Published in final edited form as:
Nat Struct Mol Biol. 2013 January ; 20(1): 1–4. doi:10.1038/nsmb.2481.

A global view of Hsp90 functions

Gabriela Chiosis,
Department of Molecular Pharmacology and Chemistry, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Chad A Dickey, and
Department of Molecular Medicine, University of South Florida Health Byrd Alzheimer's Institute, Tampa, Florida, USA

Jill L Johnson
Department of Biological Sciences, University of Idaho, Moscow, Idaho, USA

Gabriela Chiosis: chiosisg@mskcc.org; Chad A Dickey: cdickey@health.usf.edu; Jill L Johnson: jilljohn@uidaho.edu

Abstract

The Sixth International Conference on Hsp90 in 2012 revealed new functions of this key molecular chaperone. Attendees of the meeting at Les Diablerets, Switzerland, addressed new discoveries about Hsp90 and its cochaperones.

Hsp90 mediates the folding and activation of diverse client proteins essential for a variety of signal-transduction pathways. Here we summarize new insights into how Hsp90 recognizes the estimated 5–10% of cellular proteins that require Hsp90 for function, and discuss recent studies of the impact of Hsp90 inhibition on normal and cancer cell function.

All forms of Hsp90, including bacterial HtpG, mitochondrial Trap1 and endoplasmic reticulum Grp94 (also known as endoplasmin), exist as dimers, bind and hydrolyze ATP, and cycle between distinct conformational states. These include (i) an open, nucleotide-free form dimerized at the C termini, (ii) a closed form that is stabilized by ATP and is dimerized at the N termini and (iii) a distinct ADP-bound conformation. The efforts of many labs are currently focused on determining how sequence and structural differences between these homologs affect chaperone function. Another active area of research is aimed at understanding why cytosolic Hsp90 is the only homolog that requires a cohort of specialized cochaperone proteins. This meeting provided an update on these questions by presenting new results gathered by researchers from around the world.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available at http://www.nature.com/doifinder/10.1038/nsmb.2481.

Hsp90-cochaperone interactions

Cochaperones are a critical component of the cytosolic Hsp90 folding pathway, as their functions include targeting clients to Hsp90 and modulating Hsp90 ATPase activity or conformational changes[1]. The 2012 meeting introduced a new isoform of Hsp90 as well as an isoform-specific cochaperone. Didier Picard (University of Geneva, Geneva, Switzerland) discussed AARSD1, a p23-related cochaperone in skeletal muscle that exhibits selectivity for Hsp90β, one of the two isoforms of human Hsp90. Wolfgang Obermann (Ruhr University, Bochum, Germany) described a primate-specific isoform of cytosolic Hsp90, Hsp103, which contains an N-terminal extension generated by alternative splicing. Purified Hsp103 exhibited ATPase activity and was able to bind Hop, Cdc37 and Aha1, but Aha1 was unable to stimulate Hsp103's ATPase activity.

The meeting also provided new structural information on three cochaperones. The tetra-tricopeptide repeat (TPR) domain TPR2A of Hop has long been recognized as the primary site for Hsp90 interaction, but recent studies indicated the importance of the third TPR domain, TPR2B[2,3]. Phillippe Meyer (Institut de Biologie Physico-chimique, Paris, France) unveiled the crystal structure of the C-terminal and middle domains of Hsp90 bound to the TPR2A-TPR2B domains of Hop. Hop contacts two proposed Hsp90 client–binding sites, including a hydrophobic patch in the middle domain and an additional C-terminal helix. These findings suggest a model in which Hop could mask one Hsp90 client–binding site while permitting Hsp70 to present bound client to the other Hsp90 subunit. Chris Prodromou (University of Sussex, Brighton, UK) presented the crystal structure of the TPR domain of cochaperone AIP, the site of mutations associated with familial isolated pituitary adenoma. His results suggest that the C-terminal α-helix of AIP is important for interaction with client proteins and that loss of such interaction contributes to pituitary adenoma. Cara Vaughan (Institute of Structural and Molecular Biology, Birkbeck College, London, UK) presented a crystal structure of another TPR-containing cochaperone, Sgt1, which contacts the client Skp1 through its TPR domain.

