 (Millson et al., 2008; Eckert et al., 2010) and *Drosophila* Spag (Benbahouche et al., 2014), but repressed by a Pih1-Tah1 heterodimer (Eckert et al., 2010).
- in-depth comparison of conserved conformational changes in ATPase cycle (Richter et al., 2008). For lack of cooperativity, see also comments in Elnatan et al., 2017.
- intradomain and interdomain interactions stabilize active conformation (Cunningham et al., 2008).
- NudC inhibits ATPase (Zhu et al., 2010) or not (Biebl et al., 2022). NudCL2 as well (Yang et al., 2018).
- Enforced N-terminal dimerization stimulates ATPase for both human and yeast Hsp90 (human still weaker) and is viable in yeast suggesting that the large transitions between open and closed conformations may not be physiologically relevant (Pullen and Bolon, 2011).
- EM analysis shows that the TPR1 domain of a single Hop molecule can sterically block Hsp90 N-terminal dimerization by being situated between the Hsp90 monomers and interacting with the adjacent N-terminal/middle domains; nevertheless, the TPR1 domain remains available for Hsp70 (Southworth and Agard, 2011).
- there is a negative cooperativity for binding ATP to the two monomers; one monomer "only" required for activation of the other ATP-bound one (Ratzke et al., 2012a).
- in *E. coli*, ATPase activities of interacting htpG and DnaK are synergistic (Genest et al., 2015).
- ATPase activity is stimulated by crowding (using polymer crowders) by a mechanism different from that used by co-chaperones (Halpin et al., 2016).
- Confirmation by single-molecule analysis by SMACKS that N-terminal conformational dynamics are not coupled to ATP hydrolysis (Schmid et al., 2016) nor affected by inhibitors (Schmid et al., 2018).
- FKBP8 does not inhibit ATPase activity (Blundell et al., 2017).
- N-terminal domain can rotate by 180° relative to Hsp82-Sba1 structure; this is required for ATPase activity, suppressed by Aha1 and not Sba1 in the presence of nucleotide, depends on a minimal length of the charged linker and is required for only some clients in yeast (Daturpalli et al., 2017). Rotation is ATP-stabilized, enhances and is enhanced by some clients, and poises dimer for closing (promoted by p23) (Lopez et al., 2021).
- htpG has a uniquely pH-dependent ATPase (higher at alkaline pH) because an electrostatic interaction betwen H255 and ATP blocks it in the open inactive conformation (Jin et al., 2017).
- The ATPase of cytosolic Hsp90s but not Grp94 and Trap1 is strongly inhibited by ADP; can be relieved by Aha1 in eukaryotes and DnaK in bacteria; specific residues contribute to stabilizing ATP versus ADP (Halpin and Street, 2017).
- ATP binding and ATPase are stimulated by RanBP9 (Woo et al., 2017).
- ATPase stimulated by Ids2, which is released upon glucose-stimulated phosphorylation by PKA in yeast (Chen et al., 2018b).

- Differential contributions of enthalpy and entropy to thermodynamic characteristics of nucleotide binding of Hsp90s from different species (Minari et al., 2019).
- Analysis with electron resonance techniques shows a more compact N-terminally closed conformation of ADP-bound (posthydrolysis, before opening) Hsp90 than the closed ATP-bound state; vanadate stabilizes this compact state (Giannoulis et al., 2020).
- Biophysical and molecular simulation analyses of impact of conformational dynamics on ATPase (Mader et al., 2020).
- Molecular dynamics analysis of ligand-dissociation dynamics (Wolf et al., 2020).

♦ Second C-terminal ATP binding domain: also binds ATP, apparently through novobiocin-binding domain (Marcu et al., 2000a; Garnier et al., 2002b; Sóti et al., 2002). Has lower affinity, only opens up when N-terminal site is occupied (even by GA –> Söti et al., 2003) except for certain ligands (Söti et al., 2003); conversely, occupancy by GTP or novobiocin blocks binding to N-terminal site; cisplatin is a specific blocker of the C-terminal site (Sóti et al., 2002; Ishida et al., 2008), but induces a conformational change of the N-terminus (Ishida et al., 2008). Binding specificities of the two binding sites differ; GTP and UTP are specific for C-terminal site (Söti et al., 2003).

♦ Neurospora Hsp80 binds CTP and NAD (Freitag et al., 1997)

♦ binds Ca^{2+} (Kang and Welch, 1991; Minami et al., 1993).

♦ <u>Hsp90 binding drugs</u>: deoxyspergualin (Nadeau et al., 1994) and geldanamycin and relatives (Whitesell et al., 1994). Non-benzoquinone ansamycin antibiotic radicicol works like GA (Schulte et al., 1998; Sharma et al., 1998; Roe et al., 1999). Oxime derivative of radicicol with better pharmacology (Soga et al., 1999). Radicicol has higher affinity for Hsp90 than Grp94, but also binds Trap1 with lower affinity (Schulte et al., 1999; see also Felts et al., 2000). Cisplatin (CDDP) binds, induces conformational change, and inhibits chaperone activity (Itoh et al., 1999; Sóti et al., 2002); specific effects on steroid receptor ligand binding and Hsp90 association while other substrates are not affected (Rosenhagen et al., 2003). Coumarin antibiotics such as novobiocin bind Hsp90 and reduce levels of Hsp90 clients (Marcu et al., 2000a; Marcu et al., 2000b). Filter binding assay (Carreras et al., 2003). Fluorescent version of GA can be used for fluorescent polarization assays (Llauger-Bufi et al., 2003). Detailed thermodynamic analysis of drug binding to human and yeast Hsp90 (Zubrienė et al., 2010).

♦ Yet other drugs and drug screening assays (incomplete list): Okada et al., 2003; Vilenchik et al., 2004; Zhou et al., 2004; Schax et al., 2014; Güldenhaupt et al., 2018.

♦ Hsp90 complexes from tumor cells have 100-fold higher affinity for GA and ATP, and markedly higher ATPase activity; this correlates with the fact that Hsp90 complexes from tumor cells are almost entirely complexed with Hop and p23, and can be mimicked by reconstitution of a multichaperone complex (Kamal et al., 2003). Preferential GA binding contradicted by a more recent study that also shows time-dependence for GA binding (Gooljarsingh et al., 2006). However, see also effect of sumoylation (Mollapour et al., 2014).

♦ GA and ATP binding are mutually exclusive (Grenert et al., 1997).

♦ Sti1 binds to Hsp82 dimer as dimer and induces a large conformational change (Prodromou et al., 1999). Binding to Hop not affected by Hsp70, but vice-versa it is stimulated (Hernández et al., 2002b). Two molecules of Hop can bind Hsp90 dimer independently, but asymmetric trimer may be the favored form *in vivo* (Southworth and Agard, 2011). Hop monomer can bind Hsp90 dimer whereas FKBP52 can also bind Hsp90 monomer (Ebong et al., 2011; Ebong et al., 2016; see also Lott et al., 2020). Hop can bind both open and closed states of Hsp90β; its interaction with the C-terminal

domain induces a conformational change between the Hsp90β monomers (Lott et al., 2020).

- Molybdate effects: antagonizes some GA effects; inhibits lck biogenesis and luciferase refolding while promoting salt-stable complexes (Hartson et al., 1999).
- Molybdate and vanadate bind Hsp90 directly (Soti et al., 1998).
- One TPR acceptor site (composed perhaps of two half-sites with lower affinity) per Hsp90 dimer (at least for FKBP52) (Silverstein et al., 1999). Unlike Hop, FKBP52 can also bind Hsp90 monomer (Ebong et al., 2011; Ebong et al., 2016).
- May have low level proteolytic activities (Montel et al., 2000).
- Hsp90 promotes degradation of membrane-bound CYP2E1 by proteasome (Goasduff and Cederbaum, 2000), possibly by promoting membrane release and in ethanol-inhibited manner (Kitam et al., 2012). Also promotes degradation of mutant glucocerebrosidase (Lu et al., 2011; Yang et al., 2014a; Yang et al., 2015a) and oncoproteins ANP32C and ANP32D (Yuzefovych et al., 2015).
- Hsp90 - yeast cyclophilin or Sti1 binding constants 14-57 nM; measured with Hsp90 on BiaCore chip (Mayr et al., 2000). Binding constant for Hop is 90 nM (Hernández et al., 2002b).
- Hsp90 - immunophilin binding constants (55 and 226 nM) and stoichiometry (1:1) (Pirkl and Buchner, 2001). At high immunophilin concentrations, two molecules of FKBP51 or 52 or a mixture thereof can bind per Hsp90 monomer (Ebong et al., 2016).
- Two molecules of p23/Sba1 bind a dimer of Hsp90 and trap it in the ATP hydrolysis state (Richter et al., 2004; see also McLaughlin et al., 2006). Cocrystal clearly shows 2 molecules of Sba1 per Hsp90 dimer (Ali et al., 2006).
- Facilitates nuclear export of 60S ribosomal subunits in an in vitro assay; ATP helps but is not absolutely required (Schlatter et al., 2002).
- Strongly stimulates PP5 phosphatase activity (Ramsey and Chinkers, 2002) by releasing phosphatase domain from an inhibitory interaction with TPR domain (Yang et al., 2005). Additional contacts to M- and C-domains contribute (Haslbeck et al., 2015). MEEVD promotes folding of TPR domain suggesting a coupled folding-binding mechanism (Cliff et al., 2005). Hsp70 IEEVD motif has lower affinity, but stimulates PP5 activity more strongly than MEEVD (Connarn et al., 2014). Cryo-EM structure of Hsp90-c-Raf-Cdc37 with PP5 shows extended contacts between PP5 and the Hsp90 C-terminal domain (Jaime-Garza et al., 2023).
- Hsp90 - Cdc37 binding constants and stoichiometry (dimer : dimer) (Siligardi et al., 2002; Roe et al., 2004). With Cdk4 as client protein the stoichiometry is $(Hsp90)_2$-Cdc37-kinase (Vaughan et al., 2006).
- Substrate release stimulated by Tpr2 even without ATP (Brychzy et al., 2003).
- Mutation of CK2 phosphorylation site of Cdc37 (S13) blocks its ability to stabilize client-Hsp90-Cdc37 complexes (Shao et al., 2003) and to recruit Hsp90 (Miyata and Nishida, 2005). Complexes contain S13-phosphorylated Cdc37 and localize to membrane ruffles in EGF-stimulated cells (Miyata and Nishida, 2007). P-S13 is specifically de-phosphorylated by Hsp90-associated PP5/Ppt1 and cycles of phosphorylation appear important for client activation (Vaughan et al., 2008; Oberoi et al., 2016); dephosphorylation is required for client release (Oberoi et al., 2016).
- Some Hsp90 associated with membrane preparations may bind iron (Kovár et al., 2004).
- *Drosophila* Hsp83 identified in *in vitro* screen for membrane-deforming proteins (Uytterhoeven et al., 2015).
- Plant Hsp90 is retained by beads with phosphatidic acid (Testerink et al., 2004).
- Hsp90 catalyzes trans-cis isomerization of geldanamycin (Lee et al., 2004a), or perhaps not (Onuoha et al., 2007).

- Novobiocin induces distinct conformation of C-terminal domain, release of Hsp90 and Cdc37 but not other co-chaperones from substrate HRI; may induce "client-release" conformation (Yun et al., 2004). Inhibits binding of immunophilins, PP5 and Cdc37, chaperone activity and dimer formation (Allan et al., 2006).
- Prevents early stages of aggregation of amyloid β peptide (Aβ) in ATPase-dependent fashion *in vitro* (Evans et al., 2006). Binds tau amyloid structures directly through hexapeptide motif (one Hsp90 homodimer binding about 50) inhibiting both assembly and disassembly (Schirmer et al., 2016). Promotes (!) formation of tau aggregates/fibrils *in vitro*; ATP-dependent, strongly boosted by Aha1, and blocked by Aha1 inhibitor (Shelton et al., 2017a). In contrast, other *in vitro* experiments show that Hsp90 promotes formation of non-fibrillar nano-aggregates (Ferrari et al., 2020), an open tau conformation and prevents fibril formation (Weickert et al., 2020). Weakly binds Aβ40 monomers but inhibits growth of fibrils, inhibited by ATP binding (Wang et al., 2021a). Hsp70-Hop-Hsp90 binds tau and prevents aggregation; complex, which has variable stoichiometry, further stabilized by p23, which also interacts directly with tau, and disassembled by CHIP; phosphorylated tau only binds multichaperone complex, but not Hsp90 by itself (Moll et al., 2022). p23 competes with the MEEVD of Hsp90 for binding to the TPR of FKBP51, thereby promoting the formation of protective complexes with Tau (Chakraborty and Zweckstetter, 2025).
- Hydrogen-exchange mass spectrometry used to determine conformational dynamics, long-range interactions and effects of drugs and Cdc37 (Phillips et al., 2007), and orthosteric and allosteric effects of inhibitors in ATPase domain (Chandramohan et al., 2016).
- Covalent immobilization of Hsp90 to aminopropyl silica via either end for determination of binding affinities and ATPase activity (Marszall et al., 2008a).
- p23/Sba1 inhibits binding of GA to Hsp90 *in vitro* (Forafonov et al., 2008).
- no Hsp90α/Hsp90β-isoform specific interactions with a number of cochaperones (p23, immunophilins, Hip, Hop, Hsp70) and substrates detected (Taherian et al., 2008).
- Clients KEAP1, MET, Hsf1, HIF1α and RHOBTB1 preferentially interact with Hsp90α, some even with ATP-independent mutants, whereas drugs have a preference for Hsp90β (Prince et al., 2015) (for Hsf1, see also Kijima et al., 2018).
- GCUNC45 (UNC45A) preferentially binds Hsp90β *in vitro* (5x), unlike p23 and Hop that have identical affinities (Chadli et al., 2008b). UNC45B apparently does not have isoform specificity (Taipale et al., 2014).
- FKBP8 also displays Hsp90β specificity (Taipale et al., 2014) or perhaps not (Blundell et al., 2017).
- Hsp90α bound to magnetic beads can fish out proper ligands and proteins (Marszall et al., 2008a; Marszall et al., 2008b).
- Hsp90 cycle (see also above and under "Structure"): There are a series of conformational intermediates, some regulated by co-chaperones, and transitions are much slower than ATP hydrolysis (Hessling et al., 2009; comment in Neckers et al., 2009b). Single-molecule assays reveal very rapid stochastic and thermal conformational fluctuations, some of which are accelerated by ATP hydrolysis in a non-directional way (Mickler et al., 2009). Similar experiments reveal ATP-modulated dynamic opening and closing of the C-terminal domain that is anticorrelated with opening of the N-terminal domain (Ratzke et al., 2010). The opening is inhibited by Sti1. With previous results (Owen et al., 2002; Retzlaff et al., 2009), this suggests long-range communication between the N- and C-terminal domains. Mixed Sti/Hop-PPIase-Hsp90 complexes are a favored intermediate and the requirements for ATP and p23 to displace Sti/Hop give directionality to the process (Li et al., 2011c). Cpr6, but not Cpr7, promotes association of Aha1, which in turn drives Hsp90 to a partially closed state; together, Cpr6 and Aha1

displace Sti1, and p23 finally the release of Aha1 (Li et al., 2013b). Thermal fluctuations dominate the cycle and drive conformational changes and nucleotide binding (which on average happens multiple times before hydrolysis takes place); hence, conformational changes per se do not need ATP binding/hydrolysis (Ratzke et al., 2012a). Unlike the thermally driven conformational changes of eukaryotic Hsp90, the ratchet mechanism of the "cochaperone-independent" bacterial htpG is strongly nucleotide-controlled (Ratzke et al., 2012b). With eukaryotic Hsp90, co-chaperones such as p23 can impose directionality, with an asymmetric interaction of the two molecules of p23 with the Hsp90 homodimer and the specifics of the nucleotide turnover (Ratzke et al., 2014). A series of tyrosine phosphorylation on Cdc37 and Hsp90 drive ordered and directional assembly and disassembly, with Y197, Y313 and Y627 promoting dissociation of Cdc37, association of Aha1 and release of client, respectively, at least for human Hsp90α (Xu et al., 2012a). Phosphorylation of Cdc37 by Yes on Y298 leads to partial unfolding of its C-terminus unmasking an SH2-binding motif; this allows a high local concentration of Yes to target the Y197 switch and to promote the release of Cdc37 and specifically kinase substrates (Bachman et al., 2018). Effect of sumoylation (Mollapour et al., 2014). ATP hydrolysis in one protomer may be largely sufficient (Mishra and Bolon, 2014). GR HBD preferentially binds to the partially closed state and decelerates ATPase (Lorenz et al., 2014). Co-chaperones FNIP1/2 decelerate ATPase competing with Aha1, promoting client interaction (Woodford et al., 2016a; see also Sager et al., 2019). Single-molecule analyses of conformational motions reveal two-step mechanism for lid closure (Schulze et al., 2016). Stimulation of ATPase by Aha1 occurs in three steps, from a weak stimulation upon binding the middle domain to a N-terminal conformational rearrangement (Wolmarans et al., 2016). Confirmation by single-molecule analysis by SMACKS that N-terminal conformational dynamics are not coupled to ATP hydrolysis (Schmid et al., 2016). ATPase activity and *in vivo* activity in yeast do not correlate; what is important is a certain dwell time in the open state (Zierer et al., 2016). 3-color single-molecule FRET shows cooperativity of nucleotide binding of the two protomers and effects of Aha1 (Wortmann et al., 2017). Genetic and biochemical evidence that Sti1 promotes recruitment of client-loaded Hsp70 and client transfer through a conformational change of Hsp90 favoring N-terminal closure (Reidy et al., 2018). Conserved N-terminal NxNNWHW motif of Aha1/Hch1 affects affinity for nucleotides and stimulation of ATPase, and is required for *in vivo* functions in yeast (Mercier et al., 2019). Kinetic model based on FRET and NMR reveals Hsp90 is a "perfect" enzyme (Lee et al., 2019). Binding of TIMP2 increases affinity of ATP and inhibitors, but also inhibits ATPase (Baker-Williams et al., 2019). Genetic analysis in yeast with the hydrolysis mutant E33A suggest that what's important is the transition from the ATP-bound closed to the ADP-bound open state, either by hydrolysis or nucleotide exchange (Reidy et al., 2023). Single-molecule analyses with Ste11 as client show equilibrium of interactions with only Cdc37/Hsp90, but progression to closed complex (energy-driven directionality) with Aha1, Sba1, and ATP (Vollmar et al., 2024). Conformationally more dynamic β-strap F6D/F8D double mutant Hsp82 has lower ATPase activity, but stimulates wt subunit in heterodimer (Magnan et al., 2024). Overall, ATPase cycle and associated conformational transitions are conserved from yeast to human; the differences can be mapped to two residues (T13/A22 and S109/Q118 in yeast Hsp82/human Hsp90β, respectively), and swapping them also swaps the biochemical characteristics (Riedl et al., 2024). NMR analysis of various steps across cycle of htpG (Qu et al., 2024a).

