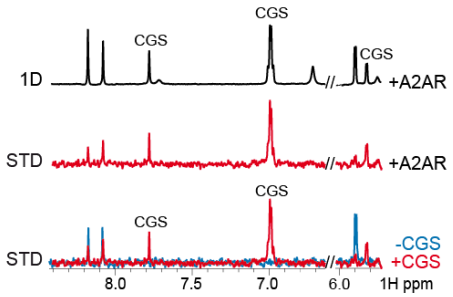
NMR and biophysical methods for membrane protein-small molecule interaction studies

Membrane proteins represent about one third of the proteins encoded by the human genome. In particular, the G protein-coupled receptors (GPCRs) family are the largest class of membrane proteins. GPCRs play a pivotal role in many physiological functions and are therefore associated with a multitude of diseases, including cardiovascular, metabolic, neurodegenerative, psychiatric, and oncologic diseases.

While advances have been made in the last decade, identification and characterization of small molecules capable to bind GPCRs remain a challenge. However, GPCRs constitute the most important family of drug targets in the human body, with 25-30% of current drugs acting on GPCRs. Drug discovery targeting GPCRs remains difficult owing to the restricted structural information on GPCRs related to the instability of these proteins when isolated from their cell membrane environments and to the absence of routine methods for identifying GPCR ligands using target-based approaches.

This research proposal aims to develop methods to identify, study and characterize ligands that bind a full native GPCR solubilized in detergents, nanodiscs or prepared in membranes, using mainly liquid-state NMR experiments. The aim is to develop NMR-based approaches that will impact the structure-based drug discovery process for the GPCR family. In particular, we are particularly interested in fragment-based approaches, which requires screening a fragment-library against a protein. We have recently shown that NMR-based screening could be used for the identification of fragments that bind a GPCR (Igonet *et al.*, Scientific reports, 2018).



Investigation of the binding of adenosine to the GPCR A2AR using NMR.
The binding mode of adenosine is modified in the presence of the compound CGS21680.

The project will provide the candidate access to a unique platform for high-field NMR, a well-equipped protein labelling facility, and access to other biophysical techniques for protein-ligand characterization.

The candidate will be in charge of the NMR and biophysical experiments. In addition, the candidate will have the possibility to participate to the preparation of the GPCR samples. The ideal candidate should be a chemist, a biochemist or a physical chemist with a solid motivation to work with membrane-associated proteins.

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