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VABILO NA PREDAVANJE
V OKVIRU DOKTORSKEGA ŠTUDIJA
KEMIJSKE ZNANOSTI

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z naslovom:

Nanobody-enabled investigation of GPCR transmembrane signalling: from structure to function to drugs

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Vljudno vabljeni!

Abstract:

Polytopic membrane proteins such as GPCRs are dynamic proteins that exist in an ensemble of functionally distinct conformational states. Crystallogenesis typically traps the most stable low energy states, making it challenging to obtain agonist bound active-state structures of GPCRs. Stabilization of an active conformation of a GPCR can be achieved in different ways. The most physiologic approach is to use a native signaling partner such as a G protein. An alternative to using a G protein is to identify another binding protein that can stabilize the same conformational state.

Antibodies evolved to bind to a diverse array of protein structures with high affinity and specificity. Last years, we generated Nanobodies that selectively recognize an active state of the human beta2 adrenergic receptor (β2AR). Such Nanobodies that faithfully mimic the effects of G protein binding were used to obtain diffraction quality crystals and to solve the very first structure of an active agonist-bound state of the human β2 adrenergic receptor[1], the M2R muscarinic receptor[2] or the μ-opioid receptor[3]. More interesting, we also identified nanobodies that stabilize the β2AR•Gs complex[4]. One of these nanobodies was used to obtain the high-resolution crystal structure of this complex, providing the first view of transmembrane signalling by a GPCR. Currently we are applying such conformational nanobodies for better drug design.

Our work illustrates the power of the Nanobody platform for GPCR research[5,6]. Nanobodies are the small (15 kDa) and stable single domain fragments harbouring the full antigen-binding capacity of the original heavy chain only antibodies that naturally occur in Camelids. Because of their unique three-dimensional structure, nanobodies have access to cavities or clefts on the surface of proteins. The nanobody platform has the competitive advantage to other recombinant scaffold libraries in that large numbers (10^9) of fragments harbouring the full antigen-binding capacity of genuine in vivo matured antibodies can be screened for high affinity binders in a couple of days, allowing one to fully exploit the humoral response of large mammals against native antigens.

For more info see: www.steyaertlab.be

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