- *C. elegans* Cdc37 binds both open and closed Hsp90 conformations, competes with Sti1 and p23, but can form ternary complexes with the phosphatase Pph5 and Aha1; nucleotide-induced closing of the Hsp90 N-terminus disrupts the latter ternary complex (Gaiser et al., 2010).

- Purification of Hsp90 complexes with PU-H71-beads selectively enriches for oncoprotein-Hsp90 complexes and complexes with a subset of co-chaperones (Moulick et al., 2011). Other types of inhibitors may not trap anything (Barrott et al., 2013). A fluorescent probe specfic for the cytosolic Hsp90 isoforms induces the internalization of eHsp90 into punctate structures specifically in transformed cells (Crowe et al., 2017). Labelling particularly high in aggressive and glycolytic breast tumors (Crouch et al., 2017).
- PU-H71 and GA trap Hsp90 in different N-terminally undimerized conformations, the former being preferentially able to bind the Y197-phosphorylated form as well as Cdc37 and some substrates (Beebe et al., 2013). PU-H71-beads pull out viral proteins, notably vFLIP, of Kaposi sarcoma-associated herpes virus (KSHV) (Nayar et al., 2013).
- A model substrate facilitates a repositioning of the N-terminal versus the middle domain through cross-monomer contacts with both (Street et al., 2012).
- Initiator methionine of both Hsp90α and Hsp90β is removed in cells (Beck et al., 2012).
- Although interaction of Cpr6 and Cpr7 with Hsp90 is normally ATP-dependent (see also Johnson et al., 2007), they interact independently of nucleotide with Hsp90 lacking the charged linker domain, and Cpr6 binds even wt Hsp90 in the absence of Cpr7 suggesting that Cpr7 mediates a conformational signal to relay the nucleotide status to the C-terminal TRP-binding domain (Zuehlke and Johnson, 2012).
- Hsp90 increases efficiency of targeting of tail-anchored proteins to chloroplasts *in vitro* (Kriechbaumer and Abell, 2012).
- Binds the chlorophyll biosynthetic intermediate Mg-protoporphyrin IX and mediates this stress signal; inhibited by tetrapyrrole accumulation (Kindgren et al., 2011; Kindgren et al., 2012).
- High affinity interaction of Cdc37 (and by extension Cdc37-Hsp90) inhibits ATP binding to Cdc37-dependent kinases and conversely, ATP-competitive kinase inhibitors prevent interaction with Cdc37-Hsp90 ("chaperone deprivation", primarily of nascent kinases) eventually resulting in degradation (Polier et al., 2013).
- Fission yeast *S. pombe* Hsp90 is able to refold thermally denatured luciferase in ATP-stimulated manner (Ishida et al., 2013).
- Detailed analysis of the interactions of Toc64, OM64 and AtTPR7 with the Hsp70s and Hsp90s in *Arabidopsis* shows differences (Schweiger et al., 2013; see also Panigrahi et al., 2013). OM64, whose TPR-mediated interaction with Hsp90 is inhibited by phosphorylation, may replace Tom70 in plants (Nickel et al., 2019).
- Specificity and selectivity of binding of CHIP, Hop, DnaJC7, FKBP51, and FKBP52 to C-terminus is influenced by affinity and possibly phosphorylation N-terminal of MEEVD (Assimon et al., 2015).
- C-terminal sumoylation of FKBP51 stimulates interaction with Hsp90 and repression of GR (Antunica-Noguerol et al., 2016).
- The epichaperome (integrated chaperome units) of certain types of cancers, as defined by what PU-H71 beads can pull down and migration in native gels, is due to chaperome network rewiring by c-Myc activity (Rodina et al., 2016; see also Calvo-Vidal et al., 2021).
- Hsp90 dissociates the chromatin remodeler RSC from DNA, but unlike p23 does not stimulate the completion of nucleosome remodeling; this biochemical activity is mirrored by continued RSC activity on chromatin and persistent DNase I hypersensitive sites *in vivo* with G170D at restrictive temperature (Echtenkamp et al., 2016). Destabilizes assembly of INO80 and SWR-C complexes with DNA cooperatively with p23 (Sba1); Hsp90 and p23 dissociate SWR-C from F-actin and bias INO80 to binding F-actin in the presence of H2A.Z-containing nucleosomes (Wang et al., 2020a).
- Yeast Hsp90 required *in vivo* for stability of a wide range of transcription factors and *in vitro* for their DNA binding (Gvozdenov et al., 2019a).

- Expression of NOD1 as fusion protein with SGT1 and coexpression with mammalian Hsp90α improves its expression in *E. coli* (Hong and Hahn, 2016).
- Allosteric regulation points modulate conformational dynamics and ATPase activity (Rehn et al., 2016).
- Protocol for producing human Hsp90β in bacteria (Radli et al., 2017).
- Hsp90 in yeast may be a substrate of the N^{α}-terminal acetylase NatA, and in its absence of the Arg/N-end rule degradation pathway (Oh et al., 2017).
- Hsp90 binds with high affinity (low nM range) to phospholipids with a preference for negatively charged and unsaturated ones; this reduces the fluidity and increases the transition temperature of membranes (Zhang et al., 2018a). Hsp90α penetrates deep into phospholipid membrane through its C-terminal domain, loses part of its α-helical core, and overexpression in *E. coli* improves membrane integrity upon heat treatment (Li et al., 2019a).
- Interaction with AIPL1 is stimulated by ATP and depends both on the FKBP-like and TPR domains of AIPL1; mutants unable to interact with Hsp90 cause a retinal degeneration (Sacristan-Reviriego et al., 2017; Sacristan-Reviriego et al., 2020; see also Yadav et al., 2022b).
- p23 binds Hsp90α with 3x stronger affinity than Hsp90β and this is mediated by stronger dimer closure due to Hsp90α-specific middle domain (Synoradzki et al., 2018).
- Hsp90β preferentially binds Ni-NTA over Co-NTA and Ni^{2+} promotes release of HIF-1α (Asakawa et al., 2018).
- Evolutionary conserved W300 of yeast Hsp82 (and equivalent of human Hsp90β) functions as a conformational switch point relaying "information" about client binding from the middle to the N-terminal domains through a cation-π interaction with a neighboring lysine (Rutz et al., 2018).
- Dimeric Hsp90, in open conformation, independently of ATP binding and hydrolysis, binds and deforms membranes through an amphipathic α-helix in the M domain; required for exosome release from multivesicular bodies (Lauwers et al., 2018).
- Hsp90 associates with liposomes containing negatively charged phospholipids through Hsc70, but not by itself (Dores-Silva et al., 2021).
- Hsp90-associated proteins are bound less tightly as pluripotent stem cells differentiate into dopaminergic neurons and this is counteracted by genetic or pharmacological stress (Kishinevsky et al., 2018).
- Hsp90 acts as a dynamic scaffold to bring together the PPIase of FKBP51 and Tau in a pro-toxic complex (Oroz et al., 2018).
- Single-molecule analyses reveal two dissociation rates for C-terminal dimerization, which is dependent on ATP (Tych et al., 2018).
- Single-molecule analyses show conformational dynamics on the time scale from seconds to hours (Ye et al., 2018).
- Conformational dynamics studied with plasmonic imaging of single nanoparticles (Wang et al., 2024f).
- Interaction with Cns1 is through its TPR domain and not modulated by nucleotides (Schopf et al., 2019).
- Complex of Hsp90-Cns1-Hgh1, possibly with Cpr7, chaperones eEF2 (Schopf et al., 2019; see also Fulton et al., 2024).
- Comprehensive comparison of the two *S. cerevisiae* isoforms: Hsp82 is more heat-stable than Hsc82, the latter has faster N-terminal closing and slightly higher ATPase activity, but co-chaperone binding is similar (Girstmair et al., 2019).
- Human Hsp90α is also thermally more stable than Hsp90β while Hsp90β is strongly stabilized by ligand binding (Ausili, 2023).

- Purification protocols for portions of recombinant human Hsp90α (Aluksanasuwan et al., 2020).
- Motor activity of yeast type I myosin Myo3 depends on Hsp90 and She4 (Wang et al., 2020a).
- Hsp90 promotes unconventional protein secretion *in vitro* possibly by promoting ATP-dependent unfolding of cargo (Zhang et al., 2020a).
- Hsp90 binds cholesterol, possibly through the first 300 amino acids (Kumar et al., 2020).
- Comparative study of how mutation, Aha1 interaction, and crowding affect conformational flexibility and ATPase (Schmid and Hugel, 2020).
- Refolding of luciferase *in vitro* and *in vivo*, both in yeast and human cells, works better without Hop/Sti1, dependent on direct interaction of Hsp90 and Hsp70 (Bhattacharya et al., 2020).
- NudC can form a complex with Hsp40 and Hsp90 with a 2:2:2 stoichiometry; it promotes direct client transfer from Hsp40 to Hsp90 by binding Hsp40, Hsp90 and to some extent the client, and by preventing Hsp70 binding; p23 is not required for the NudC-mediated maturation of the GR-LBD (Biebl et al., 2022).
- *C. elegans* CDC-37 binds DNJ-13 and together more strongly to Hsp90, preferentially in its open state (Schmauder et al., 2021).
- Triiodothyronine (T3) enhances ATP binding to Hsp90 (Fan et al., 2022c), by binding to β-sheet near ATP binding pocket, trapping ATP, but also inducing release of TRβ bound to Hsp90 (Fan et al., 2022b).
- Single-molecule experiments with optical tweezers show for two different clients and both bacterial and human Hsp90 that Hsp90 promotes local contractions/compaction in the unfolded substrate chains, stimulated by ATP, suppressing the formation of misfolded and aggregated structures (Mashaghi et al., 2022).
- Crosslinking mass spec and mutagenesis demonstrates ternary complex formation of *E. coli* HtpG, DnaK, and the J-domain protein CbpA, and binary complexes of HtpG with CbpA and DnaJ, and yeast Hsp82 with Ydj1 (Wickramaratne et al., 2023).
- one or two Aha1 molecules can bind to one Hsp90 dimer with the binding stoichiometry affecting Hsp90 conformation, kinetics, ATPase activity, and stability; two Aha1 molecules coordinate to stimulate the ATPase and the unfolding of the middle domain (Mondol et al., 2023).

Structure:

Top Refs

- Crystal structure of N-terminal domain (AA 9-232) of human Hsp90α containing geldanamycin binding pocket (Stebbins et al., 1997) and AA 1-220 of yeast Hsp82 with adenine nucleotide binding site (Prodromou et al., 1997a; Prodromou et al., 1997b; revised view in Prodromou et al., 2000). Reviewed by Joachimiak, 1997. Structure of N-terminal domain of human Hsp90 with ATPγS (Obermann et al., 1998). Radicicol and geldanamycin co-crystals (Roe et al., 1999). Cocrystal with GA derivative (Jez et al., 2003). Comparative structures of N-terminal domain of human Hsp90α without ligand and with ATP and AMPPCP (Li et al., 2012b). N-terminal domain of rice Hsp90 (Raman and Suguna, 2015).
- By NMR, p53 core domain bound to Hsp90 is predominantly unstructured (Rüdiger et al., 2002). p53 DBD adopts loosened molten globule-like state upon interaction primarily with the Hsp90 N and M domains (Park et al., 2011a; see also Park et al., 2011b). Others find no evidence of conformational changes, p53 being bound in a native-like state based on shape and charge (Hagn et al., 2011). p53 DBD is positioned near middle domain (Quintana-Gallardo et al., 2019). Secondary structures in charged linker (yeast Hsp82)

can transiently interact with a strand of the NTD, displacing it and thereby promoting binding of a hydrophobic patch of NTD to p53 (López et al., 2021).

- Backbone assignments of ATPase domain by NMR (Sale et al., 2002); NMR shows conformational changes upon ligand binding (Dehner et al., 2003).
- Crystal structure of middle domain (AA 273-525) of yeast Hsp82 and model of combination with N-terminal domain (Meyer et al., 2003).
- Cocrystal of N-terminal domain with Cdc37 (Roe et al., 2004); solution structure analysis of complex (Zhang et al., 2004b). Crystal structure and NMR analysis of interacting domains (Sreeramulu et al., 2009). Detailed mutational analysis of interface by split renilla assay (Jiang et al., 2010). In *C. elegans*, the N- and C-terminal domains of Cdc37 interact with the M-domain of Hsp90 and kinases, respectively, promoting cooperative binding (Eckl et al., 2015).
- Cocrystal of middle domain with N-terminal domain of Aha1 (Meyer et al., 2004).
- Structure of C-terminal domain and model of entire htpG (Harris et al., 2004).
- N- through middle domains of htpG without nucleotide and with ADP (Huai et al., 2005; and comments in Bracher and Hartl, 2005). Shows (i) eukaryotic charged linker may be looped out from N-domain, (ii) nucleotide binding domain is made up from both N- and middle domains, (iii) ADP induces conformational changes.
- Structure of C-terminal TPR binding tail with Hop (Scheufler et al., 2000), PP5 (Cliff et al., 2005; Cliff et al., 2006; see also Haslbeck et al., 2015), CHIP (Zhang et al., 2005a; see also Quintana-Gallardo et al., 2019 and there for additional contacts with Hsp90 middle domain), and *Plasmodium* FKBP35 (Alag et al., 2009).
- Cryo-EM structure of p53 DBD-Hsp90-CHIP complex shows the client between Hsp90 and CHIP (Quintana-Gallardo et al., 2019).
- Full-length structure in ATP-bound mode and complex with p23/Sba1 shows intimate contacts in N-terminal domain with closed lid and absence of space for substrate between monomers in the "middle" (Ali et al., 2006).
- NMR analysis of p23-Hsp90 complex; no effect of ATPγS and interactions with middle domain of Hsp90 (Martinez-Yamout et al., 2006). H/D exchange NMR analysis of Aha1-Hsp90 complex (Dyson et al., 2008). Domain details of interaction of Aha1 with Hsp90 studied with NMR (Retzlaff et al., 2010; see also Oroz et al., 2019) and various other techniques (Koulov et al., 2010). Complex with p23 not fully symmetric and p23 also induces conformational changes in Hsp90 (Karagöz et al., 2011).
- EM analysis of Hsp90-Cdc37-Cdk4 complex shows asymmetric ring-like shape with Cdk4 bound to outside of one Hsp90 molecule and bridging N-terminal and middle domains (Vaughan et al., 2006). More recent cryo-EM structure is different showing stabilization of inactive monomeric form by binding unfolded N-lobe (Verba et al., 2016). Cryo-EM structure of Hsp90-Cdc37-Cdk4 complex reveals unexpected features and explanations for the effects of Cdc37 phosphorylation and substrate recognition: Cdc37 binds middle domain of closed Hsp90 conformation (possibly after rearranging from N-terminal contacts upon initial binding to Hsp90); Cdc37 mimics features of client kinase; client kinase and Cdc37 thread through and wrap around Hsp90, respectively (Verba et al., 2016).
- Crystal structure and EM analysis of full-length htpG reveal several different conformations from open apo-protein to ADP- and ATP-bound protein (Shiau et al., 2006; discussed by Richter and Buchner, 2006). SAXS analysis of htpG structure in solution shows apo-htpG is more extended and AMPPNP-htpG is in equilibrium between open and closed states (Krukenberg et al., 2008); structural analysis of full-length eukaryotic apo-Hsp90 by SAXS and cryo-EM reveals an equilibrium between two open states (Bron et al., 2008) (see discussion in Jackson, 2008). Effects of osmolytes on these transitions (Street et al., 2010). Single particle analysis shows species-dependent

equilibrium between extended apo state and more compact/closed nucleotide-favored states, with human being primarily in the open state even in presence of ATP (Southworth and Agard, 2008). HX-MS and fluorescence spectroscopy show progression of ATP-induced conformational changes through htpG that are rate limiting for ATP hydrolysis (Graf et al., 2009). Low pH drives htpG into a Grp94-like closed state that can be modeled with His mutants and has increased chaperone activity (Krukenberg et al., 2009). A model substrate induces partial closure of apo-Hsp90 and accelerates open/closed transition and ATP hydrolysis (Street et al., 2011).