Additional studies indicated that even closely related cochaperones have distinct functions: Paul LaPointe (University of Alberta, Edmonton, Canada) described new differences in the function of two homologous cochaperones, Aha and Hch1. Similarly, J.L. Johnson (University of Idaho, Moscow, Idaho, USA) and Johannes Buchner (Technische Universität München, Munich, Germany) described functional differences between yeast Cpr6 and Cpr7. Graciela Piwien-Pilipuk (Universidad de Buenos Aires, Buenos Aires, Argentina) showed the differences between FKBP51 and FKBP52 during adipocyte differentiation. Specifically, FKBP51 restrains adipocyte differentiation. After adipogenesis, FKBP51 levels increases, whereas FKBP52 levels decreases. FKBP51 also colocalizes with glucocorticoid receptor at the beginning of adipogenesis and reduces the transcriptional activity of

glucocorticoid receptor during differentiation. Similarly, Mario Galigniana (Universidad de Buenos Aires, Buenos Aires, Argentina) described differing effects of FKBP51 and FKBP52 on neuronal differentiation.

Increasing evidence indicates that the role of cochaperones is to promote or stabilize particular conformations of Hsp90. Johannes Buchner used fluorescence resonance energy transfer (FRET) in combination with analytical ultracentrifugation to analyze the cycle of Hsp90-cochaperone interactions. Hop binds the open, nucleotide-free conformation of Hsp90. Upon ATP binding, Cpr6, which competes with Hop for binding to the C terminus of Hsp90, is unable to displace Hop on its own. However, Cpr6 interaction promotes Aha1 association, and the concerted actions of Cpr6 and Aha1 are able to displace Hop and accelerate formation of the first closed conformation. Bound ATP leads to the formation of the fully closed state, which is targeted by the cochaperone p23.

Phosphorylation control of Hsp90-cochaperone-client interactions

Hsp90 function is regulated by post-translational modifications, including phosphorylation and acetylation. Len Neckers (National Cancer Institute, Rockville, Maryland, USA) outlined how sequential tyrosine phosphorylation of Hsp90 and Cdc37, a protein kinase–specific cochaperone, provides directionality to the Hsp90 cycle. Cdc37 phosphorylation disrupts Cdc37-client interaction, and Hsp90 phosphorylation disrupts Hsp90-Cdc37 interaction. Subsequent Hsp90 phosphorylation events enhance client Aha1 interaction, then disrupt Hsp90 interaction with Aha1 and remaining cochaperones[4]. Petr Muller (Masaryk Memorial Cancer Institute, Brno, Czech Republic) provided additional information about how C-terminal phosphorylation have differing effects on the interaction of CHIP and Hop with Hsp70 and Hsp90, respectively, with CHIP preferring the nonphosphorylated form and Hop binding the phosphorylated form. Phosphorylation of Hsp90 may also contribute to its role in apoptosis. Research by Stephanie Solier (Institut Gustave Roussy, Villejuif, France) showed that Hsp90 phosphorylation by DNA-dependent protein kinase (DNA-PK) is an early event of apoptosis and that downregulation of Hsp90α can inhibit nuclear apoptosis. Interestingly, she also observed that DNA-PK is a client of Hsp90α, further revealing the complexity of kinase-Hsp90 interactions.

Structural differences between Hsp90s

New evidence suggests that eukaryotic Hsp90 is more flexible and less dependent on nucleotide for regulation than HtpG. Matthias Mayer (Zentrum für Molekular Biologie der Universität Heidelberg, Heidelberg, Germany) compared the conformational flexibility of yeast Hsp90 and *Escherichia coli* HtpG using amide hydrogen/deuterium exchange and mass spectrometry. He showed that the C-terminal dimerization domain of HtpG is more stable than its eukaryotic counterpart, suggesting that subunit exchange occurs more frequently in eukaryotic Hsp90. His studies also indicate that nucleotide has a greater role in stabilizing Hsp90 in prokaryotes than in eukaryotes. He further discussed the presence of N terminal–domain conformations that differ from available structures, suggesting that a higher degree of flexibility in this domain may be important during client binding and folding.

Using single-molecule FRET analysis, Thorsten Hugel (Technical University of Munich, Garching, Germany) found that HtpG exhibits a very low rate of opening at the C terminus. His studies indicate that HtpG adopts the closed state before ATP binding and that ATP serves to fix this conformation. His results also suggest that ATP binding to the two subunits of Hsp90 does not occur independently[5]. FRET-based triangulation of N-terminal residues suggests an alternate structure of this terminus of yeast Hsp90, and assays using single-molecule optical tweezers allowed the stability of the flexible linker between the N-terminal and middle domains to be examined.

