Understanding the function of G-Protein Coupled Receptors by atomistic and multiscale studies

G protein-coupled receptors (GPCRs) are membrane proteins responsible for transducing a wide range of signals across the plasma membrane, regulating diverse functions through their activation or deactivation by endogenous and exogenous ligands. These include metabolism, immune and inflammatory response, growth and differentiation, neurotransmission, olfaction, and vision, among others. It is therefore not surprising that GPCRs are the targets of ~34% of prescribed drugs (accounting for ~27% of the global market share) and are the primary focus of current pharmaceutical development, with more than 200 receptors to be explored clinically.

In this second edition of the biannual GPCR CECAM workshop, we explore the latest advancements regarding our understanding of how GPCRs work and interact with the extracellular and intracellular signalling molecules composing the systemic biochemical cascade. Researchers from the fields of structural, computational, and biochemical biology and physics will present their most recent findings on the conformational mechanisms regulating GPCRs' functional activity and how the native environment modulates these equilibria via protein-protein or lipid-protein interactions.

Understanding GPCRs' activation mechanisms is crucial for rationalising drug structure-activity relationships. Notable interest has been raised by the complex and not well understood biased signalling phenomenon, a promising area with significant implications for clinical pharmacology and therapeutics. The GPCR CECAM workshop will focus on these questions, which hold substantial medical, economic, and social implications due to the pharmacological relevance of these receptors.

Program

Monday September 23rd 2024 - Day 1

Opening

- 08:15 to 08:45 - Registration
- 08:45 to 09:00 - Welcome & Introduction

Session 1 - GPCR functional dynamics

- 09:00 to 09:40 - Scott Prosser - Understanding Receptor Function through studies of Ensemble Dynamics - A Model for G protein Selectivity on Class A Receptors
- 09:40 to 10:20 - Stephan Grzesiek - New data on the the activating motions of a GPCR from a large number of 1H-15N NMR probes, on GPCR arrestin interactions, and on GPCR internalization
- 10:20 to 10:40 - Coffee break
- 10:40 to 11:20 - Gebhard F.X. Schertler - The activation mechanism of GPCRs and visual pigments: Structure determination of effector complexes and signalling complexes of GPCRs and visual pigments
- 11:20 to 12:00 - Peter Hildebrand - Mechanistic insights into G-protein coupling with an agonist-bound G protein-coupled receptor

Short Talks

- 12:00 to 12:07 - Francesco di Leva - Ligand Binding Signatures in GPCRs: Insights from Free Energy Simulations of Formyl Peptide Receptor 2 Modulators
- 12:07 to 12:14 - Irina G. Tikhonova - Dynamic Structural Basis for Varied Allosteric Modulation and Signalling Bias at the Free Fatty Acid Receptor 2
- 12:14 to 12:21 - Seufert Florian - Unveiling the GPS Cleavage Mechanism in ADGRL1 with QM/MM

Lunch break

- 12:25 to 14:00 - Lunch

Session 2 - Ligand binding

- 14:00 to 14:40 - Jana Shen - Modeling the binding and dissociation of fentanyl and nitazene derivatives at the mu-opioid receptor
- 14:40 to 15:20 - Paolo Carloni - Using machine learning and molecular simulations to investigate ligand/GPCRs interactions
- 15:20 to 15:40 - Coffee break
- 15:40 to 16:20 - Christa Elisabeth Müller - Structural biology supporting medicinal chemistry of G protein-coupled receptors involved in inflammation, immunity and cancer
- 16:20 to 17:00 - Antonella Di Pizio - Modeling and simulations of olfactory receptors
- 17:00 to 17:30 - Romelia Salomon Ferrer - Evaluation of Binding Free Energy and Generative AI Methods Applied to GLP1R

Social Event

- 17:30 to 19:00 - Poster Session

Tuesday September 24th 2024 - Day 2

Session 3 - GPCR allostery

- 09:00 to 09:40 - Chris Tate - Positive cooperativity enhances coupling of two G proteins to a GPCR dimer
- 09:40 to 10:20 - Bert de Groot - Novel Activation Modulating Sites in a GPCR Identified with a Large-Scale Alchemical Mutation Scan
- 10:20 to 10:40 - Coffee break
- 10:40 to 11:20 - Jana Selent - Advancing our knowledge of the 3D GPCRome conformational landscape and ligand efficacy predictions
- 11:20 to 12:00 - Hugo Gutierrez de Teran - Understanding allosteric modulation of GPCRs from computer simulations: application to ligand design

Short talks

- 12:00 to 12:07 - Darko Mitrovic - Combining Coevolution and MD Simulations to Decode GPR68's Proton- Sensing Mechanism

- 12:07 to 12:14 - Nicia Rosario-Ferreira - HARNESSING GPCR PATHWAYS: A NEW FRONTIER IN GLIOBLASTOMA AND AGE-RELATED DISEASE RESEARCH
- 12:14 to 12:21 - Vincenzo Maria D'Amore - The activation mechanism of the adenosine A2A G protein-coupled receptor explored through minute-scale simulations
- 12:21 to 12:28 - Mahdi Hijazi - Computational design of allosteric pathways reprograms ligand-selective GPCR signaling

Lunch break

- 12:30 to 14:00 - Lunch

Session 4 - Computational methods for GPCR studies

- 14:00 to 14:40 - Ana-Nicoleta Bondar - Conserved hydrogen-bond networks as structural determinants of GPCR function
- 14:40 to 15:20 - Francesco Luigi Gervasio - Investigating GPCR activation mechanisms with OneOPES and other enhanced sampling simulations
- 15:20 to 15:40 - Coffee break
- 15:40 to 16:20 - Patrick Barth - Computational design of allosteric pathways reprograms ligand-selective GPCR signaling

Brainstorming Session

- 16:20 to 17:00 - Funding opportunities in the GPCR field

Social Event

- 19:00 to 22:00 - Social dinner

Wednesday September 25th 2024 - Day 3

Session 5

- 09:00 to 09:40 - Ilpo Vattulainen - The interplay of lipids: Dependence of the activity of GPCR proteins on the operating environment and the collective action mechanisms of lipids
- 09:40 to 10:20 - Matthew Eddy - GPCR conformational dynamics studied in vesicles that more closely resemble cellular conditions
- 10:20 to 10:50 - Coffee break
- 10:50 to 11:30 - IRINA MOREIRA - New Horizons in GPCR Research: Leveraging AI, Big Data, and Molecular Dynamics for Enhanced Understanding
- 11:30 to 12:10 - Anne Robinson - Determining Adenosine A2A receptor binding kinetics and stability in nanodiscs

Concluding Remarks

- 12:10 to 12:30 - Closing words