- Comparison with Grp94 structure (Richter et al., 2007b).
- Modeling of C-terminal domain with inhibitors (Sgobba et al., 2008).
- Structure of Hsp90 in complex with CS domain of SGT1 and CHORD-I domain of RAR1 by NMR (Kadota et al., 2008) and with CS by crystal structure analysis (Zhang et al., 2008a). Structure of Hsp90-CS-CHORD ternary complex (Zhang et al., 2010c). CD shows a symmetric complex with 2:2:1 stoichiometry for Sgt1-Hsp90-Rar1(Siligardi et al., 2017) .
- Crystal structure of N-terminal domain of *Dictyostelium* Hsp90 (Sawarkar et al., 2008).
- Modelling of conformational dynamics of N-terminal domain (Colombo et al., 2008) and full-length dimer (Morra et al., 2009). Molecular dynamics simulations of apo and nucleotide-bound htpG, yeast Hsp82 and Grp94 reveal two hinges, including a new one at the end of a 3-helix bundle in the middle domain (Morra et al., 2012). Mechanistic model of Hsp90 dynamics and regulatory interactions (Dixit and Verkhivker, 2012; Blacklock and Verkhivker, 2014b). Molecular dynamics modeling of allostery in htpG (Seifert and Grater, 2012). Molecular dynamics simulations show large conformational changes, with and without nucleotide, apparently guided by electrostatic interactions between subunits (Simunovic and Voth, 2012). Computational study of dynamics and allosteric communication in complexes with Aha1 and p23 (Blacklock and Verkhivker, 2013), and of reorganization of lid by cochaperones (Blacklock and Verkhivker, 2014a). More modelling showing communication hubs (Penkler et al., 2018). Novel allosteric regulatory sites and candidate compounds (Penkler and Tastan Bishop, 2019). Domain interactions also influence MC dynamics (Kandzia et al., 2019). Correlating allosteric and functional effects (D'Annessa et al., 2019). Molecular dynamics analysis of crosstalk between ATP pocket, client binding site, remodeled client, and co-chaperone (D'Annessa et al., 2021). Conserved network of allosteric switches and preexisting conformational states of the Hsp90 dimer are exploited by co-chaperones and GR as a client (Verkhivker, 2022a; Verkhivker, 2022b). MD simulations, NMR, and mutagenesis argue for transient existence of metastable exited state of isolated N-terminal ATP-binding domain with lid in closed conformation (Henot et al., 2022). MD analyses of GR-Hsp90 loading and maturation complexes reveal how Hsp90 and co-chaperones cooperate to (pre)organize partially folded GR (Castelli et al., 2023). Modelling allows prediction of dissociation rate constants for N-terminal inhibitors, and experimental evidence suggests that different ligands can undergo conformational selection or alter the equilibrium of conformations (Xu et al., 2024a).
- Hydrolysis of one ATP leads to allosteric changes throughout the molecule, notably through Arg380, and results in an asymmetric novel collapsed state (Wolf et al., 2021).
- Comparative structures of N-termini of Grp94 and yeast Hsp82 with different inhibitors reveals significant paralog-specific differences including conformational changes (Immormino et al., 2009).
- Comparative analysis of enthalpic contributions to binding of different ligands to N-terminus (Nilapwar et al., 2009).
- see also Hsp90 cycle.

- Crystal structure of N-terminal domain of Hsp90 of *Plasmodium falciparum* Hsp90 (Corbett and Berger, 2010). Characterization of structure of full-length (*P. falciparum*) with a variety of biochemical methods (Silva et al., 2020).
- Dimers of N-terminally truncated human Hsp90α are the building blocks of a hexameric assembly in the crystal (Lee et al., 2011) with residue W320 playing an important role at the hexameric interface (Peng et al., 2022b).
- EM and cryo-EM structures of Hop-Hsp90α complex (Southworth and Agard, 2011). It shows that one molecule of Hop makes extensive contacts with the Hsp90 dimer to promote an alternate open state that is poised for Hsp70 binding, client loading and ATP hydrolysis. Cryo-EM structure of GR-Hsp90-Hsp70-Hop complex (Kirschke et al., 2014). Several structures indicating substrate (GR LBD) transfer from Hsp70 to Hsp90 machinery, highlighting notably that GR binds Hsp90 dimer opposite of Hop (Alvira et al., 2014). Cryo-EM structures of the GR loading complex (Wang et al., 2022b) and GR maturation complex (Noddings et al., 2022) reveal: of two Hsp70 molecules bound, one delivers the GR HBD, the other scaffolds Hop; GR is partially unfolded and the N-terminal end is threaded through the Hsp90 lumen; Hsp90 is in a semi-closed conformation (through contact with the DP2 domain of Hop) with already rotated NTD; Hop is wrapped around and with DP2 also makes contact with the client; in the maturation complex, with its N-terminus still in the Hsp90 lumen, the GR HBD is ligand-bound and helix 12 in the active position; only one molecule of p23 is bound, which also interacts with GR through a helical part of its tail. Cryo-EM structures of Hsp90 with GR and FKBP51 or FKBP52 (Noddings et al., 2023): GR HBD is in ligand-bound fully folded state, but rotated in this stage advanced stage than in the afore-mentioned maturation complex, possibly facilitating GR HBD dimerization and other interactions; FKBP52 extensively interacts/cradles the GR HBD; FKBP52 allosterically interferes with p23 binding; FKBP inhibitors would clash with the GR interaction; interactions of the two FKBPs are analogous except for an altered GR-FKBP51 FK1 interface, notably around the divergent residue 119, explaining how FKBP51 is a potent inhibitor of GR function. Characterization of FKBP- and p23-containing GR-Hsp90 complexes *in vivo* by crosslinking of photoactivatable amino acid analogs at a large number of sites shows extensive contacts of FKBP51/52 with GR (FKBP51 wrapping around GR HBD), direct contacts of p23 with GR, and Hsp90-dependence of these interactions (Baischew et al., 2023b). See above for MD analyses of GR loading and maturation complexes (Castelli et al., 2023)
- Structure of UNC-45 reveals formation of chains with a potential for periodic binding of Hsp90 through C-terminus (Gazda et al., 2013).
- Solution structure analysis of the Aha1-Hsp90 complex (Seraphim et al., 2013), and of the open and closed conformation of Hsp90 (Seraphim et al., 2017) of *Leishmania braziliensis*.
- Crystal structure of NTD of *T. brucei* Hsp83 with several selective inhibitors (Pizarro et al., 2013).
- TRAP1 structure revealed an asymmetry in the closed state because of a helix swap at the middle-C-terminal domain interface that is also present in htpG (Lavery et al., 2014).
- NMR/SAXS analysis of Tau-Hsp90 interaction reveals a broad interaction surface with discontinuous contacts, only marginally affected by ATP binding (Karagöz et al., 2014).
- NMR/EM/SAXS analysis reveals extended contacts of GR HBD across N- and mostly M-domains, partially overlapping with Aha1 N-domain interactions (Lorenz et al., 2014).
- 7-azaindole derivatives can exploit differences in conformational dynamics at the base of the lid of *Plasmodium* Hsp90 relative to human (Wang et al., 2014a).
- Prediction by molecular dynamics of the novobiocin-type binding site in the C-terminus based on dynamic fluctuations induced by N-terminally bound ATP (Moroni et al., 2014).

- htpG adapts its conformation to a model substrate and in turn remodels the substrate (Street et al., 2014).
- Structure of complex with Tah1 and the metazoan Spagh/RPAP3 (Pal et al., 2014); shows how a Tah1 helix-swap allows binding of the five-helix TPR (Morgan et al., 2015). Structure of R2TP complex shows binding mode of the Pih1-Tah1 heterodimer to a Rvb1-Rvb2 hetero-hexamer and how this may connect it to clients and Hsp90 (Rivera-Calzada et al., 2017; commented in Eickhoff and Costa, 2017). Structure of R2TP core shows how RPAP3 provides a flexible tether for Hsp90 (Martino et al., 2018). Structure of RPAP3 TPR with TRBP shows how binding of TRBP to RPAP3 and Dicer is mutually exclusive (Abel et al., 2022).
- NMR analysis of dynamics of N-terminal domain bound to different ligands (Zhang et al., 2015a).
- Structure of N-terminal domain with a peptide ligand in ATP pocket (Raman et al., 2015).
- Folding kinetics of Hsp90 with single-molecule experiments (Jahn et al., 2016). High resolution structure and dynamics with FRET (Hellenkamp et al., 2017).
- Two-colour smPET fluorescence microscopy shows coordinated conformational motions (Schubert et al., 2021).
- Various biophysical methods show how fast local fluctuations and molecule-spanning dynamics may ultimately explain large allosteric changes (Sohmen et al., 2023).
- Crosslinking / mass spec analysis of effects of Hsp90 inhibitors on conformation and chaperone and client interactions also reveals *in vitro*/*in vivo* and drug-specific differences (Chavez et al., 2016).
- Structural studies and modelling of Tom70-Hsp90 interaction (Zanphorlin et al., 2016).
- Cocrystal of FKBP8 with MEEVD (Blundell et al., 2017).
- NMR structure of htpG (Pederson et al., 2017).
- Cocrystal structure and molecular dynamics of FKBP51 with MEEVD (Kumar et al., 2017).
- Structure of full-length human Hsp90β with FKBP51 and with/without Tau shows an extended Hsp90-51 interaction surface and N-terminal positioning of Tau and PPIase; binding site of Tau does not overlap with co-chaperone binding sites (Oroz et al., 2018).
- Cryo-EM structure of human Hsp90-immunophilin-p23 complex shows Hsp90 dimer in closed state with one FKBP51 binding to MEEVD and with a helix extension of TPR domain across dimer interface, strategically positioning the PPIase domain for potential interaction with clients; complex further stabilized by one p23 molecule per Hsp90 dimer (Lee et al., 2021).
- Differences in folding and domain interactions of three isoforms (Jahn et al., 2018).
- Favorable entropic contribution arises from conformational flexibility of Hsp90 in the drug-bound state (Amaral et al., 2017).
- Impact of changing K112 of human Hsp90α to R as in *Leishmania braziliensis* (Tassone et al., 2018).
- D93 (of Hsp90α) makes the most important energetic contribution to binding inhibitors (Hoxie and Street, 2020).
- Model of direct interaction of DnaK and HtpG suggests residues for allosteric signaling and an asymmetric interaction favoring substrate orientation and release to HtpG (Grindle et al., 2021).
- NMR analysis of binding of Hsp90 inhibitors (both N- and C-terminal) (McConnell et al., 2021).
- Comparison of RT and cryo structures reveals changes in water networks and unique ligand binding signatures that disappear upon cryo-cooling (Stachowski et al., 2022).
- Extended conformational ensemble is crucial for open state and modulated by charged linker (Jussupow et al., 2022).

- Cryo-EM structure of Hsp90-Cdc37-Raf1 complex reveals similarities with Cdk4 complex; Raf1 N- and C-lobes are separated with the hydrophobic core of the former in the Hsp90 dimer; Cdc37 wraps around Hsp90 and interacts with both lobes, and S13 phosphorylation of Cdc37 is essential (García-Alonso et al., 2022). Cryo-EM structures of Hsp90-Cdc37-BRAF (oncogenic V600E mutant), and the same complex with PP5 show how the latter is positioned to fully dephosphorylate client kinases (Oberoi et al., 2022). Cryo-EM structure of Hsp90-c-Raf-Cdc37 with PP5 provides further insights into the platform function of PP5 for kinase dephosphorylation and reveals that kinase client sterically interferes with dephosphorylation of Cdc37, such that the kinase must leave first (Jaime-Garza et al., 2023). Structure of Hsp90-Cdc37-Raf1 shows unfolded Raf1 N-lobe threaded through center of Hsp90 dimer, with Raf1 bound asymmetrically and Raf1-Hsp90 bridged by Cdc37 (Finci et al., 2024).
- Study of impact of ligands of ATP-binding pocket on lid conformations reveals substantial plasticity of Hsp90α (Stachowski and Fischer, 2022).
- Cryo-EM structure of ligand-bound AhR-Hsp90-XAP2 complex shows AhR threaded through lumen of closed Hsp90 dimer and XAP2 positioned as a (biochemically dispensable) brace (Gruszczyk et al., 2022). MD analysis of AhR-Hsp90 complex and impact of AhR ligands (Rosales-Hernandez et al., 2023). Cryo-EM structure of $Hsp90_2$-AhR-$p23_2$ with and without XAP2 shows AhR bridge motif (linker between the two PAS domains makes contacts in the lumen of the Hsp90 dimer and PAS-B domain makes additional contacts with Hsp90 (Wen et al., 2023).
- MD analysis of loop-to-helix transition of the plastic region of α-helix 3 in the N-terminal domain of Hsp90 (Gohda, 2022).
- Cryo-EM structure of AIPL1-Hsp90 complex shows client-like interaction of AIPL1 N-terminus with Hsp90 dimer lumen, of FKBP-like domain with Hsp90 dimer interface, and of TPR domain with MEEVD tail (Srivastava et al., 2023).
- Systematic analysis of binding of pan-Hsp90 ligands to all four human Hsp90 isoforms reveals isoform differences (Stachowski et al., 2023).
- Cryo-EM structure of GC-C expressed in CHO cells; first membrane protein and non-kinase client of Hsp90-Cdc37; "C-lobe of the pseudokinase domain packs against the N-terminal region of Cdc37 on one face of the dimeric Hsp90 core, with the N-lobe unfolding through the dimer core to interface with the MD of Cdc37 on the opposite face" (Caveney et al., 2023).
- Structure of Hsp90 dimer of insect cells in semi-open state (Finci et al., 2024).
- NMR analysis of client-Hsp90 interactions for htpG, yeast Hsc82, and human Hsp90β show a bipartite mode of interaction with disordered client domains through opposite middle domains (Qu et al., 2024b). Further NMR analysis of htpG show impact of ATP and client binding; ATP promotes distinct conformational transitions to closed state, while ATP hydrolysis, which does not require closure, drives the formation of a compact state, and client binding functions as allosteric switch, priming htpG for higher chaperone activity (Qu et al., 2024a).

Hsp90 chaperone machine:

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- promotes folding of proteins (some w/o ATP !!!) (Shaknovich et al., 1992; Wiech et al., 1992) and prevents protein unfolding and aggregation (Miyata and Yahara, 1992; Jakob et al., 1995a; Jakob et al., 1995b) by binding early unfolding intermediates (Jakob et al., 1995a) and preventing their aggregation. Maturation of lck (Hartson et al., 1996) and luciferase (Schneider et al., 1996; Thulasiraman and Matts, 1996) in retic. lysate inhibited by GA. GA promotes shift from folding to degradation of Hsp90 substrates like luciferase and Raf both in vitro and in vivo (Schneider et al., 1996). Cooperates with Hsp70 and

DnaJ in *in vitro* folding (Schumacher et al., 1996). ATP binding mutants have some residual luciferase refolding activity (Grenert et al., 1999). Ydj1 important for positive effect of Hsp90 on luciferase refolding in multicomponent system and for functional transfer of substrate from Hsp70 to Hsp90 (Wegele et al., 2006). Overcomes folding block of high (physiological) levels of Hsp70 *in vitro* with ATP-dependence being limited to the earliest phase of folding (Morán Luengo et al., 2018). Yeast Hsp70 isoform Ssa2 is more efficient than Ssa4 for luciferase refolding, which correlates with its Ydj1 binding (Gaur et al., 2020). Hsp90 works as ATP-driven chaperone for non-equilibrium protein folding, breaking different symmetries than Hsp70 (Xu, 2022).