David Agard (University of California, San Francisco, San Francisco, California, USA) presented a structure of an asymmetric closed state of mitochondrial Trap1. His results suggest that asymmetry beginning at the N-terminal domains and propagated to the interface between the middle and C-terminal domains is part of the Hsp90 folding cycle. He also raised the possibility that the first round of ATP hydrolysis may be critical for client folding, whereas the second is tied to client release.

New insights into Grp94, Trap1 and HtpG

Dan Gewirth (Hauptman-Woodward Institute, Buffalo, New York, USA), examined functional differences between cytosolic Hsp90 and endoplasmic reticulum Grp94 by using a set of chimeric proteins. None of the domain-swap chimeras could replace Grp94 function in a cellular assay of Grp94-dependent Toll-like receptor and integrin function, which indicates that Grp94 has unique properties. Surprisingly, chimeras containing the N-terminal domain of Grp94 are able to rescue the essential functions of yeast Hsp90, which suggests that the middle and C-terminal domains of yeast Hsp90 confer its specialized functions. Yair Argon (University of Pennsylvania, Philadelphia, Pennsylvania, USA) presented evidence from a mouse model system that expression of Grp94 is essential for the ability of skeletal muscle to produce insulin-like growth factors (IGFs), which are essential for muscle growth and maintenance of muscle mass. Grp94-deficient muscle fibers are functional, but small, and therefore weak overall. This activity of Grp94 is probably important for human development as well because some patients with primary IGF deficiency carry hypomorphic point mutations in Grp94.

Len Neckers found that the mitochondrial Hsp90, Trap1, regulates tumor suppression and cellular invasion, and protects mitochondria from oxidative stress by functioning as a negative regulator of oxidative phosphorylation. The latter finding was corroborated by Andrea Rasola (Università di Padova, Padova, Italy), who found that Trap1 is important for complex II of the oxidative respiration cycle, as Trap1 knockdown increases complex II activity. Complex II inhibition is known to affect tumor growth, and Trap1 expression is altered in many tumors.

Maximillian Press from Christine Queitsch’s lab (University of Washington, Seattle, Washington, USA) used a genome-wide approach to study why HtpG is not universally conserved in bacteria. He found that the presence of HtpG correlated with type III secretion systems and flagellar assembly. Most notably, HtpG was found in organisms that can

survive in multiple habitats, which indicates an important role for this bacterial Hsp90 ortholog in adaptation to different environments.

Hsp90-client interaction

Hsp90 chaperones a wide array of protein clients that share no sequence or structural homology, and questions about the nature and location of the client-binding sites persist. Emerging themes include: (i) clients bind large surface areas, probably spanning more than one domain of Hsp90, (ii) client binding induces conformational changes in Hsp90 and (iii) different clients bind different sites.

Stefan Rüdiger (Utrecht University, Utrecht, The Netherlands) used ^{1}H-^{13}C-isoleucine methyl transverse relaxation optimized spectroscopy (TROSY) and small-angle X-ray scattering (SAXS) to identify Tau binding sites on Hsp90. His structural model showed that disordered Tau binds to the open conformation of Hsp90. Tau binds a large region of the outer surface of the middle and N-terminal domain that largely overlaps the previously identified site of Hsp90 interaction with the kinase Cdk4[6]. Gary Daughdrill (University of South Florida, Tampa, Florida, USA) is conducting complementary studies using NMR to determine whether Hsp90 and the FKBP51 cochaperone bind overlapping regions of Tau. C.A. Dickey (University of South Florida, Tampa, Florida, USA) showed that a consequence of FKBP51-Hsp90 interaction was to protect Tau from proteasomal clearance and prevent it from adopting β-sheet structures during fibril formation, which promote the neurotoxic potential of Tau.

Olivier Genest from Sue Wickner's group (National Cancer Institute, Bethesda, Maryland, USA) used a genetic screen in *E. coli* to identify loss-of-function mutations in HtpG. The mutations, which localized to surface-exposed residues of the middle and C-terminal domains, impair ATP-dependent luciferase reactivation and disrupt interaction with two established clients: the ribosomal protein L2 and Δ131Δ. Homologous mutations result in reduced function of yeast Hsp90.

David Agard found that HtpG binds the most structured region of Δ131Δ and stabilizes native conformations that arise during normal conformation fluctuations. His research further suggests extensive contacts between Hsp90 and the client: the client-binding sites include surface-exposed residues on the middle of the C-terminal domain of one subunit as well as sites in the N-terminal and middle domain of the other subunit.

