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GPCR-ModSim-A Computational Platform for the structure-based drug design of GPCRs and applications to the design of potent and selective adenosine receptor antagonists

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Recent advances in membrane protein crystallography have provided extremely valuable structural information of the superfamily of G-protein-coupled receptors (GPCRs). Recently, we have developed GPCR-ModSim (http://gpcr.usc.es), a web-based, automated pipeline to generate high-quality 3D models of the remaining GPCRs and to perform molecular dynamics (MD) simulations. This server is freely accessible to research groups as a starting point to develop their SBDD in GPCRs. In this talk, I will present the last implementations of this pipeline, which include free energy calculations for the predictions of selectivity and site-directed mutagenesis experiments. Thereafter I will illustrate the recent applications of this GPCR-structure-based drug design protocols with the successful discovery of adenosine receptor (AdoRs) antagonists.

Starting from novel and simple chemical scaffolds, we have guided the combinatorial chemistry efforts for the growth and lead optimization of a unique chemical library. As a result, potent and highly selective antagonists for the A3 with high solubility have been discovered, which we are developing in the hit-to-lead pipeline and also as pharmacological tools. Thereafter, a novel family of (non-xanthine) A2B receptor antagonists that exhibit an unusually high selectivity profile will be presented. In both cases, the computer-asisted structure-activity and structureselectivity relationships established have allowed the identification of ligands that combine structural simplicity with excellent affinity (Ki≤40 nM) for the given receptor (A2B or A3) and remarkable selectivity profiles at the other AdoRs (Ki≥10000 nM).

Biography

Hugo Gutiérrez de Terán received his Ph.D. at UPB (Barcelona, Spain) in 2004, followed by a postdoctoral period at Uppsala University with Johan Åqvist (2004-2006). In 2008, he became head of the Structural Bioinformatics and Drug Design Unit at the University Hospital of Santiago de Compostela (Spain), that he was running until 2013 when he moved back to Uppsala University. He was also visiting scientist at The Script Research Institute (2012). His major research interests are the structural characterization and ligand design of G-protein coupled receptors and the applications of free energy calculations in computer-aided drug design, subjects in which he has co-authored more than 40 scientific publications.

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