- There is a balance between folding and degradation involving mutually exclusive Hsp90-HOP and Hsp90-CHIP complexes, respectively, determined by intracellular concentrations and affinities (Kundrat and Regan, 2010a).
- ATP-independent protection of tubulin against thermal denaturation and maintenance for polymerization; stoichiometry is 2:1 Hsp90:tubulin (Weis et al., 2010). Holdase function for bacterial tubulin homolog FtsZ also ATPase-independent (Balasubramanian et al., 2019).
- holds denatured proteins in folding competent state for other molecular chaperones (Freeman and Morimoto, 1996; Yonehara et al., 1996; see also Minami and Minami, 1999; Minami et al., 2000). Hsp90, Hsc70, Hsp40, and the proteasome activator PA28 are sufficient (Minami et al., 2000).
- *E. coli* htpG joins DnaK to remodel synergistically some substrates such as luciferase, after an initial action of DnaK (Genest et al., 2011). Cyanobacterial htpG binds to and collaborates with DnaJ2 and DnaK2 in substrate-specific holding/refolding (Nakamoto et al., 2014) in a pH-dependent fashion (Akter and Nakamoto, 2021)(see also Mangla et al., 2023). Luciferase refolding with yeast proteins requires Sti1 and is defective for Hsp70-binding mutants of Hsp82 (Kravats et al., 2018). Synergizes with DnaK complex and ClpB for refolding and activation of substrates, notably at high/physiological concentrations of DnaK; activity requires its ATPase hydrolysis, DnaK binding, and substrate binding (Hoskins et al., 2025).
- Substrate recognition: preference for early unfolding intermediates (Jakob et al., 1995a). Point mutations in Polo-like kinase I may point out binding site/specificity (Simizu and Osada, 2000). Several domains can bind short peptides in vitro (see "Domain mapping"; and Ishiwatari-Hayasaka et al., 2003). Short survivin peptide competes for binding of full-length, and a point mutant of full-length fails to bind (Fortugno et al., 2003). In kinases, it may recognize a hinge/loop region in the N-terminal lobe (Tikhomirov and Carpenter, 2003; Citri et al., 2004a; Xu et al., 2005; see also discussion in Citri et al., 2004b; Citri et al., 2006; Wang et al., 2014b). In Lck and HRI Hsp90 and Cdc37 also recognize primarily the N-terminal lobe, but more is required to form a salt stable compex; Hsp90 may facilitate folding by breaking interactions between subdomains (Scroggins et al., 2003; Prince and Matts, 2004). Similar results with Cdk2 (Prince et al., 2005b). Hsp90 may recognize distinct motifs of nascent versus mature kinase clients such as ErbB2 (Xu et al., 2005). Truncations of JNK trigger differential binding of Hsp90 and Cdc37 (Prince and Matts, 2005). Recognition depends on surface features within αC-β4 loop rather than sequence; substrates tend to have overall positive charge (Citri et al., 2006). Short peptide sequence appears to be Hsp90 binding site in eNOS (Xu et al., 2007a) and in IP6K2 (Chakraborty et al., 2008). Mapping of short peptide sequence, including the αC-β4 loop, proximal to PXXP motif in PKCs (Gould et al., 2009). htpG recognizes a locally structured region in a globally unfolded model substrate (Street et al., 2011). Some overlap of of residues required for ligand binding and Hsp90 binding in AhR (Soshilov and Denison, 2011). Part of the p53 interaction surface on Hsp90 resembles DNA in charge and surface (Hagn et al., 2011). Binds the oxygenase domain of nNOS, which

contains the heme/substrate binding cleft (Peng et al., 2012). Survey of large number of kinases, E3 ligases and transcription factors by immunoprecipitation reveals high proportion of structurally diverse and unrelated kinases as clients; most Cdc37-dependent; the key determinant is thermodynamic stability (lability) and not primary sequence; destabilizing mutations or stabilizing small molecule ligands increase and decrease interaction, respectively (Taipale et al., 2012; see also Taipale et al., 2014), and this does not correlate with activity (Kancha et al., 2013). This can be exploited as a drug screening tool (Taipale et al., 2013; see also Cho et al., 2020). Binding of Hsp90α to AKR1B10 requires a specific helix (Luo et al., 2013). Hsp90 provides a large surface across N- and M-domains with discontinuous contacts to recognize late folding intermediates or intrinsically disordered proteins such as Tau (Karagöz et al., 2014). Hsp90 can recognize a native protein by interacting with partially folded states that are only transiently populated (Street et al., 2014). LRR, Argonaute, and β-propeller fold proteins associate primarily with co-chaperones SGT1, p23 and PP5, and NUDC family members, respectively, along with Hsp90 (Taipale et al., 2014). Of the latter, NUDC, NUDCD2, and NUDCD3 prefer WD40 repeats, RCC1 repeats and Kelch domains, respectively (Taipale et al., 2014). Hsp90-dependence of v-Src vs. c-Src correlates with compactness and folding cooperativity (Boczek et al., 2015; see also Luo et al., 2017); further insights from large scale analysis of Src variants of the catalytic domain (Nguyen et al., 2023). Cdc37 acts as a substrate recognition factor to select Hsp90-dependent kinases by "sensing" their conformational instability (Keramisanou et al., 2016) or their propensity to an open state with separated N- and C-lobes (Verba et al., 2016). A dynamic equilibrium of Cdc37 between an extended and a more compact conformation (both on and off Hsp90) is important for client loading, and client dynamics predispose it to getting trapped by Hsp90 in subsequent steps (Keramisanou et al., 2022). Binds a short peptide within the tail of α4 integrin (Lin et al., 2019). ADP-ribosyltransferase toxins (CtxA, Ptx, ArtAB) are bound through a short peptide sequence (Kellner et al., 2019). Regions with high probability for local unfolding may correspond to interaction sites (Paladino et al., 2020). Cryo-EM structures with the GR HBD reveal details about Hsp90-cochaperone-client contacts (Noddings et al., 2022; Wang et al., 2022b). Investigation of Hsp90 clients in yeast by crosslinking to non-natural amino acid incorporated into all three domains shows that Hsp90 uses all three domains for client interactions, which involve intrinsically disordered domains (IDR) in a majority of potential clients, in general, and a specific IDR in Rsc3 (Kolhe et al., 2023; reviewed by Babu and Freeman, 2024).

- Role in quality control: required for degradation of certain misfolded substrates, e.g. apoB (Gusarova et al., 2001) and VHL (McClellan et al., 2005); "early" Hsp90 complex with Hsp70, Sti1, and Sse1 is involved in targeting VHL for degradation, but not for folding nor for maintaining solubility (McClellan et al., 2005). Together with Sse1/Sse2 part of an early quality control step with Hsp70 in yeast (Mandal et al., 2010). In yeast, this involves the ubiquitin ligases Ubr1 and Ubr2 (Nillegoda et al., 2010). Recruited to unfolded membrane-associated proteins along with CHIP (Apaja et al., 2010) and to mutant CFTR in particular along with several co-chaperones (Okiyoneda et al., 2010); knock-down of Hsp90α (and Aha1 and Hop) but not Hsp90β reduces ubiquitination and augments plasma membrane expression of mutant CFTR (Okiyoneda et al., 2010). Required for the dynamics (coalescence and movement) and degradation of Q-bodies, a cytoplasmic compartment that accumulates misfolded proteins to contribute to protein homeostasis (Escusa-Toret et al., 2013; discussed in Roth and Balch, 2013); marker of Q-bodies (Saarikangas and Barral, 2015). Hsp90 complex with exclusively Hsp90α retains adenosine A_{2A} receptor in endoplasmic reticulum prior to chaperone/COP2 exchange (Bergmayr et al., 2013). Hsp90β isoform (not α) samples cytosolic domain of serotonin transporter (SERT) (El-Kasaby et al., 2014). Hsp90β complex promotes folding

and trafficking, but destabilizes substrate CLC-2 by stabilizing CUL4 (Peng et al., 2016b). With ZTL, part of a protein quality control system in *Arabidopsis* leading to polyubiquitination and clearance of protein aggregates following heat stress (Gil et al., 2017). *HSC82* (not *HSP82*) in yeast is required for K48-ubiquitination-mediated degradation of cytoplasmic proteins, but not K11-ubiquitination-mediated degradation of nuclear proteins (Samant et al., 2018). Stress-induced increase of AtHsp90.1 may compete for substrates of E3 ligase MPSR1 leading to destabilization of the latter (Kim et al., 2019a). Cereblon independently binds Aha1 and the closed state of Hsp90α, and counteracts the effect of Aha1 in quality control of transmembrane proteins, thereby promoting their accumulation; inhibitable by both Hsp90 and cereblon inhibitors (Heider et al., 2021). Hsp90 and Sgt1 localize to "Hsp70/90/104 and proteasome-dependent heat-induced inclusions" (HAPIs), which transiently associate with Q-bodies, and are required (along with Sti1) for their formation and clearance, linking protein folding and degradation (Eisele et al., 2021).

- *in vivo* (in yeast): required for *de novo* folding of specific subset of proteins, not for most, does not generally protect from thermal inactivation, but may enhance rate of recovery (Nathan et al., 1997).
- promotes (even a small C-terminal Hsp90 fragment) MyoD1-E12 DNA binding in vitro (Shaknovich et al., 1992; Shue and Kohtz, 1994). No stable complex detectable. This seems to be the only evidence for an active role of Hsp90 as a folding chaperone.
- assembly of steroid receptor complex *in vitro*:
  - retic. lysate can do it (Smith et al., 1990; Scherrer et al., 1992) and requires ATP hydrolysis and other goodies (Hutchison et al., 1992b; Smith et al., 1992).
  - dynamic view of assembly and disassembly (Smith, 1993; Smith et al., 1995; Pratt and Toft, 1997); also reviewed in Kanelakis and Pratt, 2003.
  - Hop is an early component (Smith et al., 1993b; Smith and Toft, 1993) and it forms a 3-way complex of Hsp90-Hop-Hsp70 (Czar et al., 1994; Chen et al., 1996c) and is essential (Chen et al., 1996c; Dittmar et al., 1996). Hop functions as adaptor that directs Hsp90 to preexisting Hsp70-PR complexes, perhaps involving Hip (Chen and Smith, 1998).
  - p23 is essential (Johnson and Toft, 1994; Johnson and Toft, 1995; Johnson et al., 1996). Binding requires ATP (Johnson et al., 1996), inhibited by geldanamycin (Johnson and Toft, 1995; Smith et al., 1995), promoted by molybdate (Sullivan et al., 1997). Geldanamycin effect may be temperature-dependent (Owens-Grillo et al., 1996b).
  - wheat germ can do it with exogenous p23 (Hutchison et al., 1995; Stancato et al., 1996).
  - Hsp70 is required (Hutchison et al., 1994a)
  - factors are preassembled in foldosome (Hutchison et al., 1994b)
  - p48 (=Hip) cloning and association (Prapapanich et al., 1996)
  - FK506 (Hutchison et al., 1993) and CsA (Owens-Grillo et al., 1995) have no effect, and immunophilins are not required (Dittmar et al., 1996).
  - complete reconstitution from individual components (Dittmar et al., 1996).
  - purified Hsp70-Hop-Hsp90 + ATP sufficient to convert GR to the (unstable) steroid binding state; this step is GA sensitive; p23 or molybdate can stabilize complex (Dittmar et al., 1997; Dittmar and Pratt, 1997). Well, also need DnaJ protein (Dittmar et al., 1998). Toft lab needs p23 with PR; Hsp70 can bind PR alone in presence of DnaJ and ATP; 70, 90, and p23 are needed at 10-20-fold excess over PR (Kosano et al., 1998). BAG-1 blocks Hsp90-GR assembly at high ratio to Hsp70 (Kanelakis et al., 1999).
  - p23 (and molybdate) binds and stabilizes GR-heterocomplex in absence of ATP. Binding to free Hsp90 is ATP-dependent and Hsp90-Hop-Hsp70 heterocomplex

is not bound at all (Dittmar et al., 1997) ----> p23 binding depends on nucleotides and proteins bound to Hsp90 (see also Johnson et al., 1998).

- dominant-negative Hip mutant blocks assembly by blocking association with Hop-Hsp90 (Prapapanich et al., 1998).
- FKBP51 binds preferentially to Hsp90-PR complexes (Nair et al., 1997). Maps to C-terminal peptide sequence of FKBP51 (Barent et al., 1998; Cheung-Flynn et al., 2003). Preference also seen with GR, but not ER complexes (Barent et al., 1998). FKBP51 overexpression stimulates p23 recruitment to and function of AR (Ni et al., 2010).
- Hsp90 and Hsp70 are sufficient for GA-inhibitable folding of GR; Hop, Ydj1, and p23 accelerate, potentiate, and stabilize folding, respectively (Morishima et al., 2000a), but are also dispensable according to Rajapandi et al., 2000; assembly occurs through two (only one according to Rajapandi et al., 2000) sequential ATP- and K^+-dependent events (iterative ratcheting), first with Hsp70 and then with Hsp70 and Hsp90 (Morishima et al., 2000b; Morishima et al., 2001). Hsp70 binds in first step in ATP-bound form, then Hsp90 can bind rapidly with ATP-dependent cleft opening being rate-limiting step (Kanelakis et al., 2002).
- a combination of Hsp90, Hsc70, and co-chaperones is required for DNA binding ability of EcR/USP heterodimer in vitro (not for hormone binding) (Arbeitman and Hogness, 2000).
- first protein to bind to native apo-PR is Hsp40 (J protein); binding is rapid, ATP-independent, and high affinity; it allows subsequent recruitment of Hsp70 and other components and persists except in presence of hormone (Hernández et al., 2002a; see also Cintron and Toft, 2006).
- priming of GR by Hsp70 for opening of the steroid binding cleft by Hsp90 does not require Hsp40, and takes place with a mutant GR lacking a segment required for assembly into Hsp90 complexes (Murphy et al., 2003).
- A multichaperone complex with Hsp90+Hsp70+Hop+Ydj-1+p23 can mobilize nuclear GR in permeabilized cells (Elbi et al., 2004).
- GCUNC-45 inhibits PR hormone binding; countered by FKBP52 (Chadli et al., 2006). Inhibits preferentially Hsp90β reconstituted PR (Chadli et al., 2008b).
- Cdc37 has no effect on PR reconstitution (Felts et al., 2007).
- no significant difference between Hsp90α and Hsp90β for PR assembly (Chadli et al., 2008b).
- Tpr2 can replace type I and II J proteins for PR and Chk1. Over- and underexpression *in vivo* is inhibitory (Moffatt et al., 2008).
- Liganded and unliganded hormone binding domain (HBD) of the glucocorticoid receptor (GR) have the same affinity for Hsp90; while two molecules of HBD can bind initially, co-chaperone binding leads to an asymmetric structure; Aha1 and HBD cannot bind simultaneously (Lorenz et al., 2014).
- Hsp90 recovers and augments GR ligand binding by promoting Hsp70 release and preventing aggregation; Hsp40/Hsp70 inhibit ligand binding by partial unfolding and opening of ligand binding pocket; recovery (but not stabilization) requires ATP hydrolysis and p23 or Hop, and direct contacts and possibly coupling between ATPase domains of Hsp70 and Hsp70 (Kirschke et al., 2014).
- addition of p23 to client-loading complex $Hsp90_2Hsp70_2$Hop-GR with antiparallel Hsp70 dimer displaces Hop and Hsp70 (Morgner et al., 2015; see also Schmidt et al., 2015).
- Stable intermediate consists of $(FKBP51)_1(GR)_1(Hsp90)_2(p23)_2$; when FKBP52 replaces FKBP51 to form dynamic transfer complex, p23 is expelled (Ebong et al., 2016), consistent with IP results with cell extracts (Schülke et al., 2010).

- Differential requirements of GR and MR HBDs for co-chaperones *in vitro* mimic functional requirements in yeast (Sahasrabudhe et al., 2017).
- Both Hsp90α and β assemble as homodimers with GR *in vitro*, unlike *in vivo* where heterodimers can also be found (Morishima et al., 2018).
- Assembly of GR HBD complexes with *C. elegans* and human proteins reveals cooperativity, unexpected disruptive effects of p23 and Hop, and similar acceleration of hormone binding by Hsp90 alone; contact sites within complex, notably with client, mapped by crosslinking/mass spec (Kaziales et al., 2020).
- Cryo-EM structures of reconstituted complexes with details on loading and maturation complexes with GR HBD as client (Noddings et al., 2022; Wang et al., 2022b). Structures of more mature ligand-bound and functional stage with FKBP52 (and FKBP51) (Noddings et al., 2023).
- Interaction of Hop TPR2B with middle domain of Hsp90 may stall loading complex by inhibiting Hsp90 ATPase, and the shift of Hsp70 binding to TPR2B may release it to support further client processing; release of Hsp70 dependent on TPR1, possibly as exit site after client transfer and arrival of p23; when p23 enters the complex, which still contains Hop, the interplay between Hop DP2, p23 (including direct contacts between DP2 and p23), and the client releases TPR2B from the Hsp90 middle domain, enabling Hsp90 closure (Dahiya et al., 2022).

- <u>reconstitution of pp60$^{v\text{-}src}$</u> complex with retic. lysate (Hutchison et al., 1992a); complex with Hsp90 and p50 stabilized by molybdate, vanadate and tungstate (Hutchison et al., 1992c). Stimulation of kinase activity in purified system requires ATP binding (and in some assays hydrolysis) and Hsp90 binding of phosphorylated Cdc37, and only the Hsp90β isoform is able to do it (Boczek et al., 2015).
- Assembly of <u>nNOS complex</u> with Hsp90, Hsp70, Hsp40, Hop, and p23 is insufficient for heme-mediated activation; also requires GAPDH (Morishima et al., 2022).
- <u>B-Raf</u>: Cdc37 and Hsp90 (M domain is critical) suppress aggregation of the kinase domain of B-Raf *in vitro* and are released upon nucleotide binding of the kinase (Eckl et al., 2016). Assembly of kinase-Hsp90-Cdc37 complexes with additional components reveals that the large PPIases of C. elegans (FKB-6) and human (FKBP51/52) further stabilize the complex in the closed ATP-bound state; contact sites within this client complex mapped by crosslinking/mass spec (Sima et al., 2021).
- <u>subunit composition of Hsp90 complexes</u> with AhR (Chen and Perdew, 1994; Nair et al., 1996), eIF-2α kinase (Matts et al., 1992), fes tyrosine kinase and HSF-1 (Nair et al., 1996; see also Zou et al., 1998; Guo et al., 2001) is similar/identical (Hsp70, FKBP52, p23). Mutant p53 complexes also contain Hsp70, p23 and Cyclophilin-40 (Whitesell et al., 1998). Co-IP of Achlya Hsp90 also brings down Hsp70, FKBP51 and p23 (Brunt et al., 1998). FKBP52-Hsp90 complex may be targeted to GR by independent binding of FKBP52 to GR (Silverstein et al., 1999).
- pp60$^{v\text{-}src}$, fes and Raf-1 complexes with Hsp90 also contain <u>p50</u> (now known to be presumably Cdc37) (Brugge et al., 1981; Oppermann et al., 1981; Stancato et al., 1993; Stancato et al., 1994; Wartmann and Davis, 1994; Nair et al., 1996; Perdew et al., 1997). Cdc37 binds catalytic domain of Raf directly and may direct Hsp90 to it (Silverstein et al., 1998). Androgen receptor complexes may also contain and require Cdc37 (Rao et al., 2001; see also Gray et al., 2007).
- <u>subunit composition in yeast</u>: with GR there is Hsp90, Sti1, Ssa and Ssb, Ydj1 and Sba1 (Bohen, 1998). The latter is released most clearly with hormone (Bohen, 1998). The Lindquist lab has only seen Hsp90, Ydj1 and Ssa (Kimura et al., 1995).
- <u>maturation of reovirus protein σ1</u>: Hsp90 associates with immature homotrimer forms; release from Hsp90 and maturation blocked in vitro by GA; p23 also associated with σ1 and released by GA (Gilmore et al., 1998).

