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Jessica Holien, Drug Des 2015, 4:2
http://dx.doi.org/10.4172/2169-0138.S1.007

International Conference and Expo on
Drug Discovery & Designing
August 11-13, 2015 Frankfurt, Germany

Designing protein-protein interaction modulators: LRH-1 and 14-3-3

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Protein-protein interactions (PPIs) play important regulatory roles in cells, for example in the cell division cycle or in cell signalling and often become dysregulated in cancers. Thus it is not surprising that modulators of PPIs – ideally small "drug-like" molecules - are urgently being sought and developed by the Pharmaceutical Industry to treat unmet medical need. However, the characteristics of the PPI interface make this task non-trivial. Structure-based computational molecular modelling is at the heart of PPI modulator design. However, the established design principles need to be significantly modified and revised for the difficult and unique nature of PPI interfaces.

LRH-1 is an orphan nuclear receptor that has been implicated in breast cancer progression due to its ability to stimulate aromatase expression, recruit estrogen receptor to its target sites, and improve motility and invasion of breast cancer cells contributing to metastasis. For post-menopausal women, current breast cancer hormonal therapies inhibit aromatase or modulate ER action (SERMs). Although effective, these treatments have low compliance rates due to significant adverse effects, including bone loss, joint pain, cognitive disturbances and compromised liver function. LRH-1 activity is regulated by co-activator and co-repressor proteins which bind to a co-regulator site. We computationally screened virtual compound libraries against the co-regulator site of a 3D crystal structure of LRH-1 to select ~200 candidate molecules. These small molecular weight compounds were tested in functional assays and we have identified two chemical classes of active compounds. One of these chemical classes has been successfully modelled into the co-regulator site of LRH-1. Using this model we selected and purchased ~100 new compound analogues for screening in functional assays. Many of the new compounds showed good inhibitory activity for LRH-1. We are using this information to further improve the potency and specificity of this chemical class of compounds towards LRH-1 in an attempt to find better breast cancer treatments for post-menopausal women.

14-3-3 With at least 200 interaction partners, 14-3-3 proteins are an especially important and challenging target for PPI modulation. We have found that 14-3-3 proteins can be regulated through a mechanism that interferes with their dimeric state. From extensive site-directed mutagenesis studies we have gained a unique insight into the molecular basis of 14-3-3 dimerisation; namely, we have established that dimers are held together by critical inter-molecular salt bridges between conserved residues D21:K85 and E89Q:R18. The physiological lipid sphingosine interferes with these dimer stabilizing salt bridges, thereby rendering the protein susceptible to phosphorylation at a residue normally buried at the dimer interface. Using a classical in silico screening approach we managed to identify several small molecules which induce apoptosis in cancer lines *in vitro* via a disruption of the dimer interface. However, understanding how these small molecules disrupt the dimer interface is outside the scope of classical structure-based drug design techniques. We have devised methodology to further explore the effect our lead compounds have on the dimer interface of 14-3-3. With a molecular understanding of how inhibitors disrupt 14-3-3 dimers we will be able to enhance our current chemical series and rationally design new molecules to modulate the physiological regulation by 14-3-3.

Biography

Jessica Holien is leading a project to develop therapeutics for treating leukaemia. The potential new drugs will target two separate protein-protein interactions, involving Homeobox (HOX) and the 14-3-3 proteins.

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