

Preparing and investigating the human adenosine A_{2A} receptor trapped in lipid nanoparticles

Keywords: Bioproduction; protein purification; lipid nanodiscs; cryo-EM

Duration: 5-6 months starting January or February 2027

Location: IMPReSS department of the PCBIS Drug Discovery platform, ESBS, Illkirch
(www.pcbis.fr/departements/impress)

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Project description:

Global context

The adenosine A_{2A} receptor (AA_{2A}R) belongs to the G protein-coupled receptor (GPCR) superfamily, the largest family of membrane signaling proteins, characterized by a conserved seven-transmembrane (7TM) architecture [1]. Activated by adenosine, AA_{2A}R couples primarily to Gs proteins to stimulate cAMP production and plays key roles in neuromodulation, cardiovascular regulation, and immune responses [2]. AA_{2A}R has also emerged as a prototypical model for GPCR structural biology, with numerous high-resolution structures of the receptor determined by X-ray crystallography and cryo-electron microscopy, providing major insights into ligand recognition and the molecular determinants of the receptor activation outside its native membrane environment [3]. Building on these advances, the present collaborative project gathers two French and one Austrian teams to further our understanding of AA_{2A}R activation mechanisms by structurally and functionally investigating the receptor in a more physiologically relevant membrane environment, using native or native-like nanoscale lipid particles.

Objectives of the internship

The main objective of the internship will be to contribute the production, preparation and biochemical characterization of AA_{2A}R stabilized in either active or inactive conformations and isolated in three distinct environments: (1) detergent micelles, (2) MSP-stabilized nanodiscs, and (3) amphiphilic copolymer-stabilized lipid nanoparticles directly extracted from cells using a detergent-free approach [4,5]. Eventually, these samples will be processed and analyzed via advanced cryoEM methodologies at our IGBMC partner's [6].

References

- [1] Santos et al. *Nature Rev Drug Discov.* 2017, 16: 19-34.
- [2] IJzerman et al. *Pharmacol rev.* 2022, 74: 340-372.
- [3] García-Nafria & Tate. *Mol Cell Endocrinol.* 2019, 488: 1-13.
- [4] Lecas et al. *Anal Chim Acta.* 2020, 1113: 26-35.
- [5] Chu et al. *Methods.* 2025, 244: 55-64.
- [6] Marechal et al. *Nat Commun.* 2022, 13: 2380.