Global Hsp90 proteome investigations

Didier Picard incorporated all public data sets and experimentally reported interactions from the literature to generate a searchable comprehensive protein-protein interaction network of the Hsp90 machine (http://www.picard.ch/Hsp90Int)[7]. Research presented at this meeting indicates that Hsp90 influences the activity of 10–30% of the proteome; however, only a subset of this fraction is sensitive to inhibition by small molecules that bind the ATPase pocket of Hsp90. Perhaps these inhibitors act as sensors of the strength of the Hsp90-client protein interaction and thus of the thermal and conformational stability of the client protein.

Both Bernhard Kuster (Munich Technical University, Freising, Germany) and Didier Picard (in collaboration with Manfredo Quadroni, University of Lausanne, Lausanne, Switzerland) reported analyses of proteome-wide changes in cells treated with geldanamycin and other Hsp90 inhibitors[8]. Some tumor-suppressor gene products were degraded, whereas some oncoproteins were induced, which suggests that the composite effects of Hsp90 inhibition in cancer cells may not always be beneficial. The Hsp90 machinery was also remodeled by Hsp90 inhibition, such that levels of some cochaperones increased, whereas others decreased. They found that Hsp90 client protein downregulation by Hsp90 inhibition corresponds in many cases to reduced protein half-life.

G. Chiosis (Memorial Sloan-Kettering Cancer Center, New York, New York, USA) reported a new affinity-purification method that takes advantage of the ability of Hsp90 inhibitor PU-H71 to tightly bind and stabilize Hsp90 in a client- and cochaperone-bound conformation. The interactome identified using this method in chronic myeloid leukemia overlapped with the well-characterized altered proteome in this cancer, which indicates that this technique can provide global insights into the biology of individual tumors, including primary patient specimens[9].

In yet another new approach, Mikko Taipale from Susan Lindquist's laboratory (Whitehead Institute, Cambridge, Massachusetts, USA) used a quantitative protein-protein interaction assay, LUMIER with BACON, to study features determining the unusual client specificity of Hsp90 (ref. 10). This study provided important evidence demonstrating that the thermodynamic stability of the client determines the strength of its Hsp90 association. Strong interactors are on average more sensitive to Hsp90 inhibition and, as corroborated by the Chiosis lab, are also more likely to be captured by PU-H71 affinity purification[9]. This study indicated that Hsp90 and Cdc37 regulate a common subset of kinases and specifically recognize a partially unfolded kinase conformation, converting it to the folded conformation[10].

Protein assembly, transport, transcription and heme insertion

Walid Houry (University of Toronto, Toronto, Canada) has examined the role of two Hsp90 interactors, Pih1 and Tah1, which, together with the AAA+ DNA helicases Rvb1 and Rvb2, form the R2TP complex. His research indicates that Hsp90 facilitates assembly of the R2TP complex, which in turn stabilizes and promotes the assembly of complexes in which Hsp90 is no longer present. These complexes have important biological roles such as chromatin remodeling, box C/D small nucleolar ribonucleoprotein (snoRNP) biogenesis, apoptosis, phosphatidylinositol 3-kinase-related protein kinase (PIKK) signaling and RNA polymerase II assembly. In a similar vein, Bérengère Pradet-Balade (Institut de Génétique Moléculaire de Montpellier, Montpellier, France) showed conservation of the Hsp90–R2TP complex in *Drosophila* and human cells. The Chiosis lab showed that Hsp90 could facilitate the aberrant activation of multiprotein complexes: Hsp90 increases STAT5 signaling by binding and maintaining it in a conformation that promotes transcriptional-complex stability. Unlike classic Hsp90 clients that require Hsp90 for stability, Hsp90 inhibition does not promote STAT5 degradation but does block its activity[9].

Ritwick Sawarkar from Renato Paro's laboratory (ETH Zurich, Basel, Switzerland) proposed a new role for Hsp90 as a transcriptional regulator required for RNA polymerase pausing[11]. The group found that Hsp90 associates with promoters of several coding and microRNA genes, resulting in paused RNA polymerase II–mediated transcription by stabilizing the negative elongation factor (NELF) complex. Genes shown to be rapidly regulated by Hsp90 included *p53*, *Notch*, *Traf4* and those encoding heat-shock proteins. Similarly, Wolfgang Obermann found that Hsp90, along with smyd2, regulates the methylation and transcription of *p53*. Brian Freeman (University of Illinois at Urbana-Champaign, Urbana-Champaign, Illinois, USA) showed that p23 mediates global maintenance of open chromatin states, by modulating a variety of protein-DNA interactions, and promotes the dissociation of diverse DNA-binding proteins. Following the loss of p23 *in vivo*, transcription-factor occupancy on DNA is significantly increased, with corresponding changes in the pattern of DNase-hypersensitive sites across the genome.

