In 1993, scientists at the Vrije Universiteit Brussel discovered the occurrence of bona fide antibodies devoid of light chains in Camelidae. The small and rigid recombinant antigen binding fragments (15kD) of these heavy chain only antibodies - known as Nanobodies - proved to be unique research tools in structural biology. By rigidifying flexible regions and obscuring aggregative surfaces, nanobody complexes warrant conformationally uniform samples that are key to protein structure determination by X-ray crystallography:

- Nanobodies bind cryptic epitopes and lock proteins in unique native conformations
- Nbs reduce the conformational complexity of soluble proteins and membrane proteins
- Nbs increase the polar surface enabling the growth of diffracting crystals
- Nbs allow to affinity-trap active protein

Last year, we generated Nanobodies that selectively recognize an active state of the human β2 adrenergic receptor. Such Nanobodies that faithfully mimic the effects of G protein binding were used to obtain diffraction quality crystals and to solve the first structure of an active agonist-bound state of the human β2 adrenergic receptor. We also selected nanobodies that stabilize the β2-AR·Gs complex. One of these nanobodies was used to obtain the high-resolution crystal structure of this complex, providing the first view of transmembrane signaling by a GPCR. I will focus my talk on the use of Nbs for the structural investigation of GPCR transmembrane signaling to illustrate the power of the Nanobody platform for GPCR research.