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Selecting Synthetic Photoswitches for Time-Resolved Serial Crystallography of the Human A2A Receptor

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Time-resolved serial crystallography has emerged as a method to study protein dynamics at atomic resolution. In this method, reactions need to be initiated synchronously. Many experiments have used light as a trigger system to study endogenously photoactive proteins; however, only a small fraction of proteins are naturally photoactive. Therefore, work needs to be done to ensure this method can be applied to a wider range of pharmacologically relevant proteins. Synthetic photoswitches have been developed through the field of photopharmacology that convert between binding and nonbinding conformations. Here we present the characterisation of eight synthetic photoswitches, derived from an approved treatment against Parkinson' s disease. We observed that photoisomerisation properties can differ *in crystallo* from in solution, indicating that not all photoswitches are suitable for time-resolved crystallography. We applied synthetic photoswitches to observe the process of ligand dissociation from the human A2A receptor, a G protein-coupled receptor. An understanding of this process can help guide the development of drugs with increased residence times. Using data collected at SLS, MaxIV and the SwissFEL, we follow how the binding pocket adapts to accommodate ligands and movement in the hydrogen-bonded lid of the binding pocket during ligand dissociation.

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Primary author: GLOVER, Hannah (Paul Scherrer Institut)

Co-authors: Dr TRABUCO, Matilde (leadXproo); STIPP, Robin; Mr SASSMANNSHAUSEN, Torben (University of Frankfurt); Prof. HENNIG, Michael (leadXpro); Prof. WACHTVEITL, Josef (University of Frankfurt); STANDFUSS, Joerg (Paul Scherrer Institut)

Presenter: GLOVER, Hannah (Paul Scherrer Institut)

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