# Insight into small molecule binding to the neonatal Fc teceptor by X-ray crystallography and 100 kHz magic-angle-spinning NMR

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The neonatal Fc receptor (FcRn) plays a crucial role in regulation of Immunoglobulin G (IgG) and serum albumin catabolism. It is a clinically validated drug target for the treatment of autoimmune diseases caused by pathogenic antibodies, via the inhibition of its interaction with IgG. We herein present the discovery of a small molecule that binds into a conserved cavity of the heterodimeric, extra-cellular domain composed of an α-chain and β2-microglobulin (β2m) ($FcRn_{ECD}$, 373 residues). X-ray crystallography was used alongside NMR at 100 kHz Magic-Angle-Spinning (MAS) with sedimented soluble protein, to explore possibilities for refining the compound as an allosteric modulator. Proton-detected MAS NMR experiments on fully protonated [$^{13}C$,$^{15}N$]-labeled $FcRn_{ECD}$ yielded ligand-induced chemical-shift perturbations for residues in the binding pocket, and allosteric changes close to the interface of the two receptor heterodimers present in the asymmetric unit. Generating a chemical-shift-informed overlay of X-ray structures with and without ligand suggests the need of a larger ligand to displace the α-chain with respect to β2m, both of which participate in the $FcRn_{ECD}$–IgG interaction site. Our investigation establishes a method to structurally characterize small molecule binding to non-deuterated, large proteins by NMR, even in their glycosylated form, which may prove highly valuable for structure-based drug discovery campaigns.