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## Discovering the secrets of Hsp90 binding

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Geldanamycin is an antibiotic that binds to Hsp90 and inhibits its adenosine triphosphate binding and activity as a chaperone. A derivative of geldanamycin (GM) is the Hsp90 inhibitor 17-allylaminogeldanamycin (17-AAG), which preferentially kills tumor cells and is in [phase I clinical trials](#). Hsp90 is found in all cell types, but it has been unclear how the preferential killing of tumor cells by 17-AAG is accomplished. In the September 25 [Nature](#), Adeela Kamal and colleagues at [Conforma Therapeutics Corporation](#) report that Hsp90 from tumor cells binds with higher affinity to 17-AAG and that this is due to Hsp90 being in multichaperone complexes in these cells. (*Nature*, **425**:407-410, September 25, 2003)

Kamal *et al.* performed competitive binding assays using increasing concentrations of 17-AAG to inhibit the binding of Hsp90 to GM-biotin and observed that Hsp90 from tumor cells had a 50% inhibitory concentration (IC<sub>50</sub>) of 6 nM compared with 400-600 nM for Hsp90 from control cells. Measurements comparing the binding of adenosine triphosphate (ATP) to Hsp90 also showed a lower IC<sub>50</sub> for tumor Hsp90, revealing that Hsp90 in tumor cells had a significantly higher binding affinity for 17-AAG. Hsp90 assembles in [multichaperone complexes](#) by interacting with many cochaperone proteins (e.g., p23, Hop), and co-immunoprecipitation of Hsp90 demonstrated that Hsp90 from tumor cells is present in more of these complexes. Hsp90 tumor complexes also showed a higher ATPase activity (something that Hsp90 chaperone function is dependent on) that was inhibited by 17-AAG. In addition, *in vitro* reconstituted Hsp90 complexes showed an increased apparent affinity for 17-AAG-12 nM for Hsp90 alone rising to 600 nM when complexed. The authors then performed these experiments in mice and in clinical cancer and observed a similar pattern of 17-AAG binding to *in vivo* tumor Hsp90.

"Our data show that Hsp90 in tumor cells exists in a functionally distinct molecular form. [Hsp90 could be the] Achilles heel of tumor cells, driving the selective accumulation and bioactivity of pharmacological Hsp90 inhibitors, and making tumor Hsp90 a unique cancer target," conclude the authors.

## References

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