The endocannabinoid system (ECS) is one of the most important systems in the human organism. It takes part in a vast array of physiological functions, including appetite, fat metabolism, mood regulation, pain management, cognitive functions, inflammation, and cell proliferation. **This project focuses on cannabinoid receptors (CBRs) type 1 (CB1) and 2 (CB2) – the most important proteins of endocannabinoid system. They are targets of compounds found in human organism and in plants.** Because of numerous physiological processes ECS takes part in, CB1/2 are promising therapeutic targets. Indeed, CBRs' ligands are used or studied as a treatment of pain, seizures, obesity, psychiatric disorders, neurodegenerative diseases, and many other medical conditions. Working on these crucial molecular targets and their ligands was hindered because of a lack of knowledge about their structure. Today, a new era in CBRs studies has begun, because of recently solved CB1 and CB2 structures and computational techniques allowing for analyzing biophysical details that are hidden for traditional, experimental research. It creates an excellent opportunity to develop new drugs acting via ECS, to find novel CBRs' ligands, and to gain more insight into pharmacology of this system itself. Findings of this project may help to improve patients' quality of life, and potentially initiate the revolution in the therapy of pain.

Many drugs have complex mechanism of action and interact with multiple molecular targets. For example, paracetamol was initially believed to be a cyclooxygenase 3 (COX-3) inhibitor, but today we know that it also acts via other molecular targets, including CB1 receptor. Maybe there are other drugs creating therapeutically important interactions with CBRs that we do not know about?

Recently, *Cannabis sativa* is going through a renaissance, with a considerable increase in its medical use. Unfortunately, its therapeutic properties are far from perfect. Nonetheless, it is a valuable alternative to some drugs. Therefore, it would be a very advantageous discovery, if we could find cannabinoids in other plants, with potentially better pharmacological profile.

Substances acting directly on CB1 may be associated with serious psychiatric and cognitive adverse effects. Nevertheless, targeting CB1 is a very promising strategy for treating multiple diseases. Thus, there is still need for new compounds altering endocannabinoid transmission. Two most prominent ways to avoid aforementioned adverse effects include design of ligands acting on CB1 receptors outside of the central nervous system (peripheral) and CB1 allosteric modulators. Also, CB2 allosteric modulation is proposed lately.

This project is devoted to finding novel CBRs ligands among drugs, drug metabolites, and phytochemical compounds. Additionally, we plan to find new CB1 peripheral ligands andCB1/2 allosteric modulators. With known CBRs structures, it is possible to use pharmacoinformatical methods to investigate many compounds in relatively short time. Here, we proposed a broad spectrum of advanced computational methods to find new CB1/2 ligands. First step of this project is to predict binding modes and affinities of studied compounds towards CBRs' binding sites, using methods based on molecular docking. The next part involves evaluating binding affinities of selected, potential ligands with advanced numerical methods for CB1/2 embedded in realistic membrane representation. It will also allow us to examine CBR-ligand binding more precisely and to avoid false positives. Then, an *in vitro* study will conclusively show whether selected compounds are potent CBRs ligands. Using the information gathered during *in vitro*, we will ameliorate our computational protocols and rerun selected calculations. Finally, we will conduct a second turn of *in vitro* study and show the affinity of selected compounds and whether they are agonists or antagonists.

Finding interactions of drugs and drug metabolites with CBRs may allow for attributing new mechanisms of action and for explaining mechanisms of adverse effects or drug-drug interactions. This information could contribute towards better understanding of pharmacology of certain drugs. Therefore, it could allow for better understood, and thus safer pharmacotherapy. Also, there comes a possibility of proposing new therapeutic indications for approved drugs.

Finding CBRs' ligands in plants will provide more insight into properties of their chemical constituents. Thus, we will gain more information on certain plants action, and their possible indications. Some plants could potentially find a purpose in medicine.

New CB1 peripheral ligands and CB1/2 allosteric modulators may prove to be valid drug candidates. Application of computational methods to investigate compounds from various chemical groups as potential ligands of CBRs will open new perspectives on their binding modes and important functional groups. This information is critical for future rational drug design. Thus, created tools and methods established to investigate CBRs in this project will be important for future studies with medical applications.