- p53: In purified system, Hsp90 prefers wild-type over conformationally mutant p53; inhibits binding of Hsp40 and Hsp70 to wild-type p53; Hsp90 and multi-chaperone complexes with wild-type p53 are disrupted by BAG-1 (King et al., 2001). Hsp90 binds and stabilizes native-like conformation (Müller et al., 2004; Walerych et al., 2004; Hagn et al., 2011). Hsp90 required for maintenance under heat stress and for refolding in collaboration with Hop-Hsp70 (Walerych et al., 2009). Release of partially unfolded wild-type p53 from Hsp90 is necessary for promoter binding and dependent on ATP-binding, but not hydrolysis (Walerych et al., 2010). Hsp90 protects DNA binding-competent conformation (Boysen et al., 2019) and restores native state from Hsp70-mediated unfolding in ATP hydrolysis- and HOP-dependent manner (Dahiya et al., 2019) of wild-type and mutant p53. Upon Hsp90 overexpression in yeast, a recessive misfolding-prone p53 mutant is excluded from the nucleus and radicicol can release it from this sequestration (Denney et al., 2021).
- reconstitution of functional HBV reverse transcriptase *in vitro*: purified Hsp90, Hsp70, Hsp40, and Hop are sufficient, p23 improves and accelerates; dependent on Hsp90 ATP hydrolysis (Hu et al., 2002; Hu et al., 2004).
- reconstitution of functional Chk1 with Hsp90, Hsp70, Hsp40, Cdc37 and CK2 (p23 not needed, Hop enhances) (Arlander et al., 2006; Felts et al., 2007). Effect of Tpr2 (Moffatt et al., 2008).
- Disaggregates Pih1 in ATP-dependent fashion *in vitro* (Zhao et al., 2008).
- Folding/maturation of Mal63 appears to be somewhat different from the steroid receptor paradigm in that an Hsp70-Sti1-Hsp90 intermediate is the form responsive to inducer (Ran et al., 2008).
- Sequential triage of ricin catalytic A chain from Hsc70 system to Hsp90-CHIP protects cells (Spooner et al., 2008).
- No binding and no stimulatory effects of Aha1 on several clients in reticulocyte lysate (Sun et al., 2012).
- Argonautes:
  - Argonaute-1 (= Ago1): Cyp40, in contrast to other TPR co-chaperones, facilitates RISC assembly in an Hsp90-dependent way by promoting or stabilizing the binding of small RNA duplexes to AGO1, but is not present in mature RISC in plants (Iki et al., 2012).
  - Argonaute-2 (= Ago2 = GERp95): GA inhibits interaction with Dicer (Tahbaz et al., 2004), and compromises RNA interference and miRNA action, but not siRNA loading (Pare et al., 2009). Instead, newer evidence indicates that Hsp90 is required to maintain stability of unloaded Ago2, and not for siRNA/miRNA loading or interaction with Dicer (Johnston et al., 2010; but see below). Concordant evidence now suggests that Hsp90 is required for dsRNA loading into Ago from Dicer in an ATP- and possibly even hydrolysis-dependent fashion (Iki et al., 2010; Iwasaki et al., 2010; Miyoshi et al., 2010; discussed by Landthaler, 2010). Aha1, Cdc37, p23 and FKBP4 (=FKBP52) are all required for RNA loading and p23 and FKBP4 are part of the Hsp90-Ago2 complex before loading (Pare et al., 2013). Human Ago2 also dependent on Hsp90 function in budding yeast (Wang et al., 2013d). Both FKBP4 and 5 promote Ago2 stability and facilitate RISC assembly (Martinez et al., 2013). The co-chaperone Coi12p of *Tetrahymena* promotes siRNA loading at least in part through an Hsp90- and ATP-dependent mechanism (Woehrer et al., 2015). In a purified fly system, the chaperone complex consisting of Hsp83, Hsc70, Hop, p23 and Droj2 does it by increasing the dwell time of the Dicer-R2D2-siRNA complex on Ago2; this depends on the 5'-phosphate of the guide strand and on the ATPase of both Hsc70 and Hsp83 (Iwasaki et al., 2015). Also required for the Dicer-independent loading of duplex RNA, but not single-stranded RNA, in the human system (Naruse et al., 2018). Single-

molecule experiments show that the Hsp90 system extends the dwell time in an open/active conformation promoted by the Hsp70 system (Tsuboyama et al., 2018). In *Drosophila*, along with Cyp40 shifts the sorting of some miRNA duplexes from Ago1 to Ago2, which is essential for spermatid differentiation (Iki et al., 2020).
  - Argonaute-4 (Ago4): binds and is required for loading of heterochromatic siRNAs in the cytoplasm in plants (Ye et al., 2012).
  - R2TP/Hsp90 might sequester the Dicer cofactor TRBP, thereby regulating miRNA biogenesis (Abel et al., 2022).
  - Aha1 knockdown or Hsp90 inhibition reduce Dicer 1 levels and mature miRNAs (Liu et al., 2022c).
- Assembly of functional Nox5, associated with isolated membranes, with Hsp90β, Hsp70, HOP, Hsp40 (Ydj1) and p23 (Chen et al., 2015a).
- Molybdate fails to stabilize Hsf1-Hsp90 complexes (Kijima et al., 2018).
- Model for how ATP-driven Hsp90 cycle drives kinases out of their thermodynamic equilibrium into their active conformation (Xu, 2020).
- Alternative client transfer through NudC (Biebl et al., 2022).
- Nanoparticles coated with Hsp90 (htpG) are "ATP-propelled nanorobots", which can promote protein folding of heat-denatured substrate and prevent amyloid formation of mutant α-synuclein (Rodríguez-Ramos et al., 2023a; Rodríguez-Ramos et al., 2023b).

Mapping of Hsp90 domains:

Top Refs

- only C-terminal half required for assembly with cPR *in vitro* (Sullivan and Toft, 1993).
- domains of yeast Hsp82 required for viability and signaling in yeast (Louvion et al., 1996).
- charged linker domain: dispensable *in vivo* in yeast (Louvion et al., 1996; Meng et al., 1996), but viable shorter deletion mutant is defective for double-strand break repairs and Rad51 function, but not nuclear accumulation, is impaired (Suhane et al., 2015; Fangaria et al., 2022). A peptide (aa 232-266) and antibody against this peptide destabilizes GR-mHSP84 complex *in vitro* (Tbarka et al., 1993). Charged domain required in luciferase refolding assay (Johnson et al., 2000). Inhibits binding of C-terminal domain to novobiocin (Marcu et al., 2000a). Binds NPY (Ishiwatari-Hayasaka et al., 2003). More careful mapping in Hsp82 reveals that more extended deletions can affect co-chaperone regulation *in vitro* and viability, but that an unrelated spacer can partially rescue (Hainzl et al., 2009; see also Tsutsumi et al., 2012). Truncation of charged domain rescues secretion and chaperone defects of mutations in N-terminally adjacent hydrophobic strand (Tsutsumi et al., 2009). The sequence and/or charge, but not the length affect Hsp90 conformation, co-chaperone interaction and function (Tsutsumi et al., 2012). *CPR7* becomes essential when the charged linker of Hsp90 is deleted; this synthetic lethality can be suppressed by Cns1 overexpression as well (Zuehlke and Johnson, 2012). Charged linker is important for the structural flexibility mediating docked and undocked states of the N- relative to the the M-domain (Jahn et al., 2014). Deletion reduces affinity for ATP but not other ligands (Olesen et al., 2015). Important for DNA damage-induced nuclear localization (Fangaria et al., 2022).
- Hsp82 chimeras with Grp94 N- or M2-C domains are viable, but no Hsp82 domain can substitute for a corresponding Grp94 domain (Maharaj et al., 2016). For viability in yeast and some clients, charged linker *per se* is not important but the ability of the N-terminal domain to rotate (Daturpalli et al., 2017).
- C-terminal MEEVD dispensable *in vitro* (Sullivan and Toft, 1993) and *in vivo* (Louvion et al., 1996), except in *cns1* yeast strain (Tesic et al., 2003).
- other internal deletions in Hsp90 of chicken (Cadepond et al., 1993; Binart et al., 1995; Meng et al., 1996) and yeast (Louvion et al., 1996).

- Comprehensive fitness map of almost all amino acid positions of *S. cerevisiae* Hsp82 in different environmental conditions (Flynn et al., 2020).
- calmodulin-binding domain: positively charged amphilic helix of about 20 aa around aa 500 of mHSP90, also intramolecular interaction domain (this region may bind to another domain resembling calmodulin; binding inhibited by Ca^{2+}) (Minami et al., 1993).
- C-terminal dimerization domain (Minami et al., 1994; Nemoto et al., 1995; Meng et al., 1996; Nemoto et al., 2001a; Tanaka et al., 2001; Yamada et al., 2003); same dimerization affinity as full-length (Richter et al., 2001). Minimal dimerization domain comprises last 190 amino acids (Nemoto et al., 1995). A minimal domain comprising residues 650-697 with an essential hydrophobic segment within the C-terminal domain of human Hsp90α (AA 621-732) interacts with middle plus C-terminal domain (Yamada et al., 2003). Point mutations in this region affect also chaperone function (Allan et al., 2006). Human Hsp90α can heterodimerize with Grp94 and htpG through their middle - C-terminal domains (Yamada et al., 2003). Dispensable for ATPase of yeast Hsp90 provided dimerization is ensured otherwise (Wegele et al., 2003). Duplicated C-domain keeps Hsp82 monomeric and defective for ATPase and also *in vivo* in yeast (Wayne and Bolon, 2007). Poor dimerization of human Hsp90β compared to α can be mapped to two amino acid changes {A558 and M621 of β} (Kobayakawa et al., 2008). Polymorphism Q488H in human Hsp90α affects dimerization, but not Q488T as found in Trap1 (Kobayakawa et al., 2009). *In silico* and mutational analysis of hot spots (Ciglia et al., 2014).
- N-terminal dimerization domain (N-terminal 200 AA) (Prodromou et al., 1997a).
- domain mapping of *in vitro* assembly with Hop, Hip, Hsp70, Cyp40, FKBP51, p23 and PR (Chen et al., 1998; see also Scheibel et al., 1999b; Chadli et al., 2000). N-terminal domain sufficient for hormone-insensitive interaction with ERα HBD in purified system (Bouhouche-Chatelier et al., 2001).
- p23 binding requires N-terminal dimerization and about 200 amino acids beyond the charged domain (Chadli et al., 2000; Prodromou et al., 2000; Siligardi et al., 2004). Appears similar for RAR1 (Takahashi et al., 2003). Model for interaction based on evolutionary tracing (Zhu and Tytgat, 2004). Binding competed by Aha1 and Hop but not Cdc37 or Cpr6 (Harst et al., 2005). Evidence for Hsp90-FKBP52-Hop and Hsp90-FKBP52-p23-Hop complexes (Hildenbrand et al., 2011; see also Ebong et al., 2011; Ebong et al., 2016). Interaction between Hsp90β and p23 compatible with N-terminal fluorescent protein tags on both proteins (Picard et al., 2006).
- ATP and GA-binding domain (N-terminal 200 AA): see above.
- point mutations in N-terminal pocket block both GA and p23 binding (Grenert et al., 1997; see also Grenert et al., 1999).
- various yeast Hsp82 point mutants (A97I, G170D, S485Y, T525I) cannot bind Sba1 *in vitro* (Fang et al., 1998; see also Hawle et al., 2006).
- Chaperone domains: a small C-terminal Hsp90 fragment is sufficient to promote MyoD1-E12 DNA binding in vitro (Shaknovich et al., 1992; Shue and Kohtz, 1994). N-terminal domain of human Hsp90 (AA 9-236) prevents rhodanese aggregation in a GA-sensitive way and prevents (!) luciferase refolding; C-terminal AA 629-732 prevents rhodanese aggregation, binds a short peptide (low efficiency) and maintains unfolded luciferase in a folding-competent state (Young et al., 1997); not inhibited by TPR proteins that also bind there (Young et al., 1998). There are at least three different domains that can inhibit aggregation of substrates (Johnson et al., 2000; see also Tanaka et al., 2001), but multiple domains are required in luciferase refolding assay (Johnson et al., 2000). Yeast Hsp82 also has two domains that inhibit aggregation of substrates; activity can be inhibited by peptides and N-terminal domain also by GA and ATP (Scheibel et al., 1998); charged domain confers higher affinity for nonnative proteins and lower ATP binding onto

N-terminal chaperone domain (Scheibel et al., 1999a); charged domain required in luciferase refolding assay (Johnson et al., 2000). N- and C-terminus contribute differently to function as holder chaperone (Minami et al., 2001); the C-terminal domain presents trapped luciferase to CHIP for ubiquitinylation (Murata et al., 2001). The same minimal domain from the C-terminus that can mediate dimerization can suppress aggregation of citrate synthase (Yamada et al., 2003). Charged linker and C-terminal tail are necessary for anti-aggregation activity, and deletions in yeast Hsp82 can be rescued by appending the human charged linker at the C-terminus (Wayne and Bolon, 2010). This is also important *in cis* in yeast for maintaining viability at elevated temperature and the solubility of clients (Pursell et al., 2012).

- Amphipathic structure around W300 and residues 329 to 332 (in yeast) may be part of the client binding domain consisting of the opposing inner faces of the middle segments (Meyer et al., 2003).
- Detailed cryo-EM view of client (GR HBD) binding surfaces of loading and maturation complexes (Noddings et al., 2022; Wang et al., 2022b).
- TPR binding domain: C-terminal 90-100 AA are sufficient (Young et al., 1998; Carrello et al., 1999; see also Chen et al., 1998; Russell et al., 1999; Bell and Poland, 2000; Ramsey et al., 2000; Connell et al., 2001); also for stimulating PP5 phosphatase activity (Ramsey and Chinkers, 2002). MEEVD is required for binding Cyp40, PP5, FKBP52, and Hop (Chen et al., 1998; Carrello et al., 1999; Ramsey et al., 2000). MEEVD sufficient to bind central TPR domain (TPR2A) of Hop (Scheufler et al., 2000; Brinker et al., 2002) and Cyp40 (Onuoha et al., 2008), but there are multiple distinct binding determinants for PP5 and FKBP52 versus Hop (Ramsey et al., 2000; see also Haslbeck et al., 2015), and only full Hsp90 has wild-type affinity for Hop (Hernández et al., 2002b). Extreme N-terminus required for high affinity binding of Sti1 but not Cpr6 (Richter et al., 2003). Hop binding involves additional contacts in C-terminal and middle domains of Hsp90 (Onuoha et al., 2008). Phage display screen failed to identify specificity for binding particular TPRs (Ramsey et al., 2009). Multiple domains of Hsp90 interact with Sti/Hop resulting in inhibition of ATPase and slowing of dimer dissociation (Lee et al., 2012a; Schmid et al., 2012)
- Regions required for assembly with GR (aa 206-291 and 446-581 of chicken Hsp90) (Jibard et al., 1999).
- "Domain mapping" by limited proteolysis and bacterial two-hybrid (Nemoto et al., 1997; Scheibel et al., 1998; Bogatcheva et al., 1999; Nemoto et al., 2001a; Matsumoto et al., 2002). C-terminal portion (289-400) of domain A (1-400) interacts with N-terminal two thirds (401-546) of middle domain B (401-618); conserved residues important for structural integrity, interaction and complementation in yeast (Matsumoto et al., 2002).
- Overexpression of the two separated chaperone domains of yeast Hsp90 (N-terminal 210 and truncation of N-terminal 261 amino acids) has dominant-negative effect on cell growth and v-src activity in yeast; only N-terminal truncation affects GR activity in yeast, and arrests PR assembly at intermediate complex *in vitro* (Scheibel et al., 1999b).
- Novobiocin and ATP bind competitively to C-terminal half of chicken Hsp90, dependent on AA 657-677 and competed by a short peptide from this region (Marcu et al., 2000a; Marcu et al., 2000b). Second ATP-binding domain, specifically blocked by cisplatin (Sóti et al., 2002). May overlap with dimerization domain containing a Rossmann fold motif (Garnier et al., 2002b). Mapping of novologs to C-terminal site by methyl-TROSY and their long-range effects (Kumar Mv et al., 2018).
- N-terminal 302 AA of human Hsp90β binds both TP and RT domains of HBV polymerase whereas C-terminal 110 AA binds only RT domain (Cho et al., 2000b).
- AA 405-578 of Hsp90α sufficient for interaction with Pim-1 (Mizuno et al., 2001).

