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## The multiple facets of the Hsp90 machine

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15 The Ninth International Conference on the Hsp90 Chaperone Machine concluded in October  
16 2018, in Leysin, Switzerland. The program highlighted findings in various areas, including  
17 integrated insight into molecular mechanism of Hsp90, cochaperones, and clients' structure and  
18 function.

19 Heat shock protein-90 (Hsp90) is a molecular chaperone critical for the folding, stability, and  
20 activity of client proteins <sup>1</sup>. Hsp90 and its orthologs, including bacterial HtpG, mitochondrial  
21 TRAP1 and endoplasmic reticulum Grp94, exist as dimers, hydrolyze ATP, and cycle between  
22 distinct conformational states. Hsp90 preferentially binds proteins in near native states  
23 facilitating their remodeling for protein interactions and signaling. At the 9<sup>th</sup> International  
24 Conference on the Hsp90 Chaperone Machine approximately one-third of the attendees shared  
25 their data on Hsp90 structure and function through short talks (Figure 1). Here, we distill and  
26 summarize their findings.

27

28 **Keynote Speaker**

29 To open the meeting, the keynote speaker Paola Picotti (Institute of Molecular Systems Biology,  
30 Zurich, Switzerland), presented a recently developed mass spectrometry method that enables  
31 analysis of protein structural changes on a proteome-wide scale in complex biological extracts.  
32 The approach can detect subtle alterations in secondary structure content, larger scale  
33 movements such as domain motions, and more pronounced transitions between folding states  
34 and aggregation events<sup>2</sup>. Hsp90 chaperone machinery appears to be a good candidate for further  
35 analysis by this method.

36

## 37 **Hsp90 Dynamics**

38 Carefully orchestrated conformational changes in Hsp90 are essential for its association with  
39 cochaperones and client proteins. David Agard (University of California, San Francisco,  
40 California, USA) provided the first atomic details for the Hsp90/Hsp70/HOP/glucocorticoid  
41 receptor (GR) client-loading complex. Unexpectedly, this heterocomplex contains two Hsp70s  
42 both in the ADP-bound state, one of which appears to be involved in the delivery of GR, while  
43 the other supports the cochaperone HOP. GR is largely intact, but like in the  
44 Hsp90:Cdc37:kinase complex <sup>3</sup>, part of GR is unfolded, and threaded through the lumen of a  
45 partially closed Hsp90 dimer, where it interacts with a newly revealed client binding site on  
46 HOP. Together this suggests a common mechanism for Hsp90:client recognition.

47       Stefan Rüdiger (Utrecht University, the Netherlands) revealed that Hsp70 binds clients  
48 through highly hydrophobic regions that provide protection from misfolding. Subsequently,  
49 Hsp90 breaks this interaction and allows clients to self-fold into a native state. Cochaperones are  
50 not necessary for folding, but mainly work to slow this process. Thorsten Hugel (University of  
51 Freiburg, Germany) described cooperation between nucleotide and the two amino-terminal ATP-  
52 binding pockets in an Hsp90 dimer using multicolor, single-molecule Förster resonance energy  
53 transfer (FRET). This novel technique adds an additional dimension that allowed for the  
54 discovery that ATP and Aha1 independently, but synergistically, promote closing of the  
55 nucleotide pocket, but work antagonistically to affect subsequent reopening <sup>4</sup>. Katarzyna Tych  
56 from Matthias Rief's Lab (Technische Universität München (TUM), Munich, Germany)  
57 described the dynamics of Hsp90 carboxy-terminal dimerization using single molecule optical  
58 tweezers. Interestingly, Hsp90 carboxy-terminal association has three dissociation rates that are  
59 controlled by the presence of ATP, which stabilizes this interaction by eliminating the weakest

60 interaction state.

61 Vinay Dahiya from Johannes Buchner' group (TUM, Munich, Germany) described the  
62 chaperoning mechanism of Hsp70 and Hsp90 for “the guardian of the genome,” p53. Hsp70  
63 together with Hsp40 unfolds and inactivates p53. The Hsp70 NEF, Bag1 supports the release of  
64 p53 from Hsp70 and, in coordination with HOP, Hsp90 and ATP promotes the folding of p53  
65 and restores its DNA binding activity. Shannon Doyle from Sue Wickner's Lab (NCI, NIH,  
66 Bethesda, Maryland, USA) showed that Hsp90 and Hsp70 directly interact in both *Escherichia*  
67 *coli* (*E. coli*) and yeast. The region of interaction on Hsp90 involves residues in the middle-  
68 domain that also interact with several cochaperones and clients, while the interaction region on  
69 Hsp70 utilizes residues in the J-protein binding region of Hsp70 <sup>5</sup>.

