Computational studies of the structural and chemical biology of A2A adenosine and D2 dopamine receptor signaling

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Sweden

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Computational studies of the structural and chemical biology of A2A adenosine and D2 dopamine receptor signaling

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4

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Research Abstract
This project is focused on understanding GPCR dimerization and strategies to discover ligands of receptors using structure-based methods. The A2A adenosine (A2AAR) and D2 dopamine (D2DR) receptors form dimers in the membrane and there is great interest in exploiting A2A/D2 interactions in development of drugs against Parkinson´s disease (PD). We will predict the structure of the A2A/D2 dimer with a combined modeling and experimental approach and use

simulations to understand how dimerization affects signaling at the molecular level. Efficient treatment of neurological disorders such as PD often requires modulation of multiple targets. A ligand with the ability to bind to both the A2AAR and D2DR could contribute to improved drugs for PD. We will use molecular docking to screen up to 10 million molecules against A2AAR and D2DR models. Compounds predicted to bind to both receptors will be tested experimentally. Discovered ligands will represent a new class of drug candidates against PD. We will also explore strategies for design of A2A agonists using structure-based screening of virtual libraries. We will first design compound libraries based on replacing chemical groups of adenosine with commercially available fragments. Thousands of molecules will then be docked to an A2A crystal structure to identify potential ligands. Predicted ligands will be synthesized and tested experimentally, which will lead to the discovery of novel agonists to this medically important target.

Further information available at:

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Investments < €500k

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