Jürgen Soll and Serena Schwenkert (Ludwig-Maximilians University, Munich, Germany) discussed the role of cytosolic chaperones in post-translational preprotein targeting to the endoplasmic reticulum, mitochondria and chloroplasts. A large subset of chloroplast pre-proteins bind Hsp90 and cochaperones such as FKBPs and Hop. This process may help transport the preproteins to their target destinations in an import-competent state and prevent their aggregation and misfolding. Dennis Stuehr (Cleveland Clinic, Cleveland, Ohio, USA) presented evidence that Hsp90 interacts with the heme-free forms of heme-binding proteins and subsequently helps drive heme insertion in an ATP-dependent manner.

Hsp90 as a disease target

New links between Hsp90 and cancer progression and metastasis were also revealed. Using chromophore-assisted light inactivation (CALI) of protein function coupled with large-scale antibody libraries, Dan Jay (Tufts University, Boston, Massachusetts, USA) identified extracellular Hsp90α as a protein required for cancer invasiveness. Extracellular Hsp90 was more abundant outside of a variety of cancer cells, including fibrosarcoma, breast cancer and gliobastoma cells. Hsp90 is secreted by exosomes and can combine with other extracellular cochaperones to remodel the extracellular matrix, affecting cancer invasion.

The meeting ended with a therapeutics session to discuss three Hsp90-inhibitor clinical trials: NVP-AUY-922 (Novartis), STA-9090 (Synta Pharmaceuticals) and PU-H71 (Samus Therapeutics). This was followed by a discussion where the following questions were major points of debate: Will an Hsp90 inhibitor ever be a drug? Do we have alternate ways to target the pathway? What is the contribution of Hsp90 paralogs to the observed activity of these inhibitors, and are there applications of Hsp90 inhibitors beyond cancer?

Paul Clark, presenting for Paul Workman (Institute of Cancer Research, London, UK), and Weiwen Ying (Synta Pharmaceuticals, Lexington, Massachusetts, USA) presented data showing that HER2-overexpressing breast cancer and EGFR-mutant and ALK-translocated non–small cell lung cancer (NSCLC) were especially sensitive to Hsp90 inhibition in the clinic, in agreement with previous reports. A phase 2 trial of ganetespib (STA-9090) as monotherapy in NSCLC showed efficacy in four out of eight patients with advanced ALK-

positive NSCLC who had not received prior ALK inhibitor therapy. Seven patients experienced durable disease responses lasting an average of approximately one year.

A drawback in the Hsp90-inhibitor trials is the inability to measure the efficacy of drug delivery to the tumors. Replacing the iodine atom in the Hsp90 inhibitor PU-H71 with the radionuclide ^{124}I produces a positron emission tomography (PET) ligand. G. Chiosis presented clinical data using [^{124}I]PU-H71 as a noninvasive imaging tool to determine tumor pharmacokinetics and intratumor concentrations of PU-H71 in a selected group of patients with advanced malignancies. Studies using this agent in humans showed for the first time that Hsp90 inhibitors are retained for as long as eight days within the tumor mass, following a single dose.

Another point of discussion was the combination of Hsp90 inhibitors with inhibitors of an Hsp90-sheltered oncoprotein, to create a double-hit strategy that could also prevent the development of resistance. Preliminary results from such a combination, of retaspimycin and everolimus, in RAS-mutated NSCLC were described by Christian Fritz (Infinity Pharmaceuticals, Cambridge, Massachusetts, USA) using a mutant KRAS-p53 mouse lung-cancer model[12]. In yet a different approach, Jennifer Howes from Paul Workman's laboratory (Institute of Cancer Research, London, UK) performed a large siRNA screen to find druggable targets within cancer cells that could be sensitized by Hsp90 inhibition. In addition to HSF1, she identified cell-cycle proteins and post-translational modifiers. Combining an Hsp90 inhibitor with certain chemotherapies may also yield clinical benefits, as suggested by data presented by Weiwen Ying. An interim analysis of the phase 2b portion of a randomized phase 2b/3 GALAXY trial with the Hsp90 inhibitor ganetespib, a second-line treatment for advanced NSCLC, revealed that the combination of ganetespib with docetaxel improves overall survival in adenocarcinoma patients compared to those receiving docetaxel alone.

