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Development of novel therapeutics that can target multiple receptors for treatment of Parkinson's disease

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Parkinson's disease is caused by disruption of cells which provide dopamine to the striatum in the brain. Therefore, the main approach made for treatment of the disease has based on increasing dopaminergic signaling by using dopamine agonists, preventing dopamine breakdown via monoamine oxidase enzymes or supplying additional dopamine in the form of L-dopa. Even though L-dopa is known as the most effective drug so far, its efficacy decreases with time due to the use of high dosage of the drug. Moreover, it also causes motor complications such as motor fluctuations and dyskinesia. In this multidisciplinary project, we have aimed for developing hetero-bivalent ligands that target A_2AR (Adenosine-2A-receptor)-D_2R (Dopamine-2-receptor) hetero-tetramer, which has been shown to be the dominant stoichiometry of A_2AR-D_2R. Firstly, we design and dock hetero-bivalent ligands to the receptors and investigate the molecular mechanism of allosteric interactions within the hetero-tetramer by means of accelerated molecular dynamics simulations. Subsequently, successful drug candidates are synthesized and tested *in vitro* for their activities. More importantly, the drug candidates are also tested by *in silico* and *in vitro* models for their permeation against blood-brain barrier. So far, hetero-bivalent ligands have been only used as molecular tools for detecting the existence of the receptor dimers. On the other hand, the current study will provide a chance to test the capability of hetero-bivalent ligands for being used as therapeutic molecules. In this way, we expect to develop more effective therapeutic molecules to alleviate the symptoms of Parkinson's disease hence increasing the quality of patient's life.

Biography

Ozge Sensoy has her research studies focused on understanding molecular mechanisms of biologically important systems and also providing mechanistic insight at the molecular level. She has been working with GPCRs and their interacting partners which are responsible for cellular signaling. She has been awarded an international COST grant which is based on developing heterobivalent molecules capable of binding more than one target for treatment of symptoms of Parkinson's disease.

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