70

### 71 **Hsp90 Phosphorylation and Regulation**

72 Hsp90 and its cochaperones are subject to post-translational modifications (PTMs) including  
73 phosphorylation. Ioannis Gelis (University of South Florida, Tampa, Florida, USA)  
74 demonstrated that during the chaperone cycle, Hsp90 phosphorylation occurs in a cochaperone  
75 regulated manner. This is exemplified by the Hsp90/Cdc37 heterocomplex, in which the  
76 phosphorylation of Cdc37 primes Hsp90 for phosphorylation of tyrosine 197, and controls  
77 disassembly of the client recruitment complex. Thus, Hsp90 cochaperone complexes are highly  
78 dynamic and highly regulated at many steps throughout the chaperone cycle <sup>6</sup>.

79 Matthias Mayer (Universität Heidelberg, Germany) revisited previous works on PTMs of  
80 Hsp90 and how they fine tune Hsp90 function. His data based on yeast growth assays revealed  
81 that some phosphomimetic mutations of Hsp90 grow more efficiently than the wild-type Hsp90  
82 and more potently activate steroid hormone receptors, apart from GR. This supports the idea that

83 PTMs can tune Hsp90 specificity for chaperoning specific clients, even those that evolved from  
84 the same gene.

85

### 86 **Structure and function of Hsp90 Orthologs**

87 Dan Gewirth (Hauptman-Woodward Institute, Buffalo, New York, USA) presented data on the  
88 structure of the Pre-amino (Pre-N) domain of Grp94, the endoplasmic reticulum (ER) Hsp90,  
89 along with functional data showing its role in client protein maturation. The Pre-N domain  
90 regulates the ATPase activity of the chaperone and appears to functionally substitute for  
91 cochaperones of Hsp90, which are missing in the ER <sup>7</sup>.

92 Olivier Genest (CNRS, Aix Marseille University, France) showed that Hsp90 is essential  
93 under heat stress in the aquatic bacterium *Shewanella oneidensis* <sup>8</sup>. He found that TilS, a tRNA  
94 modifier, is a client of Hsp90 and that an interplay takes place between folding by Hsp90 and  
95 degradation by the protease HslUV to finely regulate the level of TilS.

96

### 97 **Modulation of Hsp90 by Cochaperones**

98 The chaperone function of Hsp90 is tightly regulated by cochaperones. Pierre Goloubinoff  
99 (University of Lausanne, Switzerland) proposed Hsp70 as the major cochaperone of Hsp90.  
100 Deletion studies in *E. coli* demonstrate that, unlike the deletion of Hsp70/Hsp40, which  
101 upregulated many chaperones and proteases while suppressing metabolic and respiratory  
102 enzymes, deletion of *E. coli* Hsp90 did not dramatically impact protein levels. This work also  
103 revealed that Hsp90 promotes the degradation of aggregation-prone clients of Hsp70/Hsp40  
104 through the HslUV protease.

105 Kaushik Bhattacharya from Didier Picard's group (University of Geneva, Geneva,

106 Switzerland) addressed the question of the importance of the HOP protein in eukaryotes <sup>9</sup>. He  
107 found that the complex Hsp70-HOP-Hsp90 physically interacted with the proteasome. Although  
108 in the absence of HOP the proteasome activity is reduced, he showed that proteostasis is  
109 maintained by a “super-chaperone” complex minimally consisting of Hsp90, Hsp70, a J-protein  
110 and a nucleotide exchange factor, resembling the chaperone complex found in prokaryotes.  
111 Michael Reidy from Dan Masison’s group (NIDDK, NIH, Bethesda, Maryland, USA) reported  
112 that Sti1 (HOP) has two distinct functions for yeast Hsp90. The first function is to connect  
113 Hsp70 to Hsp90 by binding directly to both chaperones. The second function is to facilitate  
114 transfer of clients from Hsp70 to Hsp90 by priming Hsp90 for client loading.

