

# GPCRs as Targets for Serial Crystallography

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Using time-resolved serial crystallography to observe structural snapshots of protein dynamics at high resolution is a method that is becoming gradually more commonplace. Advancements in method development for this technique have allowed a wider range of proteins to be studied; looking at processes spanning endogenous photoresponses, enzyme kinetics and ligand binding. G protein-coupled receptors represent a pharmacologically relevant superfamily of proteins that are interesting targets for study with time-resolved serial crystallography. Data from time-resolved serial crystallography has the potential to enhance the drug design process by revealing protein transitional states that can be either targeted or used to provide information about protein flexibility. Our goal is to study the inherent dynamics of GPCRs critical for receptor function and to use this information to develop more targeted ligands. Here, we present the results of time-resolved serial crystallography experiments conducted at MaxIV and the SLS on the human A2a receptor. Through synthetic photoswitches, based on the marketed drug istradefylline for the treatment of Parkinson's disease, light is used as a trigger to investigate the dynamics associated with ligand dissociation from the receptor orthosteric binding pocket. Our time-resolved data highlights key structural features involved in the transition upon ligand photoswitching. This includes the rearrangement of extracellular loops 2 and 3 that form a lid over the binding pocket, which has been shown by molecular dynamic simulations, crystal structures and kinetic analyses to be crucial for ligand dissociation and long target resident time. Additionally, lessons learned from this investigation, in terms of experimental design and sample preparation, can be applied to future projects using GPCRs as targets for serial crystallography. Helping to lower the barrier of entry to time-resolved serial crystallography and ultimately leading to more rationally designed drugs.

Co-authors:

Torben Saßmannshausen, Quentin Bertrand, Matilde Trabuco, Chavdar Slavov, Arianna Bacchin, Fabio Andres, Yasushi Kondo, Robin Stipp, Maximilian Wranik, Georgii Khusainov, Melissa Carrillo, Demet Kekilli, Jie Nan, Ana Gonzalez, Robert Cheng, Werner Neidhart, Tobias Weinert, Filip Leonarski, Florian Dworkowski, Michal Kepa, Josef Wachtveitl, Michael Hennig, Joerg Standfuss

**Presenter(s)** : GLOVER, Hannah (leadXpro)

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