Our understanding of the roles of Hsp90 in diseases other than cancer has also seen advances over the last two years. Studies by Heiichiro Udono (Okayama University, Okayama, Japan) showed that Hsp90 and Hsp70 have roles in the human immune response, where they regulate the translocation of extracellular antigen to the cytosol for cross-presentation to CD8$^+$ cytotoxic T cells. This cross-presentation requires structural flexibility of the antigen, which indicates that unfolded antigen may be a new target for chaperones. Biophysical measurements by Magnus Kjaergaard from David Klenerman's and Sophie Jackson's laboratories (University of Cambridge, Cambridge, UK) revealed that Hsp90 may promote the stability of oligomeric Tau and β-amyloid, thought to be toxic species involved in the pathology of Alzheimer's disease. Hsp90 has previously been implicated in promoting the survival of pathogens, notably *Candida albicans* and trypanosomes, and this list is now expanding. Abhinav Joshi from Sushma Rathaur's laboratory (Banaras Hindu University, Varanasi, India) showed that filarial worms were protected by an Hsp90-actin complex. Antje Hombach from Joachim Clos's laboratory (Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany) discussed the impact of several phosphorylation sites in Hsp90 on the two major life-cycle stages of the parasite *Leishmania donovani*[13]. Utpal Tatu (Indian Institute of Science, Bangalore, India) found *Giardia lamblia* splice variants of Hsp90, which he suggested could scavenge naturally occurring Hsp90 inhibitors, thereby

providing a survival advantage to Giardia in its complex microenvironment. Ariberto Fassati (University College London, London, UK) suggested that Hsp90 could promote reactivation of latent HIV-1 by regulating NF-κB activity and viral transcription.

Targeting Hsp90-cochaperone interaction

Although inhibitors that block the Hsp90 ATP-binding site show promise in clinical trials, these compounds induce the heat-shock response and therefore have undesirable side effects. For this reason, targeting Hsp90 cochaperones provides a promising alternative. Ahmed Chadli (Georgia Health Sciences University, Augusta, Georgia, USA) showed that a natural product that selectively inactivates p23 destabilizes Hsp90 clients and promotes cancer-cell apoptosis, with only mild induction of heat-shock genes. Lynne Regan (Yale University, New Haven, Connecticut, USA) showed that introducing an engineered TPR protein that tightly bound the C-terminal tail of Hsp90 into HER2-positive breast cancer cells had a dominant-negative effect by competing with the TPR2A domain of cochaperone Hop for binding to Hsp90. This TPR mimetic inhibited Hsp90 function, reduced HER2 levels and promoted cancer-cell death without inducing heat-shock genes. A subsequent high-throughput screen identified compounds that disrupt the Hsp90-TPR2A interaction. These compounds promoted Hsp90 client degradation without Hsp70 overproduction in cancer cells.

References

1. Li J, Soroka J, Buchner. J Biochim Biophys Acta. 2012; 1823:624–635.
2. Schmid AB, et al. EMBO J. 2012; 31:1506–1517. [PubMed: 22227520]
3. Lee CT, Graf C, Mayer FJ, Richter SM, Mayer MP. EMBO J. 2012; 31:1518–1528. [PubMed: 22354036]
4. Xu W, et al. Mol Cell. 2012; 47:434–443. [PubMed: 22727666]
5. Ratzke C, Nguyen MN, Mayer MP, Hugel T. J Mol Biol. 2012; 423:462–471. [PubMed: 22878379]
6. Vaughan CK, et al. Mol Cell. 2006; 23:697–707. [PubMed: 16949366]
7. Echeverría PC, Bernthaler A, Dupuis P, Mayer B, Picard D. PLoS ONE. 2011; 6:e26044. [PubMed: 22022502]
8. Wu Z, Moghaddas Gholami A, Kuster B. Mol Cell Proteomics. 2012; 11:M111 016675.
9. Moulick K, et al. Nat Chem Biol. 2011; 7:818–826. [PubMed: 21946277]
10. Taipale M, et al. Cell. 2012; 150:987–1001. [PubMed: 22939624]
11. Sawarkar R, Sievers C, Paro R. Cell. 2012; 149:807–818. [PubMed: 22579285]
12. De Raedt T, et al. Cancer Cell. 2011; 20:400–413. [PubMed: 21907929]
13. Morales MA, et al. Proc Natl Acad Sci USA. 2010; 107:8381–8386. [PubMed: 20404152]