115         The R2TP complex is a cochaperone of Hsp90 that includes RuvBL1 and RuvBL2, two  
116 AAA+ proteins involved in cancer progression <sup>10</sup>. Walid Houry (University of Toronto, Toronto,  
117 Canada) developed a screen to find inhibitors of the RuvBL2 protein. He successfully identified  
118 a compound that inhibits RuvBL2. Chris Prodromou (University of Sussex, Brighton, UK)  
119 described the 3D structure of the yeast and human R2TP complex that was recently solved using  
120 X-ray crystallography and single-particle EM <sup>11</sup>. These structures revealed the importance of the  
121 Hsp90 cochaperone complex as a hexamer-ring and that in yeast, binding of a single Tah1  
122 coupled to Pih1 could promote Rvb1p-Rvb2p ATPase activity. Philippe Meyer (Sorbonne  
123 Université, CNRS, Paris, France) presented the crystal structure of the human RPAP3 in  
124 complex with PIH1D1, important cochaperones in the R2TP complex that regulate Hsp90  
125 activity. This work revealed that the TPR2 domain in RPAP3 recruits Hsp90, which stimulates  
126 Hsp90 ATPase activity in synergy with Aha1. This stimulation activity is abolished if the amino-  
127 terminus of RPAP3 is deleted.

128         Markus Zweckstetter (DZNE, Göttingen, Germany) described the 3D structure of Hsp90

129 in complex with misfolded transthyretin, which was similar to the binding previously described  
130 for tau <sup>12</sup>. The impact of cochaperones on Hsp90 structure was also described using the example  
131 of FKBP51, which binds to all three domains of Hsp90 with varying affinities and results in  
132 reduced ATPase activity by stabilizing an open conformation of the amino-terminal domain.  
133 When bound to Hsp90, the catalytic site of FKBP51 remains accessible supporting the idea that  
134 Hsp90 likely acts as a scaffold to support the functional interaction of misfolded proteins with  
135 cochaperones. Mehdi Mollapour (SUNY Upstate Medical University, Syracuse, New York,  
136 USA) described the cooperative function of new cochaperones, Tsc1 and FNIP1/2. They work  
137 cooperatively to decelerate Hsp90 chaperone cycle and play a role in the chaperoning of both  
138 kinase and non-kinase clients <sup>13</sup>. He also showed how phosphorylation, SUMOylation and  
139 ubiquitination of the cochaperone Protein Phosphatase-5 (PP5) regulate its activation, substrate  
140 binding and degradation in cancer.  
141

142 **Moonlighting Functions of Hsp90**

143 Several newly emerged moonlighting functions of Hsp90 at the nucleus and plasma membrane  
144 were revealed at this meeting. Brian Freeman (University of Illinois, Urbana, Illinois, USA),  
145 using an elegant single cell approach with a fluorescently marked DNA locus, demonstrated how  
146 Hsp90 is involved in chromosome motion within interphase cells. He showed that Hsp90 and  
147 p23 keep ARP-containing chromatin remodelers in a dynamic state allowing them to interact  
148 with target gene promoters, in turn directing actin polymer formation and chromosome motion.

149 Gergely Lukacs (McGill University, Montreal, Canada) showed that both eukaryotic  
150 (Hsc70 and Hsp90) and prokaryotic chaperone (DnaK) systems can reshape the conformational  
151 energetics of mutant CFTR channel final fold towards that of the wild-type at the single  
152 molecule level and in cells. This mechanism has implications in the regulation of metastable  
153 ABC-transporters and other membrane proteins. Dragana Vidovic, from Ineke Braakman's group  
154 (Utrecht University, The Netherlands) reported that Hsp90 is required for a crucial step in  
155 folding of CFTR. More specifically Hsp90 is involved in folding of the CFTR nucleotide-  
156 binding domain. Wild-type CFTR in the presence of compromised Hsp90 function is folded like  
157 the pathogenic mutant CFTR  $\Delta$ F508. Michael Heider and Vanesa Fernandez-Saiz from Florian  
158 Bassermann's Lab (TUM, Munich, Germany) described Cereblon (CRBN), the target of  
159 immunomodulatory drugs (IMiDs), as a novel regulator of the Hsp90-Aha1 axis that mediates  
160 maturation of transmembrane proteins such as CFTR. They also showed that Hsp90-CRBN  
161 interaction was abrogated upon IMiD-treatment, thus explaining CRBN-dependent IMiD  
162 induced destabilization of its transmembrane clients.

163 Shiran Dror from Anat Ben-Zvi's group (Ben-Gurion University of the Negev, Beer  
164 Sheva, Israel) presented his work on the role of Hsp90 in myosin assembly in *C. elegans*. He

165 showed that knockout or overproduction of Hsp90 and some of its cochaperones resulted in loss  
166 of motility phenotypes due to myosin filament disorganization. Looking at chaperone  
167 localization patterns in the sarcomere, he proposed that Hsp90 machinery is important for  
168 regulating myosin translocation across the sarcomere allowing the formation of proper filaments  
169 of myosin. Yu-Chun Wang from Patrik Verstreken's lab (VIB, Leuven, Belgium), showed a  
170 previously unexpected role of Hsp90 in membrane remodeling. *In vitro* and *in vivo* evidence  
171 indicated that Hsp90 interacts with membranes via an amphipathic helix, deforms the  
172 membranes and allows exosome release. This activity can be inhibited by Hsp90 inhibitors <sup>14</sup>.

