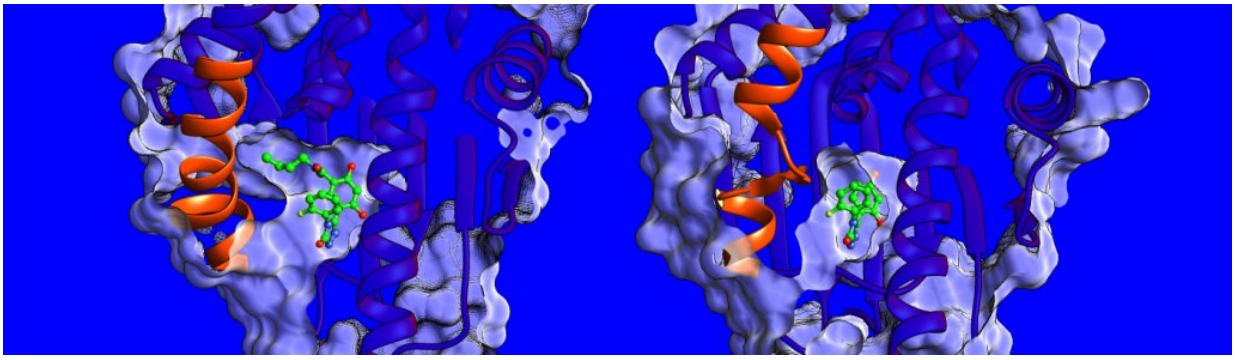
A matter of mobility: multidisciplinary paper suggests new strategy for drug discovery

January 15 2018



Differences in the structure and dynamics of the helical region (shown in orange) of the HSP90 protein. Credit: Heidelberg Institute for Theoretical Studies

A joint industry/academia study of a cancer target protein reveals unusual relation between binding site flexibility and drug-target lifetime. The results, published in *Nature Communications*, suggest a new strategy for drug discovery. The research was done in the framework of the Kinetics for Drug Discovery K4DD consortium, supported by the Innovative Medicines Initiative.

Most drugs exert their therapeutic effect by binding to a target protein molecule, thereby interfering with the normal function of the protein. Traditionally, it has been considered that the more tightly a drug binds its target protein, i.e. the greater its binding affinity is, the more effective it

will be. However, drugs must function in the constantly changing environment of living organisms. It is therefore increasingly recognised that not only binding affinity and thermodynamics, but also drug-target residence times and kinetics must be optimized during the process of drug discovery.

Kinetics put to the test: Studying a cancer target

A multidisciplinary team of scientists from K4DD partners Merck KGaA (Darmstadt), Heidelberg Institute for Theoretical Studies (HITS), and the Instituto de Biologia Experimental e Tecnológica (iBET) (Lisbon), applied state-of-the-art experimental and computational approaches to investigate the determinants of target residence times for a set of inhibitors of a widely studied cancer target, heat shock protein 90 (HSP90). HSP90 inhibitors can disrupt the cell cycle and potentially stop tumour growth. The team recently published some of their results in *Nature Communications*.

Surprising results: greater binding site mobility leads to longer residence times

"At the moment, there is little known about the factors influencing drug-target residence times so we decided to measure the binding thermodynamics and kinetics, solve the structures of HSP90-inhibitor complexes and simulate their dynamics," says Dr. Marta Amaral, one of the corresponding authors. The structures determined by X-ray crystallography show that the binding pocket of HSP90 is lined by a region that can take the form of a helix or a loop when bound to different inhibitors (see image below).

The researchers found that compounds binding with a helix present bind for a longer time. "We were really surprised," says Prof. Rebecca Wade

(HITS), "when we found out that an important contributor to the long residence times was the greater mobility of the helical region of the binding pocket when the inhibitor bound." This unusual binding mechanism opens a new avenue for drug design: Scientists can consider less rigid protein targets and identify molecules that stabilize more mobile forms of the protein upon binding – somewhat like a ski boot with an adaptable inner liner that continually adjusts to the foot. The findings of this study suggest a new way to find more effective drug candidates with optimal kinetic and thermodynamic properties.

More information: M. Amaral et al. Protein conformational flexibility modulates kinetics and thermodynamics of drug binding, *Nature Communications* (2017). DOI: 10.1038/s41467-017-02258-w

Provided by Heidelberg Institute for Theoretical Studies