Self-learning systems in the design of compounds modulating GPCR receptors activation.

G protein-coupled receptors constitute a large and diverse protein family targeted by more than 1/3 of currently approved drugs. GPCRs diversity is not primarily due to their global structure, as they share a similar seven transmembrane helices topology, but rather due to their sensitivity to subtle differences between compounds causing their pronounced selectivity for a given receptor type or a signaling pathway. This project is aimed to develop self-learning systems that are fitted to specific GPCR pharmacology. Such systems will decrease the number of compounds that need to be tested experimentally in a pre-clinical phase of drug discovery. Additionally, machine learning (ML) algorithms implemented during this project in the form of a web application will enable to process Big Data that has been collected for GPCRs and their ligands so far. By ML-assisted comparison of molecular determinants of selective and non-selective ligand-receptor binding, safer and more efficient drugs will be designed. The current project will involve both, ligand-based and structure-based approaches joined together as input for algorithms to accurately assess the ligand selectivity for the receptor subtype. In this way, data on the actual biological response for a ligand will be combined with the description of the physicochemical properties of a receptor-ligand complex.

Among members of the GPCR family three, structurally and pharmacologically, diverse groups of receptors were selected for the algorithm training: CC chemokine receptors, cannabinoid receptors, and a subset of class B receptors. How to modify their signaling associated with diseases without over-influencing their physiological activation is the basic purpose of the current project.