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Rational design approaches to find novel ligands targeting the aryl hydrocarbon receptor: Successful applications and mechanistic studies

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The aryl hydrocarbon receptor (AhR) is a ligand activated member of the basic helix-loop-helix (BhLH) family of transcription factors. The AhR is activated by a variety of compounds, both synthetic and natural, including halogenated aromatic hydrocarbons such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), and mediates their biological activity. The AhR is a cytosolic transcription factor bound to several co-chaperones. Upon ligand binding, the AhR translocates from the cytoplasm to the nucleus and regulates genes, including several drug metabolizing enzymes that can influence the therapeutic activity of a number of compounds. The AhR regulates proliferation and differentiation of cells. In addition, the AhR induces immunosuppressive regulatory T cells with therapeutic implications in hyperimmune disorders. The role of the AhR has been also studied by us in cancer and *in vivo* zeebrafish tissue regeneration. Up to now, the AhR-LBD-PASB domain remains experimentally unresolved. Hence, the homology models of the AhR-LBD PASB domain were prepared to identify new AhR ligands by virtual ligand screening. Successful applications in finding novel agonists, selective modulators (sAhRM) and full antagonists of the AhR will be described. Recent mechanistic studies using computational molecular simulations on the AhR models will be reported. The results obtained demonstrate that in the absence of experimentally resolved structures, computational chemogenomics techniques are still a successful tool in the hands of interdisciplinary teams for the discovery of novel AhR-targeted therapeutics.

Biography

William H. Bisson completed his Ph.D in 2003. at Medicinal and Computational Chemistry at the ETH Zurich, Switzerland. In 2004, he joined as a Research Fellow at the Scripps Research Institute in La Jolla, CA. Later in 2006, he started as a Research Associate at the nearby Sanford-Burnham Medical Research Institute. In 2008 he joined as a Research Associate at the Oregon State University and in 2010 he came back to Switzerland, at the University of Geneva as Senior Research Scientist. Currently, he is Assistant Professor at Oregon State University working successfully in inter-disciplinary projects mostly in cancer using computational chemogenomics.

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