Advanced labelling technologies to tackle challenging therapeutic targets by NMR

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Biomolecular Nuclear Magnetic Resonance (NMR) is an established method for hit identification and validation/characterization of ligand interaction with therapeutic targets, which is of a great interest for the pharmaceutical industry. This technique allows also to solve 3D structures of protein targets, and to study dynamics and their interactions with physiological partners. However, the standard NMR spectroscopy approach is traditionally dedicated to study ligands, small size proteins and isolated protein domains whose molecular weight do not exceed *c.a.* 30 kDa. This limitation is critical since numerous human enzymes are larger in size or are physiologically relevant only in the full-length context or in complex with other proteins.

In this context, we have developped novel approches based on advanced strategies for isotopic labelling to extend field of applications of solution NMR to large and challenging biological targets(1). In this communication, I will present our latest results demonstrating how innovative *in vivo* and *in vitro* labelling approaches allow to investigate protein well beyond standard biological NMR limits. I will illustrate the pertinence of the methyl-based NMR to bring insights into interactions with ligands, structural rearrangements and dynamics of proteins with molecular weight ranging from 30 kDa to 1 MDa.