- Middle domain interacts with sGC (Papapetropoulos et al., 2005; Sarkar et al., 2015) through PAS domain (Sarkar et al., 2015).
- Trap1-Hsp90 chimeras (Johnson et al., 2000).
- Evidence for domain crosstalk (see also dimerization): Cooperativity of two nucleotide-binding sites (Soti et al., 1998; Sóti et al., 2002). ATP/GA/radicicol binding to N-terminus antagonizes novobiocin binding to C-terminal domain (Marcu et al., 2000a; Marcu et al., 2000b). A conserved heat-labile interaction between a "middle" domain and the N-terminal chaperone domain appears to inhibit chaperone activity (Tanaka et al., 2001). Sequences within last fourth modulate ATP hydrolysis by N-terminal domain (Owen et al., 2002). Hydrophobic patch (residues 342-352 in yeast) N-terminal of catalytic loop required for interdomain communication between N- and middle domains (Meyer et al., 2003). Genetic evidence for complex interactions (see e.g. Johnson et al., 2007). Structure of C-terminal domain is not significantly affected by other domains as determined by double electron-electron resonance measurements, but the Kd of dimerization, determined with a panel of methods, is moderately affected (Oranges et al., 2024).
- Oligomerization requires residues 311-350 of Hsp90α (Nemoto et al., 2004) -> activation of Hsp90 may involve opening of oligomerization/client-binding domain by disruption of intramolecular interaction between AA 289-389 and AA 401-546.
- Aha1 binds to middle domain with Kd of 2.9 µM and may facilitate interaction between N-terminal and middle domains (Lotz et al., 2003; Meyer et al., 2003). It induces a conformational switch in the catalytic loop of the middle domain resulting in the release of the "catalytic" arginine 380 (yeast) (Meyer et al., 2004). Binding mutually exclusive with p23, Cdc37, and Hop but not Cpr6 (Harst et al., 2005); not in the case of *C. elegans* Cdc37 (Eckl et al., 2013). Hsp90α-specificity maps to the Hsp90α middle domain (Synoradzki and Bieganowski, 2015). Conserved N-terminal NxNNWHW motif of Aha1 binds N-terminal domain of Hsp90 (Mercier et al., 2019). Phosphorylation of Y313 of Hsp90 facilitates Aha1 recruitment including with Hsp90 N-terminal domain prior to N-terminal closure (Xu et al., 2019).
- Cdc37 binds N-terminal ATPase domain (Roe et al., 2004) and blocks ATPase by insertion of a side chain into the pocket, by binding the open face of the lid, and by holding the Hsp90 clamp open like a brace (Roe et al., 2004). Binding blocked by Hop and Aha1 but not p23 and Cpr6 (Harst et al., 2005). Human and *C. elegans* Cdc37 preferentially bind N-terminal and middle domains, respectively (Eckl et al., 2013 also Eckl et al., 2015; Verba et al., 2016).
- MDM2 binding peptide maps to AA 623-634 of human Hsp90 (Burch et al., 2004), but perhaps binding domain is the N-terminal ATPase domain of Hsp90 (He et al., 2019).
- N-terminal domain binds CHORD-protein Chp1 in ATP-independent fashion (Hahn, 2005; Wu et al., 2005).
- SGT1 also binds Hsp90 N-terminal domain with CS domain, without p23-like contacts to middle domain (Botër et al., 2007). RAR1 and SGT1 bind overlapping surfaces that are distinct from the p23 and Aha1 binding sites (Kadota et al., 2008; Zhang et al., 2008a). Full-length SGT1 but not its CS domain alone compete with p23 for Hsp90 binding (Kadota et al., 2008).
- N-terminal domain binds GCUNC-45 in TPR-dependent fashion (Chadli et al., 2006; Chadli et al., 2008a). Both FKBP52 and GCUNC-45 can bind the N-terminal domain through a non-contiguous MEEVD-like sequence within/near ATP binding pocket; binding reduced by nucleotides or GA (Chadli et al., 2008a).
- Role of lid for ATPase (Richter et al., 2006).
- Both N-termini are accessible in p23-Hsp90 complexes and can be tagged with fluorescent proteins without interfering with binding (Picard et al., 2006).

- GR regulation depends on two solvent exposed hydrophobic sites in the C-terminus of Hsp90 that have the potential to bind GR as peptides (Fang et al., 2006).
- Comprehensive survey of effects of Hsp82 point mutants, notably in middle domain, on ATPase activity, co-chaperone interaction, and GR and v-Src function; two mutants discriminate between the two substrates (Hawle et al., 2006; see also Johnson et al., 2007).
- N-terminus sufficient to bind melusin (Sbroggiò et al., 2008).
- Charged plus middle domain are sufficient to stimulate cell migration when added to medium; middle domain binds CD91 best (Cheng et al., 2008).
- Secreted Hsp90α lacks C-terminal EEVD motif and that motif anchors Hsp90α intracellularly through interaction with TPR co-chaperones, in particular PP5 (Wang et al., 2009b).
- Point mutants I578F and G313N in yeast Hsp82 fail to become nuclear in quiescent cells (Tapia and Morano, 2010).
- N-terminal plus charged domain sufficient to bind WT1 (Bansal et al., 2010).
- Changing R98 of P. falciparum Hsp90 to K as in human does not change higher affinity for GA (Pallavi et al., 2010).
- Hsp90α interacts with MMP-2 using the middle domain (Song et al., 2010b).
- Novobiocin-like inhibitors render a region of human Hsp90α encompassing residues 548-714 protease-resistant and can be crosslinked to residue 560, thereby suggesting a model of how they can stall the machinery in an open conformation (Matts et al., 2011b).
- Interaction with p53 is through several Hsp90 domains, including the outside of middle domain (Hagn et al., 2011). p53 DBD is positioned near middle domain (Quintana-Gallardo et al., 2019).
- A model substrate facilitates a repositioning of the N-terminal versus the middle domain through cross-monomer contacts with both (Street et al., 2012).
- Purified AMPKα/γ subunits bind N-terminal and middle domains with high affinity (Zhang et al., 2012c).
- Several structurally clustered point mutants in the middle domain severely affect substrate binding in the *E. coli* htpG (Genest et al., 2013). Biochemical experiments confirm that an extended surface of the middle domain with the C-terminal domain, even without the very C-terminal dimerization domain is able to bind a model substrate (Street et al., 2014). Flexibility and residues at the domain interface (e.g. H446 in htpG, T525 and others in yeast) are essential to adapt to the substrate (Street et al., 2014).
- N-terminal domain sufficient to bind substrates HAX-1 and Ire1 (Lam et al., 2013).
- Extended surfaces are involved in binding Tau and the GR HBD (Karagöz et al., 2014; Lorenz et al., 2014). Surface overlapping Tau binding surface across N and M of open conformation binds globular misfolded transthyretin monomer (Oroz et al., 2017). Structure of full-length human Hsp90β with FKBP51 and with/without Tau shows an extended Hsp90-51 interaction surface and N-terminal positioning of Tau and PPIase; binding site of Tau does not overlap with co-chaperone binding sites (Oroz et al., 2018). p23 competes with the MEEVD of Hsp90 for binding to the TPR of FKBP51, thereby promoting the formation of protective complexes with Tau (Chakraborty and Zweckstetter, 2025).
- Both N- and middle domains bind PKCγ (Lu et al., 2014).
- Middle domain binds BTB domains of insect factors (Cai et al., 2014).
- C-terminal portion of middle domain of human Hsp90α is responsible for conferring the Hsp90α slow growth phenotype on complemented yeast (Synoradzki and Bieganowski, 2015; see also Synoradzki et al., 2018).
- Both IKKβ and eNOS bind to middle domain and compete (Natarajan et al., 2015).

- SDF2 binds M-domain (Siragusa et al., 2015).
- Nox5 binds M-domain (Chen et al., 2015a).
- Co-chaperones FNIP1/FNIP2 bind M- and C-domains (Woodford et al., 2016a). Binding of FNIP1/2 and Tsc1 differentially affected by mutations around catalytic residue of Hsp90 (Backe et al., 2022b).
- Tom70 TPR also binds internal peptide in C-terminal domain (Zanphorlin et al., 2016).
- NM and C bind GR and REB-ERBα, respectively (Okabe et al., 2016).
- Short 27 amino acid peptide of Hsp90α with dual lysine motif, from junction between charged region and middle domain, is sufficient to stimulate migration/invasion *in vitro*, but not completely *in vivo* (Zou et al., 2017).
- Middle domain of HtpG binds nucleotide-binding domain of DnaK (Kravats et al., 2017) directly (Doyle et al., 2019). Homologous domain in yeast also involved in binding Hsp82 and Ssa1 (Kravats et al., 2018) directly (Doyle et al., 2019). Analysis of Sti1-dependence in yeast supports this conclusion and shows a inverse correlation between Hsp70-binding and Sti1-dependence (Reidy et al., 2018). Further evidence for direct interaction of mammalian Hsp90 and Hsp70 (Bhattacharya et al., 2020).
- C-terminal domain contributes to tighter binding of FKBP8 to MEEVD (Blundell et al., 2017).
- M and C domain can bind a portion of Tsc1, but MEEVD is required for binding of full-length Tsc1 (Woodford et al., 2017).
- Hsp90β binds Ni-NTA through charged domain (Asakawa et al., 2018).
- Binds and deforms membranes through a conserved amphipathic α-helix around K399 in the M domain (Lauwers et al., 2018).
- Ids2 interacts with middle domain (Chen et al., 2018b).
- Interaction domain with SMYD2 maps to the sequence motif (M/I/L/V)PXL about ten amino acids N-terminal of MEEVD, and shared with the very C-terminus of p23; nevertheless, binding to Hop and Aha1 may be sterically interferred with; peptides containing it block Smyd2-mediated methylation of ERα (Obermann, 2018).
- Both N- and C-terminal domain are able to bind tail of α4 integrin in ATPase- and dimerization-independent mode and hence, one Hsp90 molecule can bind two molecules of integrin (Lin et al., 2019).
- Short disordered sequence directly upstream of MEEVD is important for efficient ubiquitination of substrates by CHIP (Quintana-Gallardo et al., 2019).
- TIMP2 and Aha1 competitively bind to middle domain and are sensitive to the mutation V411E (Baker-Williams et al., 2019).
- Hsp90α K585 charge required to promote interdomain electron transfer of nNOS (Zheng et al., 2020b).
- Cereblon binds middle domain of closed state (Heider et al., 2021).
- Secondary structures in charged linker (yeast Hsp82) can transiently interact with a strand of the NTD, displacing it and thereby promoting binding of a hydrophobic patch of NTD to p53 (López et al., 2021).
- C/EBPβ interacts with M- and C-domains (Qi et al., 2021).
- NudC CS-domain binds middle domain of Hsp90, both open and closed conformations of Hsp90 (Biebl et al., 2022).
- PGK1 binds to C-terminus of Hsp90 (Tang et al., 2022b).
- Amino acids 208-218 are essential for binding HDAC11 and SDCBP, which compete for binding to Hsp90 (He et al., 2023).
- Binds collagen-1 through its N-terminal domain (Singh et al., 2023).

- NMR analysis of client-Hsp90 interactions for htpG, yeast Hsc82, and human Hsp90β show a bipartite mode of interaction with disordered client domains through opposite middle domains (Qu et al., 2024b).
- Interaction of Hsp90β with circular RNA circFOXK2 and indirectly with TACO1 requires Q279 (Deng et al., 2025a).
- Residues 319-323 and 622-629 of Hsp90 are required for interaction with PGAM2 (Li et al., 2025b).

Hsp90 and disease:

Top Refs

- major target of protective antibodies in candidal infections (Matthews and Burnie, 1992). Antibodies recognize Hsp90 both on the cell surface and in the cytoplasm (Burt et al., 2003).
- reduced Hsp90 levels in *Candida albicans* attenuate virulence in mouse model (Shapiro et al., 2009).
- tumor-specific antigens (Ullrich et al., 1986; Blachere et al., 1993; Srivastava et al., 1994; Udono and Srivastava, 1994; Ishii et al., 1999), possibly by playing a role in antigen processing/presentation.
- Hsp90 like Grp94 (gp96) can promote re-presentation of peptides by MHC I molecules following binding of a common receptor, the α2 macroglobulin receptor CD91 (Binder et al., 2000; Basu et al., 2001).
- Overexpression of Hsp90 in budding yeast enhances its virulence in mice (Hodgetts et al., 1996).
- Hsp90 is predominant antigen of humoral immune response of ovarian cancer patients with stage IV disease (Vidal et al., 2004). High blood levels are associated with poor prognosis in ovarian cancer (Duan et al., 2023).
- 17-AAG ameliorates an AR-mediated neurodegenerative polyQ disease by inducing degradation of AR (Waza et al., 2005). With USP19, Hsp90 promotes aggregation of polyQ proteins (He et al., 2016); Hsp90 brings together Htt and USP19 (He et al., 2017).
- Immunodominant epitope of human Hsp90 is the relatively conserved pentapeptide starting with P295 (Kishimoto et al., 2005).
- Associated with NSF, dynamin-1, Unc18-1 and Sumo in neuronal intranuclear inclusions (Pountney et al., 2008).
- Women with infertility have autoantibodies to Hsp90, β in particular (Pires and Khole, 2009). Immunization of mice with immunodominant peptide leads to ovarian dysfunction (Choudhury and Khole, 2013).
- Hsp90-derived peptides can induce antitumor immunity (Kang et al., 2022a).
- Carotid atherosclerosis patients have increased soluble Hsp90 and anti-Hsp90 antibodies (Businaro et al., 2009), and Hsp90 is increased in atherosclerotic plaques (Madrigal-Matute et al., 2010) and Hsp90 inhibitors prevent migration of vascular smooth muscle cells into such lesions (Kim et al., 2014).
- Citrullinated Hsp90 as autoantigens and the corresponding antibodies as markers of interstitial lung disease associated with rheumatoid arthritis (Harlow et al., 2013). Inhibition of Hsp90 protects against osteoarthritis in a rat model (Siebelt et al., 2013).Citrullination is at buried arginine residues R502 and R510 in Hsp90β and Hsp90α, respectively, and leads to disruption of tertiary structure (Travers et al., 2016).
- Increased expression of Hsp90 in rheumatoid arthritis also promotes bone resorption; Hsp90 inhibition and overexpression inhibit and promote osteoclast differentiation, respectively (Wang et al., 2023).

- Elevated serum levels of Hsp90α may be a marker for hypertension (Skórzyńska-Dziduszko et al., 2016).
- Serum levels of Hsp90α are dramatically elevated in children with severe sepsis and is associated with poor outcome parameters (Fitrolaki et al., 2016).
- Patients with idiopathic pulmonary fibrosis (IPF) have elevated Hsp90 levels, and Hsp90 inhibition and Hsp90β knock-down in lung fibroblasts reduce proliferation and ECM production, and Hsp90 inhibition fibrosis in a mouse model (Sontake et al., 2017; see also Khosla, 2024; Lee et al., 2024); similar results and evidence that these effects are through TGFβ signaling (Dong et al., 2017a; Sibinska et al., 2017). Inhibitor reduces myocardial fibrosis through TGFβR1-Hsp90 complex (Cáceres et al., 2018). S-nitrosylation of Hsp90β Cys589 promotes interaction with TGFβR2 and cardiac fibrosis (Zhang et al., 2021c).
- The Hsp90β mutant C521A, which prevents N-nitrosylation at this site, favors Aha1-promoted eNOS over Cdc37-promoted NFκB signaling, and reduces atherosclerosis upon AAV-mediated expression in a mouse model (Zhao et al., 2022).
- Plasma levels as biomarker for lung (Shi et al., 2014) and liver (Fu et al., 2017; Wei et al., 2020a) cancers.
- Potentially relevant to allergy and asthma, eHsp90α mediates disruption of airway eptihelial permeability induced by house dust mites; through autocrine activation of RhoA, mimicked by recombinant Hsp90α, and blocked by an antibody to Hsp90α (Dong et al., 2017b). 17AAG or Hsp90α KD reduce pyroptosis by impacting cGAS-STING pathway; 17AAG reduces asthma induced by house dust mites in a mouse model (Huang et al., 2024a).
- Association of copy number variation (CNV) of *HSP90AB1* and systemic lupus erythematosus (Zhang et al., 2019).
- SARS-CoV-2 shares an immunogenic epitope with Hsp90β (hexapeptide at end of charged domain) that could theoretically trigger an autoimmune response (Lucchese and Flöel, 2020; Marino Gammazza et al., 2020).
- HtpG secreted by *Pseudomonas aeruginosa* activates macrophages through TLR and CD91 (Lee et al., 2020).
- Alcohol metabolism via CYP2E1 promotes Hsp90 acetylation resulting in reduced NO production, which may contribute to liver disease (Yang et al., 2021).
- Serum levels of Hsp90 correlate with severity of atopic dermatitis and anti-Hsp90 IgE autoantibodies are elevated in about half the patients (Sitko et al., 2021).
- Cerebral ischemia and reperfusion may promote necroptosis and ferroptosis through the Hsp90-GCN2-ATF4 pathway, which is mimicked by Hsp90 overexpression in a cellular model (Zhou et al., 2024b).

Hsp90 and viruses:

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- Hsp90 inhibition or Hsp90 knock-down impair maturation of respiratory syncytial virus; Hsp90 associated with viral filaments and inclusion bodies (Radhakrishnan et al., 2010). Hsp90 along with Hop interacts with large polymerase protein (L) and is required for stability and function (Munday et al., 2015).
- Inhibition impairs HIV-1 replication (Vozzolo et al., 2010), including in hyperthermic cells (Roesch et al., 2012). Ritonavir-resistant HIV is hypersensitive to Hsp90 inhibition and Hsp90β overexpression can rescue their infectivity defect (Joshi and Stoddart, 2011). Hsp90β in HIV virions and CA mutants are hypersensitive to Hsp90 inhibition (Joshi et al., 2013). Ensures reactivation of HIV-1 from latency by maintaining IKK (Anderson et al., 2014) and p-TEFb (Pan et al., 2016). Inhibition prevents HIV rebound viremia (Joshi et al., 2016).

