HYPERPOLARIZED MAGNETIC RESONANCE FOR DRUG DISCOVERY

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Nuclear magnetic resonance spectroscopy (NMR) provides non-invasive insight at atomic level and is a method of choice for many applications and particularly in Drug Discovery. **It is unfortunately known for its low sensitivity, which is the major bottleneck to robust intermolecular recognition and molecular interaction.** In our group, we have played a key role in the development of a new method that **boosts the sensitivity of molecules in NMR by more than 10'000-fold.** The molecules ('hyperpolarized') can be **detected at low ligands concentration and therefore allow strong affinities detection. dDNP would be a game changer in numerous applications involving the observation of small molecule, such as metabolic imaging, metabolomics, drug discovery.**

One of the most exciting new prospects that it has enabled is the potential to considerably improve the detection and identification of ligands, and shorten the discovery time of new drug candidates. This advance is currently being validated on simple model protein and be transfer soon to more challenge targets.

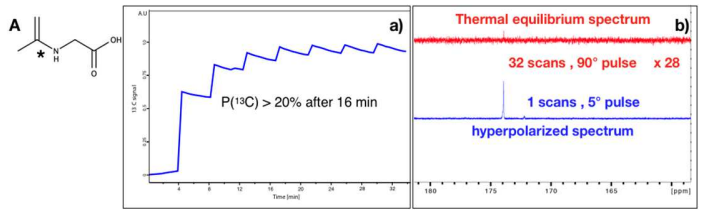

Figure 2: a) Cross-polarization of 100 µL of 50 mM of molecule A in 400 mM D2O-phosphate buffer pH 8.5, H_2O/D_2O/glycerol (10/30/60), 25 mM Tempol at 1.2 K and 7.05 T. b) sample was dissolved with 10 mL of 400 mM D_2O-phosphate buffer pH 8.5 and transfer in a 700 MHz Bruker spectrometer for a series of 128 small-angle scans. The highest signal (blue) is then compared to the thermal equilibrium spectrum (red)

In this context, we propose to revisit a secondary labeling approach (where amines groups in amino acids where labeled with [1,1-13C] acetic anhydride) with our recent d-DNP advances and in the context of NMR fragment based drug discovery (FBDD). 1H ligand-observed approaches (STD / WaterLOGSY) is powerful for big protein (> 30 KDa) but can't be applied for small proteins. We show how ligands can be secondary labeled and hyperpolarized to probe interactions with their target proteins (66 kDa and 8 KDa). We show that the labelling i) doesn't affect the interaction and ii) is used for an ultra-rapid interaction determination, via the detection of a change in hyperpolarized T1 of the weak ligands 13C-tag.

We are looking for PhD candidates to develop a complete new library based on secondary ^{13}C labeling, to validate on HSA (model protein) the proof-of-concept and characterize the new synthesised compounds (T_1, $T_{1\rho}$, affinity test). **To learn and become autonomous on the dDNP instrument** (sample formulation for dDNP / dDNP optimization (DNP parameters / transfer / injection), **to participate at the dDNP NMR sequence development** (combination single scan T_1 + $T_{1\rho}$) and finally **develop full application** on challenges targets such as ribosome targets at µM concentrations or pursue applications **in the field of drug discovery or metabolomics**.

If you are holding a Master in Chemistry, Physical- or Bio-Chemistry and enjoy teamwork but do not fear autonomy, and have a strong scientific background, you can **get directly in touch and send your CV to sami.jannin@univ-lyon1.fr**

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The CRMN is located in the great city of Lyon, is affiliated to the Lyon-1 University, the CNRS (French National Center for Scientific Research) and the Ecole Normale Supérieure de Lyon. The center is equipped with state of the art NMR spectrometers (world's first 1 GHz spectrometer). It hosts research groups of worldwide-recognized excellence.