[P39] Rational design of ligands targeting GPCR heterodimers – application to V1B CRHR1 dimer in the treatment of stress, anxiety and depression

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G protein-coupled receptors (GPCRs) are a family of membrane proteins whose function is to activate specific cellular signaling pathways in response to extracellular stimuli. They are involved in many physiological and pathological processes and are the target of 40% of drugs currently on the market [1]. In the past decades, many studies have demonstrated that some GPCRs are able to cross-react, forming homo-, hetero-dimers and even higher ordered oligomers [2]. Arginine vasopressin receptor 1B (V1BR) and Corticotropin-releasing hormone receptor 1 (CRF1R) are involved in the activation of the hypothalamic-pituitary-adrenal (HPA) axis. Both receptors are activated in the hippocampus by two peptide hormones: arginine-vasopressin (AVP) for V1BR and corticotropin-releasing factor (CRF) for CRFR1R. Once activated by their respective hormones, these two receptors synergistically regulate adrenocorticotropic hormone (ACTH) release from the pituitary gland, as a functional adaptation to stress. Experimental data suggests that V1B and CRFR1 receptors can form heterodimers with a pharmacology differing from that of isolated receptors [3]. One can assume that there is a physiopathological relevance for their physical association.
In order to demonstrate this association, heterobivalent ligands targeting both receptors in their heterodimeric forms are currently being designed in our laboratory (D. Bonnet). Finally, *in vitro* and *in vivo* studies will be conducted by our biological partners (G. Guillon, IGF Montpellier).

This poster will summarize all the steps performed to design heterobivalent ligands:
- Homology modeling of the V1B receptor
- Molecular docking of several known V1B receptor antagonists
- Consistency of docking results with SAR (Structure Activity Relationship) data
- Studying of the available CRFR1 X-ray structure [4] by molecular dynamics to confirm that a bivalent ligand will effectively be able to access the binding pocket

In a next step, we will model the V1BR-CRF1R dimer, on the basis of available site directed mutagenesis data, to depict the dimer interface and propose chemical linkers needed to join previously docked antagonists in their respective pockets and therefore design the final heterobivalent ligands.

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