- EBV: Hsp90 found in EBV particles (Johannsen et al., 2004) and required for EBNA1 accumulation and EBV transformation (Sun et al., 2010), and for nuclear localization of BALF5 and replication (Kawashima et al., 2013). Curcumin derivative C210 induces EBV lytic cycle but inhibits virion production (Chen et al., 2024b).
- Extracellular Hsp90 serves as cofactor for cellular entry of Kaposi sarcoma-associated herpesvirus (KSHV) (Qin et al., 2010); may also relate to Hsp90 interaction with KSHV K1 protein (Wen and Damania, 2010).
- MEEVD-derived synthetic peptide disrupts Hop-Hsp90 interaction (Veale et al., 2021; Okpara et al., 2024), and tethered to cell-penetrating peptide is non-toxic and inhibits the lytic cyle of Kaposi sarcoma-associated herpesvirus (KSHV) (Okpara et al., 2024).
- KD or inhibition of Hsp90 in tobacco blocks early stages of replication of genomic RNA of Bamboo mosaic virus (Huang et al., 2012).
- Hsp90 knock-down in tobacco impairs replication of Red clover necrotic mosaic virus (RCNMV) (Ahsan et al., 2012).
- KD or pharmacological inhibition blocks HTLV-1 replication and function (Gao and Harhaj, 2013).
- GA and siRNA specifically against Hsp90β, not α, blocks cellular entry and replication of enterovirus 71; extracellular Hsp90β interacts with virions and added recombinant Hsp90 blocks cell entry; Hsp90 also required for stabilization of capsid protein and intracellular assembly (Tsou et al., 2013; Wang et al., 2013c).
- Associated with Rift Valley Fever Virus virions and KD or inhibition impair early stages of replication/transcription (Nuss et al., 2014).
- KD or inhibition impair replication of Chikungonya virus (Das et al., 2014; Rathore et al., 2014).
- KD or inhibition impair, overexpression promotes replication of norovirus, at least in part through Hsp90 binding genomic RNA and stabilizing capsid protein VP1 (Vashist et al., 2015).
- Knock-down or pharmacological inhibition interferes with folding of enzymatic L component of the polymerases and replication of measles, VSV and Nipah viruses (Bloyet et al., 2016; see also Katoh et al., 2017; see also Dalidowska et al., 2022).
- Knock-down or pharmacological inhibition reduces replication of porcine circovirus type 2 (Liu et al., 2016).
- Inhibition or knock-down blocks rabies virus (Xu et al., 2016).
- Synthetic peptide derived from telomerase, which binds extracellular Hsp90, is delivered into cells by LRP1-mediated endocytosis and inhibits HCV replication by blocking Hsp90 interaction with FKBP8, and ROS production (Lee et al., 2016b); also inhibits HIV-1 reactivation through Hsp90 (Kim et al., 2016).
- Hsp90 overexpression boosts, and inhibition or knockdown repress deaminase and mutational activities of APOBEC-3B/-3C/-3G on HBV DNA *in vitro* and *in vivo* (Chen et al., 2017c).
- Hsp90 represses endogenous retroviruses and their gene regulatory effects in ESCs through the KAP1 complex (Hummel et al., 2017).
- Tomato yellow leaf curl virus (TYLCV) infection alleviates effects of Hsp90 inhibition, induces Hsp90/Hsp70 aggregation with the viral protein CP, and is increased (!) when Hsp90 is inhibited (Moshe et al., 2016; Gorovits and Czosnek, 2017).
- Hsp90 is in baculovirus virions, is required for viral replication, and nuclear egress of virions, probably by somehow supporting the accumulation of the P40/ARPC1 component of the Arp2/3 complex and nuclear actin polymerization (Li et al., 2019b; see also Lyupina et al., 2011).
- KD or inhibition impair processing and integrity of Rubella non-structural protein p150 and viral replication (Sakata et al., 2019).

- KD of Hsp90β, but not Hsp90α, blocks MERS-CoV replication and spreading (Li et al., 2020b).
- KD, inhibition, and overexpression of Medaka Hsp90β block and stimulate nervous necrosis virus infection (Zhang et al., 2020c).
- KD or overexpression affects pseudorabies virus replication (Zhang et al., 2021b).
- KD or inhibition destabilizes L protein and replication of snakehead vesiculovirus (Zhang et al., 2021d).
- KD or inhibition of Hsp90α or β isoforms compromise betanodavirus replication in fish cells (Zenke and Okinaka, 2022).
- Depletion of TTC4 or inhibition of Hsp90 impairs protein production and replication of bovine herpesvirus type 1 (Thompson et al., 2022).
- Pharmacological inhibition or KD compromises stability of p17 (which itself stimulates Hsp90-Cdc37 activity by promoting the phosphorylation of Cdc37 by CK2) and its ability to promote the maturation and accumulation of viral proteins, along with Hsp90, in viral factories for assembly (Huang et al., 2022).
- Hsp90 inhibition inhibits binding of the P and L proteins into functional polymerase of rabies (Dalidowska et al., 2022).
- Silencing of Hsp90 in white shrimp impairs white spot syndrome virus, and coinjection of recombinant Hsp90 promotes it (Yingsunthonwattana et al., 2022; Yingsunthonwattana et al., 2024).
- VP35 of grass carp reovirus needs both membrane-associated and cytosolic Hsp90, as receptor for clathrin-mediated endocytosis and for folding, respectively (Jiang et al., 2022). Hsp90 inhibition or knockdown reduces entry, replication, and propagation, and overexpression increases entry of grass carp reovirus (Hou et al., 2023).
- Hsp90β KO reduces viral assembly of SARS-CoV-2 (Zhao et al., 2023).
- Hsp90α but not Hsp90β stabilizes Orf9b of SARS-CoV2 as part of a complex with cullin-5/Tom70, as demonstrated with specific knock-downs and overexpression experiments; targeting Hsp90α imapirs SARS-CoV2 replication (Zhou et al., 2024a).
- GA inhibits proliferation of *Bombyx mori* nuclear polyhedrosis virus, possibly relating to the interaction of Hsp90 with actin-4 (Chen et al., 2023b); overexpression promotes proliferation, but Hsp90 K64Q acetylation mimic inhibits it (Zhang et al., 2024b).
- Silencing of *Hsp90* or *Sgt1* renders tomato more susceptible to whitefly-transmitted crinivirus tomato chlorosis virus (Ontiveros et al., 2023).
- Hsp90β, and possibly not Hsp90α, KD or KO or 17-AAG suppress porcine coronavirus infection (Zhao et al., 2024).
- Severe fever with thrombocytopenia syndrome (SFTS) virus needs Hsp90β, not Hsp90α, for replication, viral protein expression, and the formation of inclusion bodies (Wang et al., 2024b).
- Interacts with RNA-dependent RNA polymerase (L protein) of Rift Valley fever virus to stabilize it and Hsp90 inhibitor blocks viral replication (Alem et al., 2024).
- Inhibition impairs FCV particle production (Pérez-Ibáñez et al., 2024).
- RACK1B-SGT1-Hsp90 complex is required in plants for hypersensitive response to viral infections, and viral proteins such as CRP of Chinese wheat mosaic virus and 7K of wheat yellow moasic virus disrupt this complex impairing the NLR-mediated immune responses (Hu et al., 2024a).
- Interaction experiments, KD, and geldanmycin treatment show that Hsp90 proteins are negative inhibitors of salicylic acid signaling and plant resistance through binding of NPR3, and that begomovirus betasatellite-encoded protein βC1 antagonizes that by binding Hsp90 (Zhang et al., 2024a).

- Flavivirus replication is *not* dependent on Hsp90, but NS5 of West Nile virus blocks JAK/STAT signaling by disrupting Hsp90-JAK1 interaction (Roby et al., 2020). Similary, NS5 of Zika virus disrupts EGFR-Akt signaling (Hajari et al., 2025).

Cell surface and extracellular Hsp90:

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- Hsp90 added to medium stimulates neurite outgrowth (Ishimoto et al., 1998). Hsp90α and Hsp90β on surface of neural cells and antibodies to them inhibit cell migration (Sidera et al., 2004). Hsp90 interacts with extracellular domain of HER-2, important for HER-2 function and HER-2 stimulated cell migration (Sidera et al., 2008).
- Vascular smooth muscle cells secrete Hsp90α (not Hsp90β) upon oxidative stress and this extracellular form can induce MAPK in the same cells (Liao et al., 2000), and IL-8 through TLR-4, MAPK and NFκB (Chung et al., 2009).
- Role of Hsp90 in innate response to bacteria: FRAP evidence for immobile Hsp90 (and Hsp70) in cell membranes; antibodies block transfer of LPS from CD14 to an immobile multimeric complex (Triantafilou et al., 2001b); Hsp90 (and Hsp70) are LPS receptors, more important in the absence of CD14, and along with CXCR4 and GDF4 are part of an LPS-stimulated receptor cluster in lipid rafts (Triantafilou et al., 2001a; Triantafilou et al., 2002). A peptide matching the middle domain can block the interaction with LPS and its signaling, and in a cell-permeable form affects clients (Wu et al., 2012a).
- Hsp90 promotes prekallikrein activation *in vitro* and anti-Hsp90 antibodies in the medium block activation on endothelial cells (Joseph et al., 2002).
- Recombinant Leishmania Hsp83 acts as mitogen of mouse B-cells (Rico et al., 1999; Rico et al., 2002). So do plant Hsp90s through TLR4 but in an LPS-independent fashion (Corigliano et al., 2011).
- Campylobacter jejuni protein JlpA interacts with cell surface Hsp90α to activate epithelial cells (Jin et al., 2003). Neisseria adhesin activates monocytes through a complex composed of Hsp90-Hsp70-TLR4 (Cecchini et al., 2011). Overexpressed and recombinant Hsp90α blocks Neisseria adhesion/invasion (Montanari et al., 2012).
- Hsp90α, but not Hsp90β, is on the cell surface and in the tissue culture medium, and required for MMP2 maturation and cell invasiveness (Eustace et al., 2004; see comment in Picard, 2004; Wang et al., 2009b). Conversely, MMP2 is required for stimulatory effect of Hsp90α (Wang et al., 2009b). Antibodies to Hsp90α block metastasis in mouse model and plasma levels of Hsp90α (lacking MEEVD) are elevated in cancer patients (Wang et al., 2009b). Serum levels in patients with colorectal cancer are elevated (Chen et al., 2010a). Breast cancer cells secrete both isoforms and those interact with proenzymes and active forms of MMP2 and MMP9 (Stellas et al., 2010). Hsp90α stabilizes MMP-2 by preventing its autocatalytic cleavage even in the absence of ATP; Hsp90β is itself rapidly cleaved by MMP-2 explaining the apparent isoform-specificity (Song et al., 2010b). Hsp90 complex with secreted co-chaperones p23, Hop, Hsp70 and Hsp40 increases activation of MMP-2 (ATP-independent!) (Sims et al., 2011). Mammary epithelial cells secrete Hsp90β and its interaction with MMP3 is essential for invasion and morphogenesis (Correia et al., 2013). Antibody also blocks tumor growth of mammary tumor stem cells (Stivarou et al., 2016).
- Glucose and diabetes increase levels of surface Hsp90α, association with annexin II and expression of the latter on the surface of endothelial cells (Lei et al., 2004). Cell surface localization of Hsp90α promoted by phosphorylation by PKA on T89 (T90); results in reduced eNOS activity (Lei et al., 2007).

- Hsp90 and Hsp70 part of a membrane-associated, even raft-associated, receptor complex for Dengue virus (Reyes-del Valle et al., 2005).
- Surface Hsp90 is part of a receptor for Infectious bursal disease virus (IBDV) on chicken cells (Lin et al., 2007). miRNA-mediated knock-down of Hsp90α but not β inhibits IBDV infection (Yuan et al., 2012). Interaction with VP2 induces autophagy and inactivation of the mTOR-Akt pathway (Hu et al., 2015).
- Hsp90 on cell surface of some EBV-immortalized B-cells, and promotes activation of γδ T-cells by these cells (Kotsiopriftis et al., 2005).
- MS patients make antibodies that target Hsp90β on the cell surface of oligodendrocyte precursors inducing cell death (Cid et al., 2004; Cid et al., 2005).
- Wound healing: Hypoxia induces secretion of pre-existing Hsp90α, probably via exosome pathway, which in turn promotes wound healing (Li et al., 2007). TGFα stimulates massive secretion of Hsp90α by keratinocytes but not dermal fibroblasts through exosome pathway, and this Hsp90α stimulates migration of several cell types by binding to LRP1/CD91 (Cheng et al., 2008; Woodley et al., 2009). A 115 aa fragment of Hsp90 encompassing part of the charged region and the adjacent middle domain is sufficient to promote wound healing (Cheng et al., 2011). Burn wounds increase Hsp90α levels, which in turn accelerates wound healing (Zhang et al., 2014). Also works with pig model and human keratinocytes and even with a 27 AA fragment (AA 263-289) (O'Brien et al., 2014). Hypoxia induces secretion of both Hsp90α and Hsp90β, but only Hsp90α can protect cells against hypoxia through LRP1 signaling (Dong et al., 2016). C-terminally truncated Hsp90α has normal wound healing activity in the mouse (Bhatia et al., 2018). Hsp90α promotes wound healing with iPSC-derived keratinocytes (Wu et al., 2019c). Wounding stress promotes massive secretion of eHsp90α, most of which is in trypsin-sensitive form in the supernatant fraction in concentrations similar to those of recombinant Hsp90α shown to promote wound healing; impact of KOs of GRAPS55 or ATG5 indicate that secretion is by autophagosomes through two parallel pathways (Chang et al., 2024a).
- Recombinant Hsp90α promotes wound healing by epithelial cells in the cornea (Wang et al., 2022a).
- Hsp90 and IL6 in cardiomyocyte exosomes (Datta et al., 2017).
- Cachexia-inducing tumor cells secrete Hsp70 and Hsp90 associated with exosomes and this is required for the effect; recombinant Hsp70 and Hsp90 also function as cachexins, and effect is through TLR4 (Zhang et al., 2017). Also the case with human pancreatic cancer cells, and effect is inhibited by Hsp90-neutralizing antibodies (Wu et al., 2022).
- Stimulation of migration/invasion of Hsp90α KO MDA-MB-231 breast cancer cells by added full-length Hsp90α or 27 AA peptide depends on Hsp90α-specific dual lysine motif (K270/K277); when introduced into Hsp90β, it converts it to Hsp90α in these assays (Zou et al., 2017). A monoclonal antibody to this region blocks tumor growth and metastasis (Zou et al., 2017).
- Hsp90α stimulates migration of glioblastoma cells by transactivating EGFR in an TLR4-dependent (and at least partially LPS-dependent) fashion (Thuringer et al., 2011). Stimulated by hypoxia and dependent on association with coreceptor LRP1 and EphA2, and Akt activity (Gopal et al., 2011); EphA2 and eHsp90 crosstalk to affect cytoskeleton (Daoud et al., 2017). Stimulates epithelial-mesenchymal transition (EMT) of prostate cancer cells in MMP-dependent manner; can be mimicked by overexpression of Hsp90α with N-terminal signal sequence (Hance et al., 2012; Nolan et al., 2015). Hypoxia-induced motility is specifically dependent on extracellular Hsp90α and intracellular Hsp90β binding to extracellular and cytosolic domains of LRP-1, respectively (Jayaprakash et al., 2015).

- eHsp90 (α) promotes stemness of prostate cancer cells, its inhibition imapirs spheroid formation, and surface Hsp90α is associated with CSC population (Nolan et al., 2017).
- Hsp90α stimulates migration and invasion through CD91 and ErbB2 (Chen et al., 2010a). Skin cell migration induced through CD91/LRP-1 is mediated by Akt1/2 (Tsen et al., 2013).
- Antibody to cell-surface Hsp90 blocks melanoma migration and metastasis in mice (Stellas et al., 2007).
- Cell-impermeable Hsp90 inhibitor blocks cell migration and invasion (Tsutsumi et al., 2008).
- Extracellular Hsp90 has neuroprotective function by inducing cytokine production and Aβ clearance by microglia; Hsp90 also associates with Aβ plaques in Alzheimer diseased brains (Kakimura et al., 2002). Induces a unique and less inflammatory innate gene response in microglia (Okusha et al., 2022).
- Secreted Hsp90 required by *Eimeria tenella* for invasion of vertebrate cells (Péroval et al., 2006).
- Extracellular Hsp90 loaded with peptides is internalized to early endosomes through SREC-I in a Src-dependent fashion for antigen cross-presentation (Murshid et al., 2010).
- Extracellular Hsp90 of tumor cells is internalized in presence of optically tethered and by themselves cell-impermeable Hsp90 inhibitors through an endosome-*in*dependent route; uptake is blocked by Hsp90 antibodies, may only occur in tumor cells and labelled compounds can be used to monitor tumors in mice (Barrott et al., 2013). Labelling by probe correlates with metastatic potential in culture and in mice (Osada et al., 2017). Evaluation of sources of imaging errors (Wang et al., 2021c).
- Hsp90α is involved with annexin II in activating plasmin (McCready et al., 2010).
- Secreted Hsp90β associates with TGFβ through LAP resulting in TGFβ inhibition in osteosarcoma cells (Suzuki and Kulkarni, 2010). Hsp90 promotes synthesis of collagen in TGFβ-activated fibroblasts (García et al., 2016).
- Hsp90α, but not β, is secreted by activated endothelial cells and localizes to the leading edge to facilitate angiogenesis (Song and Luo, 2010).
- Under stress, endothelial cells increase secretion of eHsp90α, which increases monocyte migration through LRP1, and increased serum levels correlate with progression of atherosclerosis in type 2 diabetes (Ding et al., 2022).
- Hsp90 may modulate adhesion and invasion via integrin-FAK-c-Src pathway (Liu et al., 2011; see also Radovanac et al., 2013), also potentially via interactions with secretory vesicles at the leading edge (Ghosh et al., 2015) and with integrin α2 and integrin αL (Ghosh et al., 2016). However, Hsp90 promotes inside-out activation of α4 integrin (Lin et al., 2019).
- Secretion of Hsp90α by 293T and cranial mesenchymal cells is inhibited by Hectd1-mediated polyubiquitination; recombinant Hsp90α and an antibody promotes and inhibits, respectively, emigration of these mesenchymal cells (Sarkar and Zohn, 2012).
- Hsp90α phosphorylated on T7 by DNA-PK still gets secreted, even preferentially (Quanz et al., 2012).
- Cdc37 also on cell surface and antibodies to it block invasion and disrupt its interactions with Hsp90 and ErbB receptors (El Hamidieh et al., 2012).
- Hsp90α signaling through CD91-IKK-NFkB correlates with TCF12 expression and E-cadherin downregulation in metastatic colorectal cancer (Chen et al., 2013b).
- Hsp90α secreted by prostate cancer cells induces an inflammatory program in cancer-associated fibroblasts (Bohonowych et al., 2014).
- Hsp90α/β is involved in the assembly and/or maintenance of the fibronectin matrix (Hunter et al., 2014). Hsp90β added to cells promotes incorporation of fibronectin into

matrix (Chakraborty et al., 2020). Wild-type Hsp90α also promotes fibronection matrix assembly, but not some Hsp90α point mutants, of which some but not all affect interaction with fibronectin (Chakraborty et al., 2023).

