Post doctoral position announcement:
Characterisation of cholesterol – GPCR interactions by solid state NMR

As part of an Initial Training Network on the "Structural Biology of Membrane Proteins" (Marie Curie EU program SBMPs, http://www.sbmp-itn.eu), an Experienced Researcher position is available starting from 2011 in the group headed by Pr Alain Milon, "NMR and protein – membrane interactions", Institute of Pharmacology and Structural Biology, Toulouse, France (http://www.ipbs.fr/english/teams/milon/index.htm).

G-protein coupled receptors (GPCRs) are playing a major role in signal transduction in eukaryotic cells and as such, they are of utmost pharmacological importance, being the target of about half of the major drugs currently used (1). It has been shown for several years that the lipidic environment, and in particular the sterol composition of membrane may influence the functional activation of GPCRs (2-4), and a specific cholesterol binding site has been found in the X-ray structure of the human β2 adrenergic receptor (5). Although the precise location of these cholesterol molecules bound to a GPCR are now known, much remains to be understood about their functional role and the way they actually modulate ligand binding and receptor activation. In particular the dynamics of exchange between bulk membrane cholesterol and receptor bound cholesterol remains to be determined and connected to the relevant functional time scales. Recent progresses in expression – purification of GPCRs and the availability of atomic resolution X-ray structures open the way to biophysical analyses of these interactions.

The "NMR and protein – membrane interaction group" has developed extensive expertise in the heterologous expression of GPCRs in *Pichia pastoris* and in *E. coli* (1, 6-11) and a variety opiate receptor constructs are available. It possesses a thorough expertise in analyzing sterol dynamics in model membranes by solid state NMR, using both wide line static approaches (12-17) and CP-MAS based approaches (15, 18-20). Using advanced liquid state NMR approaches and stable isotope labeling it has solved recently the 3D structure of the outer membrane protein A from *Klebsiella pneumoniae*, a 210 aa membrane protein domain (21, 22).

Based on this expertise, we will study cholesterol – protein interactions in lipid bilayers, micelles, and lipid cubic phases. Several membrane proteins will be used: kpOmpA, which is very stable in many environments and available in high amount with suitable stable isotope labeling, will be used to establish and develop NMR based strategies; GPCRs of the opiate family and the human β2 adrenergic receptor will be the target for understanding the functional role of cholesterol at a molecular level.

This position is opened for 12 month on the Marie Curie grant with a possibility of extension.
Applicants should :
- have a PhD experience of either liquid or solid state NMR,
- have less than 5 years of research experience since the beginning of their PhD,
- not hold the french nationality,
- and not have resided in France for more than 12 months during the past 3 years.

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