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POSTER ABSTRACT PRESENTATIONS

SESSION TITLE: STRUCTURE OF MEMBRANE PROTEINS

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Abstract P-4: Cryo-Electron Microscopy of G-Protein Coupled Receptor Complexes for Drug Discovery Approaches

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Background: Seven helical transmembrane G-protein coupled receptors (GPCRs) involved in various extracellular ligand recognition and signal transduction processes are prominent targets of about a third of existing drugs (Sriram and Insel, 2018). The study summarizes current advances and opportunities in the field of structural biology of GPCRs using cryo-electron microscopy and its applications for the target-based drug discovery.

Results: An atomic resolution structural information about receptors is of extreme value for predicting novel compounds, binding modes and resolving receptor selectivity issues, in general (Ceska *et al.*, 2019). Obtaining this information is not straightforward though: the established crystallization pipeline requires considerable time and much efforts in expression systems testing, protein purification adjustment, crystallization conditions screening and diffraction data processing.

One of the ways to bypass the crystallization step is the use of cryo-electron microscopy for receptor structure determination (Ceska *et al.*, 2019). Due to the size limitation of about 100 kDa for the single-particle Cryo-EM approach, wild type receptors with a typical size of 40 kDa are not suitable for this method (Ishchenko, Gati and Cherezov, 2018). A large spectrum of possible conformational states and the absence of preferred orientation make single particle classification even more challenging. As GPCRs perform their functions in cells via interaction with heteromeric G-proteins and arrestins, it appears the most natural way to use these complexes for overcoming the size barrier(García-Nafría and Tate, 2019). An active receptor state can also be achieved by having the complexes with synthetic smaller analogues of G-proteins - mini G-proteins (García-Nafría and Tate, 2019). Up to date 9 complexes with 8 unique receptors are published encompassing Gs-bound, G0-bound and Gi-bound states and mini-Gs in case of A2a receptor structure(García-Nafría and Tate, 2019).

Conclusion: Cryo-electron microscopy is an emerging tool for obtaining high-resolution structures of GPCRs with the potential in the drug discovery field. A number of ways are developed to stabilize the receptor and to overcome the Cryo-EM size limitation.

Key Words: GPCR - g-protein complexes • Cryo-EM • target-based drug design

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