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Research Title: Combining computational and structural studies of the molecular chaperone Hsp90: translating the understanding of molecular functional mechanisms into drug-discovery.

Report on the research. In this research collaboration with the laboratory of prof. David Agard at UCSF, we have extended our computational approaches for the discovery of new allosteric regulators for the chaperone Hsp90, a protein fundamental for cancer and neurodegeneration. In particular, we have focused on the study of one representative of the Hsp90 family of proteins, namely TRAP-1, whose structure has been recently solved by the Agard Lab. In the context of our collaboration, we have run Molecular Dynamics (MD) simulations of TRAP-1 in different ligand states and run analyses of MD simulations data, to identify those C-Terminal Domain (CTD) residues that move coherently with the ATP-binding pocket. Controlling these residues by specific ligands should provide the highest probability of influencing the functional motions of the protein in an allosteric fashion. Therefore, this method can be used to identify new druggable sites, to design potential allosteric ligands and to explore the allosteric effects they induce on the protein, thus adding a new dimension to structure-based drug design.
Using this approach, the glycosylated benzofuran **1** was identified as a CTD binding hit, able to afford functional allosteric modulation of TRAP-1 activity. In the Agard Lab, we have used biochemical, spectroscopic and structural methods, combined to computational studies, to define how the ligand and protein dynamically adapt to each other. We are now using this information to modify and optimize the initial hit and to develop new derivatives targeting specifically TRAP-1 CTD, transforming the hit into an effective anticancer lead by taking ligand-dependent functional dynamics explicitly into account. Four possible areas of modification have already been identified (see **figure 1**) and new small molecule derivatives have been prepared and are currently under test in the Agard Lab.

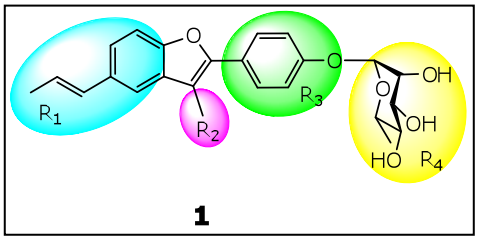

Figure 1. The starting lead for the development of allosteric inhibitor leads.

The preliminary results are extremely promising and we hope to submit a paper, as well as grant proposals in the near future.