Agnieszka K. Bronowska, Int J Chem Res 2018
http://dx.doi.org/10.18689/2642-1615.a1.004

Computational Identification of Novel Binding Sites to Expand the Druggable Human Proteome

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The druggable human proteome may be larger than previously estimated: structured proteins may have multiple binding sites (allosteric and/or cryptic) which are not targeted during the conventional structure-based drug discovery procedures. Metamorphic aka intrinsically disordered proteins may also display transient structured binding sites, which may render those challenging targets druggable. Understanding and accurately predicting those binding sites could significantly expand the set of drug targets.

During my talk, I will present the recent all-atom MD simulation data on drug ability of proteins containing PAS domains (human AhR receptor, IPAS, and HIF-3alpha, including PAS domains previously unreported (NCOA1-NCOA3 nuclear receptor coactivators). I will show the novel binding sites we have identified for human STAT3, JAK3 and human sequestrosome p62, suitable for targeting by small molecule inhibitors.

I will also talk about methods used for reliable identification of novel cryptic and transient protein binding sites: solvent mapping, mixed-solvent atomistic simulations (Mix MD) and a new approach employing enhanced-pressure molecular dynamics (EPMD) simulations, developed in my laboratory.

Biography:

Dr. Agnieszka K. Bronowska has been appointed Lecturer in Computational Medicinal Chemistry at Newcastle University in January 2016. Before her appointment she was a BIOMS Research Fellow at the University of Heidelberg, Germany, and earlier she worked as a postdoc in the group of Prof. Steve Homans in Leeds.Agnieszka's research focuses on development of new methods applicable to computational drug design and atomistic molecular simulations of proteins, protein-ligand complexes and complex nanomaterials. She is particularly interested in expanding druggable proteome by developing allosteric ligands and in rendering intrinsically disordered proteins (IDPs) druggable via binding-induced shifting of conformational ensemble.