173 Christine Queitsch (University of Washington, Seattle, Washington, USA) described that  
174 the effects of Hsp90 on the evolutionary rate of protein kinases is comparable to effects of gene  
175 expression and protein interactions. She showed that a single mutation can render a non-client  
176 transcription factor Hsp90-dependent and that Hsp90-dependent *de novo* mutations do not  
177 account for most Hsp90-dependent phenotypes.

178

### 179 **Hsp90 in Maladies**

180 Hsp90 is involved in various maladies including cancer, neurodegenerative diseases, and  
181 pathogenic infections. Laura Blair (University of South Florida, Tampa, Florida, USA)  
182 demonstrated that Aha1 increases tau aggregation. In contrast, cyclophilin 40 (CyP40) disrupts  
183 tau fibrils reducing neurotoxicity *in vivo* <sup>15</sup>. These findings provide strong rationale to develop  
184 therapeutics for tauopathies by targeting molecular chaperones. Aaron Voigt (RTWH Aachen  
185 University, Germany) demonstrated that mitochondrial Hsp90 TRAP1 is an important player in  
186 Parkinson's disease (PD) and his data suggest that enhancing TRAP1 abundance or activity in  
187 neurons might be an avenue for future PD therapies.

188            Oliver Krämer (Johannes Gutenberg University Mainz, Germany) presented his work on  
189 the involvement of Hsp90 and the histone deacetylase 6 (HDAC6) in acute myeloid leukemia  
190 (AML) cells. He showed that a combination of inhibitors directed towards HDAC6 and Hsp90  
191 triggered apoptosis of AML cells, providing new promising ways to treat AML. Ramona Schulz-  
192 Heddergott (University Medical Center of Göttingen, Germany) described that stabilization of a  
193 cancer-relevant Hsp90 client p53-R248Q contributes to STAT3 hyper-activity. Vice versa,  
194 Hsp90 inhibition by 17AAG leads to degradation of the p53 mutant and thus, down-regulation of  
195 p-STAT3. This data suggests that the cancer-relevant Hsp90 client p53 mutants represent an  
196 actionable drug target for treatment with Hsp90 inhibitors.

197            Stephanie Diezmann (University of Bristol, Bristol, UK) described how Hsp90 and lack  
198 of the cochaperone Sti1 (HOP) enables phenotypic variation via loss-of-heterozygosity and  
199 aneuploidy in the ameiotic human fungal pathogen *Candida albicans*. She proposed the  
200 environmentally responsive chaperone Hsp90 as a novel mechanism for the creation of genetic  
201 diversity in *C. albicans*. Harriet Mok from Jason Mercer's group (University College London,  
202 UK) highlighted the importance of Hsp90 in the life cycle of a poxvirus family member, vaccinia  
203 virus (VACV). Using microscopy and virus-specific assays, she showed that multiple isoforms  
204 of Hsp90 are required during late stages of vaccinia infection including successful genome  
205 release into the host cytoplasm and replication.

206            Joachim Clos (Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany)  
207 discussed the translome changes in *Leishmania donovani* following Hsp90 inhibition. This  
208 protozoan parasite showed increased synthesis of proteins that are involved in oxidative stress  
209 protection, proteolysis, chromatin assembly, and chaperoning following Hsp90 inhibition. These  
210 results underscore the importance of Hsp90 in the control of the parasite's life cycle.

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## **Hsp90 in the Extracellular Environment**

The extracellular molecular chaperone Hsp90 (eHsp90, released or surface-bound) is responsible for chaperoning clients outside the cell. Wei Li (University of Southern California, Los Angeles, California, USA) provided a remarkable overview of the roles of extracellular Hsp90 $\alpha$  in repairing injured tissues and in supporting tumorigenesis. During wound healing, secreted Hsp90 $\alpha$  interacts with the extracellular domain of a receptor (LRP-1) that is stabilized by Hsp90 $\beta$  inside the cell. Hsp90 $\alpha$  protects cells from hypoxia-triggered apoptosis and promotes cell motility to close the wound. Surprisingly, the activity of Hsp90 $\alpha$  is independent of its ATPase activity and can be fulfilled by a short region of Hsp90 $\alpha$  of only about 115 amino acids, called fragment-5<sup>16</sup>. These properties of secreted Hsp90 $\alpha$  have been taken advantage of by tumor cells to gain invasion and metastasis, representing an alternative target for anti-tumor therapeutics. Natasha Boel from Adrienne Edkins' group (Rhodes University, Grahamstown, South Africa) investigated the role of Hsp90 in the dynamics of the fibronectin (FN) matrix. She showed that Hsp90 interacts with FN, and that inhibition of Hsp90 by novobiocin resulted in FN turnover via a LRP-1 receptor mediated response<sup>17</sup>.