- Stimulation of migration may involve interaction with LOXL2 (McCready et al., 2014).
- Elastin-derived peptides promote secretion of Hsp90α and stabilization of MMP-2 and uPA (Donet et al., 2014).
- EGF stimulates Hsp90α surface display on membrane protrusions (and cell migration), and MMP9 activity, via PLCγ and PKCγ (Yang et al., 2014b).
- Extracellular Hsp90 pool is involved in recycling of NadA, which highjacks the endosome pathway to enter cells, back to the cell surface (Bozza et al., 2014).
- Stabilizes replication competent HCV RNA in complex with Ago2-miR-122 in exosomes (Bukong et al., 2014).
- Extracellular levels of Hsp90 as markers for leukemia (ALL) (Milani et al., 2015).
- Serum levels elevated in lupus patients (Saito et al., 2015).
- Hsp90α serum levels elevated in lung cancer patients and correlating with stage and therapeutic response (Shi et al., 2014).
- Plasma Hsp90α good marker for liver cancer and treatment response (Fu et al., 2017; see also Wei et al., 2020a). eHsp90α good marker for breast cancer, gradually elevated with cancer stage (Hou et al., 2021).
- Hsp90α and β colocalize with heparan sulfate proteoglycans and binding is reduced by treatment of cells with heparin, heparinase or sodium chlorate (Snigireva et al., 2015). Interfering with its synthesis impairs Hsp90 stimulation of migration/invasion (Snigireva et al., 2019).
- Apoptotic cells display Hsp90 with Hsp70 and Hsp60 on the surface and their interaction with LOX-1 facilitates uptake of dying cells (Zhu et al., 2016a).
- Hsp90α stimulates migration of mesenchymal stem cells (Gao et al., 2015).
- Primary cells from mouse carcinoma model secrete Hsp90β, but not Hsp90α, and specific inhibition of eHsp90 does not inhibit migration (Vartholomaiou et al., 2017).
- Hsp90 supports/buffers FANCA mutants associated with mild Fanconi anemia and possibly other genetic dieases (Karras et al., 2017).
- Only Hsp90β is secreted by two colon cancer cell lines (de la Mare et al., 2017).
- Combination of TGFβ and (extracellularly) added Hsp90β stimulate adhesion, migration and anchorage-independent growth of a metastatic colon cancer cell line through integrin αvβ6 (de la Mare et al., 2017).
- Both Hsp90α and Hsp90β on the surface of monocyte-derived macrophages and required for their stimulation by PAMPs; inhibitable by cell-impermeable biotinylated GA Bzowska et al., 2017).
- Antibodies to Hsp90 stain the cell surface/wall of *Cryptococcus neoformans* (Chatterjee and Tatu, 2017).
- Exosome-mediated secretion of Hsp90α induced by hypoxia (see also Li et al., 2007), H_2O_2 and TGFα (through EGF receptor), and this is dependent on PRAS40 (Guo et al., 2017b). Hsp90 secretion also induced by heat stress and various inhibitors of endosomal trafficking and Ca^{2+} homeostasis (Takeuchi et al., 2015).
- Hsp90/p-IKK secreted in small extracellular vesicles by hypoxic melanoma cells stimulates proangiogenic activity of cancer-associated fibroblasts (Tang et al., 2022a).
- eHsp90α increased in mouse model of pulmonary fibrosis and by TGF-β1, and a blocking antibody reduces inflammation and collagen deposition (Dong et al., 2017a; Zhong et al., 2022). eHsp90α correlates with IPF and stimulates myofibroblasts through LRP1 (Bellaye et al., 2018). eHsp90α also promotes senescence (Zhong et al., 2022).

- Potentially relevant to allergy and asthma, eHsp90α mediates disruption of airway eptihelial permeability induced by house dust mites; through autocrine activation of RhoA, mimicked by recombinant Hsp90α, and blocked by an antibody to Hsp90α (Dong et al., 2017b).
- KD or anti-Hsp90α antibody prevent mite-induced epithelial barrier dysfunction (Ye et al., 2019).
- Promotes survival, anticancer drug resistance and signaling in SCLC cells (Du et al., 2018).
- Exosomes: critical reassessment shows that Hsp90 is not present in classical exosomes, but in other kinds of small extracellular vesicles and non-vesicular particles (Jeppesen et al., 2019).
- Interacts with *S. aureus* lipoprotein Lpl1; KD, inhibition or antibodies added to medium of host cells reduces invasion and pathogenicity of *S. aureus* (Tribelli et al., 2019; see also Ammanath et al., 2023).
- TIMP2 and Aha1 are co-chaperones for eHsp90 with opposite effects on MMP2 as substrate; the ternary complex with TIMP2 as scaffold is in a standby less active state (Baker-Williams et al., 2019).
- Hsp90α secretion correlates with ADAM10 expression and is reduced upon "inhibition" of ADAM10; Hsp90α plasma levels correlate across a broad panel of cancers, notably when there is high expression of ADAM10 (Liu et al., 2019).
- eHsp90α and clusterin interact and synergize in a LRP1-mediated fashion to promote EMT, migration and metastasis of breast cancer cells (Tian et al., 2019).
- Marine medaka Hsp90β on the surface acts as receptor for red-spotted grouper nervous necrosis virus; connects to clathrin for endocytosis (Zhang et al., 2020c).
- Majority of eHsp90α is not free but exosome-associated, on exosome surface in a protease-sensitive way; exosomes of Hsp90α KO cells fail to stimulate migration and recruitment of stromal cells (Tang et al., 2019).
- Cell surface Hsp90 as a receptor for rotavirus (Rico et al., 2020; Rico et al., 2021).
- eHsp90α from cancer-associated fibroblasts derived from endothelial-mesenchymal transition promote macrophage M2-polarization (Fan et al., 2019), and so does recombinant Hsp90α, through CD91/TLR4 signaling (Fan et al., 2022a).
- Triple KD of Cdc37/Hsp90α/Hsp90β in oral cancer cells reduces extracellular vesicles and their ability to polarize M2 macrophages (Ono et al., 2020).
- p53 null or GOF mutants promote expression of RCP, which in turn stimulates secretion of Hsp90α through exosomes, promoting cancer cell migration, invasion, and metastasis (Zhang et al., 2020b).
- Promotes packaging of GOF p53 mutants but not wild-type into small extracellular vesicles, which can promote the conversion of fibroblasts into cancer-associated fibroblasts (Ma et al., 2021).
- Experiments with neutralizing antibodies in xenografts and *in vitro* experiments indicate that eHsp90α promotes lymphangiogenesis in breast cancer (Hou et al., 2021).
- Morgana interacts with extracellular eHsp90, but neither is required for the non-canonical secretion of the other; however, in complex with Hsp90, it promotes cancer cell migration and metastasis in mice through TLR2, TLR4, and LRP1 (Seclì et al., 2021a).
- Thermoplasty-stimulated secretion of Hsp90 by epithelial cells promotes their proliferation but inhibits remodeling of smooth muscle cells (Fang et al., 2021).
- eHsp90α promotes migration and invasion of pancreatic cancer cells, and this is mediated by LRP1 and blocked by neutralizing anti-Hsp90α antibodies (Xue et al., 2022a).

- Hsp90 on the surface of tumor cell-released autophagosomes (TRAPs) is required for the stimulation of $CD4^+$ T-cells by TRAPs to produce IL-6 (Chen et al., 2019).
- Strong increase in membrane-associated Hsp90 by stimulation of T-cells (Scarneo et al., 2022).
- DNCB labels Hsp90 and stimulates monocytes through CD91; impaired by Hsp90α KD (Kim et al., 2022).
- Surface complex induced by all-trans retinoic acid to promote integrin-mediated internalization of bacterial flagellin (Hoang and Kim, 2022).
- Exosome-associated Hsp90 promotes diabetic wound healing; signaling blocked by neutralizing antibodies (Ren et al., 2022a).
- Hsp90α secreted from capsular residual epithelial cells, involving autophagy, promotes differentiation to fiber cells (Li et al., 2023a).
- Rab37 stimulates secretion of Hsp90α by adipose tissue-derived mesenchymal stem cells and Hsp90α KD impairs their differentiation (Huang et al., 2023a).
- Secretion of eHsp90α by muscle is increased upon exercise and helps to convert the irisin receptor (αVβ5 integrin) into a high affinity state (A et al., 2023; and comment by Bourboulia et al., 2023).
- eHsp90α directly binds and aligns collagen-1 fibers promoting invasion; an unidentified factor of conditioned medium greatly potentiates its alignment ability; ATPase activity is not required, but biotinylated ganetespib inhibits, and an open conformation and dimeric form are crucial (Singh et al., 2023).
- Hsp90 on the surface of *Plasmodium* female gametes is essential for fertilization; blocked by antibody (Cha et al., 2024).
- Humanized antibody to eHsp90α suppresses invasive and spheroid-forming activities of colorectal cancer and pancreatic ductal carcinoma cell lines, and various cancer-promoting parameters in xenograft experiments (Fan et al., 2024).
- Antibody to eHsp90α protects human chondrocytes against IL-1β *in vitro*, and articular cartilage and subchondral bone in rat model of osteoarthritis (Yu et al., 2024).
- TNBC cells secrete Hsp90, which induces monocyte differentiation to tumor-associated macrophages; Hsp90 KD or ganetespib prevent this induction, the latter also in a syngeneic mouse cancer model (Hong et al., 2024).
- eHsp90α LRP1-dependently stimulates homologous recombination repair in NSCLC cells (Du et al., 2024).
- Extracellular Hsp90 from lysed *Candida albicans* cells is a virulence factor by activating NFκB signaling (Fang et al., 2024).
- Myocardial hypertrophy from pressure overload promotes secretion of Hsp90α, which activates β-catenin through interaction with N-cadherin; KD or inihibition with antibody attenuates hypertrophic response (Pan et al., 2025).
- The nondigestible oligosaccharide stachyose binds membrane-associated Hsp90β on intestinal epithelial cells to alter the microsomal profile of exosomes, which in turn changes the colonic microbiome (Li et al., 2025a; discussed by Berthet and Viennois, 2025).
- Nanobody as PET tracer for surface Hsp90 failed to distinguish between tumor and background, questioning existence of surface Hsp90 *in vivo* (Narykina et al., 2025).
- Surface Hsp90 mediates Tau internalization and degradation through endocytosis, inhibited by biotinylated GA (Nguyen et al., 2025).

Unusual stuff:

Top Refs

- Hsp90 gel shifts CpG oligonucleotides (ODN) known to stimulate immune responses (Bandholtz et al., 2003). Hsp90α but not Hsp90β binds CpG ODN to stimulate avian macrophages (Bhat et al., 2010). Extracellular Hsp90 converts CpG ODN into potent inducers of inflammatory responses in dendritic cells by trafficking into static early endosomes (Okuya et al., 2010). Associated with (self-) DNA, it strongly stimulates interferon-α production (Saito et al., 2015).
- Hsp90 specifically binds a domain of the 3' UTR of the genomic RNA of Bamboo mosaic virus (Huang et al., 2012). Hsp90β binds *BAZF* mRNA and may mediate its VEGF-induced stabilization (Miwa et al., 2013). Recombinant Hsp90 binds genomic RNA of murine norovirus (Vashist et al., 2015; see also Vashist et al., 2012).
- Hsp90 binds both amorphous calcium phosphate precipitates and hydroxyapatite, possibly to protect cells from the formation of the latter; this also induces conformational changes in Hsp90 promoting oligomeric states (Ho et al., 2012).
- Hsp90 binds certain types of phosphorothioate oligonucleotides and enhances antisense oligonucleotide activity *in vivo* (Liang et al., 2016).
- Hsp90 may serve as receptor for internalization of oxalate monohydrate crystals (Fong-Ngern et al., 2016), and promotes crystal growth (Yoodee et al., 2022).
- Peptide from a specific monoclonal binds C-terminal region of Hsp90α and blocks CS anti-aggregation activity (Girola et al., 2016).
- Vaccination with an Hsp90 expression plasmid ("DNA vaccine") is protective in a mouse model of systemic lupus erythematosus (Liu et al., 2020).
- Associates with promoter-proximal sequences of the sirtuin genes in *Plasmodium falciparum* upon heat stress (fever) to inhibit their expression, thereby promoting the expression of the var genes (Tabassum et al., 2021).
- Hsp90α/β binds SARS-CoV-2 RNA (Kamel et al., 2021).
- Recombinant *Schistosoma japonicum* Hsp90α enhances the number of dendritic cells and Th17 cells *in vitro* (Xu et al., 2020).
- lncRNA: Upon binding of Hsp90 to lncRNA GALNT5 uaRNA in gastric cancer, some clients such as AKT and IKK are further stabilized (Guo et al., 2018). Hsp90α binds lncRNA *AC245100.4*, promoting IKK chaperoning and prostate cancer growth (Cui et al., 2020). Hsp90β binds lncRNA RP3-326I13.1 to promote MMP13 expression (Zhou et al., 2022). Hsp90β binds lncMST as part of complex with EPRS resulting in increased HDAC6 expression (Lu et al., 2022b). Hsp90β and Cdc37 bind lncRNA *ENST00000440406* (renamed *HSALR1* for Hsp90β-associated lncRNA 1), which acts as scaffold to stabilize complex with Akt, mediating TGF-β1-induced chronic obstructive pulmonary disease (Yi et al., 2023). lncRNA *MALAT1* stabilizes Hsp90, promoting neuronal necroptosis in an ischemia model (Huang et al., 2023c).
- The antigen of monoclonal antibody with inhibitory effect on hepatocellular cancer stem cellness turns out to be Hsp90α (Liu et al., 2023).
- *Gingko* Hsp90 (N-terminal domain plus charged region) can bind double-stranded telomere repeats (Feng et al., 2024).

Hsp90 relatives:

Top Refs

- Grp94 (=endoplasmin=HSP90B1) (Hsp90 family member in the endoplasmic reticulum).
- Hsp75, found as a protein that interacts with and chaperones Rb during M phase and after heat shock (Chen et al., 1996a). Trap1, probably identical to Hsp75, found in two-hybrid with type I TNF receptor (Song et al., 1995). Binds radicicol and GA (Schulte et

al., 1999; Felts et al., 2000). New evidence shows Trap1 = Hsp75 is a mitochondrial protein with a GA / radicicol inhibitable ATPase (Felts et al., 2000). Not only in mitochondria in *Dictyostelium* (Morita et al., 2002).

- Hsp90 pseudogene (?) lacking GA-binding domain (Schweinfest et al., 1998). Instead, Hsp90N appears to contain an N-terminal myristoylation signal and activates Raf-1 by recruitment to the membrane; Hsp90N does not bind Cdc37 (Grammatikakis et al., 2002). Hsp90N is an artefact of a unique chromosomal translocation (Zurawska et al., 2008).
- Other members of GHKL ATPase superfamily: DNA gyrase B (Grenert et al., 1997; Prodromou et al., 1997a), the class I histidine kinase domain of EnvZ (Tanaka et al., 1998), the histidine kinase domain of CheA (Bilwes et al., 1999), pyruvate dehydrogenase kinase (PDHK) (Bowker-Kinley and Popov, 1999) and MutL have a similar fold (four β-strands and three α-helices) in their ATP-binding region (reviewed in Dutta and Inouye, 2000), suggesting a common mechanism linking ATP hydrolysis and relative subunit motion. However, domain arrangements are different (Huai et al., 2005). Smchd1 is a member of the GHKL ATPase superfamily with structural similarity to Hsp90 and its ATPase can be inhibited by radicicol (Chen et al., 2016). GHKL proteins may be part of a larger protein family with microrchidia proteins (MORC) (Inoue et al., 1999).
- $p52^{rIPK}$, the inhibitor of $p58^{IPK}$, has a very (!) limited homology to the charged region of Hsp90 (Gale et al., 1998).
- Hsp105 in spermatozoa of rat: related to Hsp90 by peptide mapping, antigenically, and by sequence within a short stretch of the charged domain of Hsp90 (Itoh and Tashima, 1990; Itoh and Tashima, 1991; Matsumori et al., 2002).
- Plants have an additional Hsp90 homolog targeted to the chloroplast stroma: in *Arabidopsis*, it is heat- and light-inducible, and a point mutant is chlorate-resistant and partially defective in greening (Cao et al., 2003).
- N- and C-terminal regions of α-spectrin and β-spectrin, respectively may have more than 50% sequence similarity with human Hsp90 (Bhattacharyya et al., 2004; see also Kudlicki et al., 1987).
- Sacsin: contains several sacsin repeating region (SRR), which is characterized by an Hsp90-like ATPase domain with a larger repeat unit. The SRR has ATPase activity but is not inhibited by geldanamycin or radicicol (Anderson et al., 2010), and is contained within a larger region with chaperone activity (Anderson et al., 2011). Structure of an Hsp90-like domain (Menade et al., 2018).

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