Nanobody GPS by PCS: An Efficient New NMR Analysis Method for G Protein Coupled Receptors and Other Large Proteins

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NMR chemical shift changes can report on the functional dynamics of biomacromolecules in solution with sizes >1 MDa. However, their interpretation requires chemical shift assignments to individual nuclei, which for large molecules often can only be obtained by tedious point mutations that may interfere with function. We present here an efficient pseudocontact shift NMR method to assign biomacromolecules using bound antibodies tagged with lanthanoid DOTA chelators. The stability of the antibody allows positioning the DOTA tag at many surface sites, providing triangulation of the macromolecule nuclei at distances >60 Å. The method provides complete assignments of valine and tyrosine 1 H- 15 N resonances of the β 1 -adrenergic receptor in various functional forms. The detected chemical shift changes reveal strong forces exerted onto the backbone of transmembrane helix 3 during signal transmission, which are absorbed by its electronic structure. The assignment method is applicable to any soluble biomacromolecule for which suitable complementary binders exist.

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