Patricija van Oosten-Hawle (University of Leeds, Leeds, UK) explained how a proteotoxic stress perceived in one tissue induces a response in other tissues leading to molecular chaperone activation via a pathway termed transcellular chaperone signaling (TCS). Using *C. elegans*, she showed that the zinc finger transcription factor PQM-1 is involved in mediating TCS<sup>18</sup>. Importantly, she found that activating Hsp90 by TCS reduced the formation of toxic amyloid beta aggregates.

234 **Small molecule inhibitors of Hsp90**

235 Hsp90 inhibitors that target the ATP binding pocket in the amino-terminal domain are currently  
236 evaluated in cancer patients. Brian Blagg (University of Notre Dame, Notre Dame, Indiana,  
237 USA) presented the design and development of two new scaffolds that selectively inhibit the  
238 Hsp90 $\beta$  isoform <sup>19</sup>. As a result of these studies, new isoform-dependent substrates were  
239 identified that can be selectively modulated via inhibition of Hsp90 $\beta$ . In addition, it was  
240 observed that selective inhibition of Hsp90 $\beta$  induces the degradation of HSF1, and thus, there is  
241 no induction of the heat shock response. Initial studies suggest that Hsp90 $\beta$ -selective inhibition  
242 may overcome some of the obstacles encountered with the pan-Hsp90 inhibitors that have  
243 struggled in clinical trials. Timothy Haystead (Duke University, Durham, North Carolina, USA)  
244 presented data on tethered inhibitors of Hsp90 amino-terminal domain causing aggregation and  
245 reinternalization of the Hsp90 protein such that it accumulates intracellularly at high  
246 concentration. This observation led to development of a series of imaging agents for the  
247 detection of early metastatic disease as well as imaging of inflammatory responses to immune  
248 challenge.

249

250 **Understanding Hsp90 Function Through Artificial Intelligence**

251 William E. Balch (The Scripps Research Institute, La Jolla, California, USA) used a new  
252 Gaussian Process-based machine learning approach referred to as Variation Spatial Profiling  
253 (VSP) to show that diversity at the population level is sensitive to the buffering capacity of the  
254 proteostasis program. Based on Spatial CoVariance (SCV), genetic diversity contributing to  
255 misfolding disease found in the population can be displayed as high-dimensional phenotype  
256 landscapes. Application of these technologies reveal a map of the specific sequence-to-function-

257 to-structure features of the client protein fold that are responsive to Hsp70-Hsp90  
258 chaperone/cochaperone management at molecular resolution <sup>20</sup>. Gennady Verkhivker (Chapman  
259 University School of Pharmacy, Irvine, California, USA) described the step-wise fashion by  
260 which the Hsp90-Cdc37 heterocomplex recognizes client kinases through differential  
261 stabilization of kinase lobes. This work revealed that Hsp90 binds after Cdc37 and helps shed  
262 light on unique dynamics signatures of protein kinase clients/nonclients that dictate chaperone  
263 addiction and explain divergences in the regulatory mechanisms among structurally similar  
264 kinases.

265

#### 266 **Recognition of Colleagues in the Hsp90 Field**

267 For the past sixteen years two leaders in the field, Didier Picard (University of Geneva,  
268 Switzerland) and Johannes Buchner (TUM, Munich, Germany), have organized the Hsp90  
269 conference biannually. At this 9<sup>th</sup> International Conference, they were recognized for their  
270 valuable contribution and outstanding service to the Hsp90 field and community. They were both  
271 acknowledged and thanked for their continuous support of students, post-doctoral fellows and  
272 new group leaders (Figure 1).

273

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321 **Figure legend**

322

323 Figure 1. Above- Participants of the Ninth International Conference on the Hsp90 Chaperone

324 Machine. Below- Brian Freeman (far left) and Mehdi Mollapour (far right) presented recognition

325 trophies to the meeting organizers, Johannes Buchner, Didier Picard (middle). Photos by

326 Abhinav Joshi.

