Lecture 9: Andrzej Bojarski

Virtual screening in the identification of novel ligands of several GPCR targets

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GPCRs (G-protein coupled receptors) are a key part of the cell interface between its external and internal environments. As GPCRs are involved in etiology of many diseases, despite that they are targets of many existing drugs, a lot of efforts are still focused on development of new medicines acting selectively on a given receptor subtype, having a specific receptors profile or operating through other than orthosteric mechanism of action (like e.g. allosteric modulation).

Although the first crystallographic structure of GPCR (rhodopisn) was solved in 2000, a real breakthrough came in 2008, and since then x-ray structures of more than 30 GPCRs of different classes, in unbound form or in a complex with agonists and antagonists, were obtained. Availability of many templates for homology modeling of GPCRs spread application of different computational approaches to support search and design of new ligands of desired activity.

About five years ago we have developed and applied a multistep virtual screening (VS) protocol to search for new serotonergic 5-HT7 receptor ligands [1]. The same general VS protocol was next applied in search of agents acting on different targets (e.g., 5-HT6 receptor, serotonin transporter [2], metabotropic glutamate receptor), each time with updated and improved filters and results analysis tools. The evolution of the VS protocol, its applications and future perspectives are presented.

[1] Kurczab, R.; Nowak, M.; Chilmonczyk, Z.; Sylte, I.; Bojarski, A. J. The development and validation of a novel virtual screening cascade protocol to identify potential serotonin 5-HT(7)R antagonists. Bioorg. Med. Chem. Lett. 2010, 20, 2465-2468.

[2] Gabrielsen, M.; Kurczab, R.; Siwek, A.; Wolak, M.; Ravna, A.W.; Kristiansen, K.; Kufareva, I.; Abagyan, R.; Nowak, G.; Chilmonczyk, Z.; Sylte, I.; Bojarski, A.J. Identification of novel serotonin transporter compounds by virtual screening. J. Chem. Inf. Model. 2014, 54, 933-944.