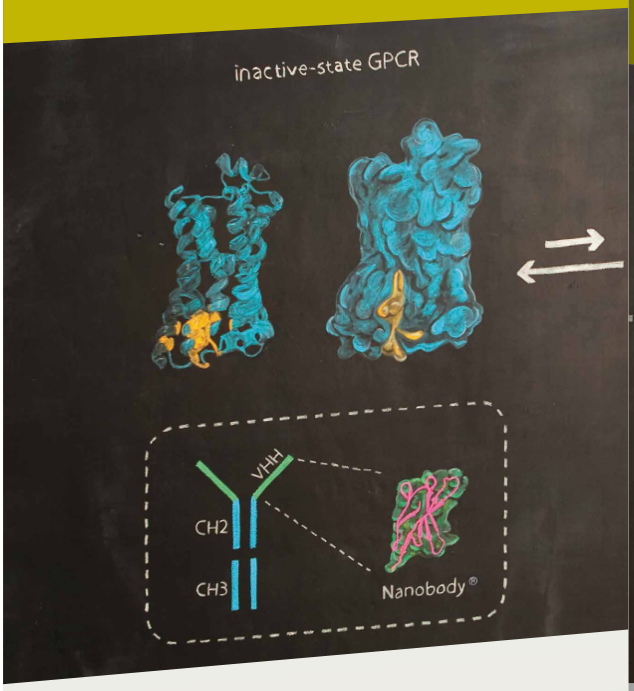
IOF Knowledge Center



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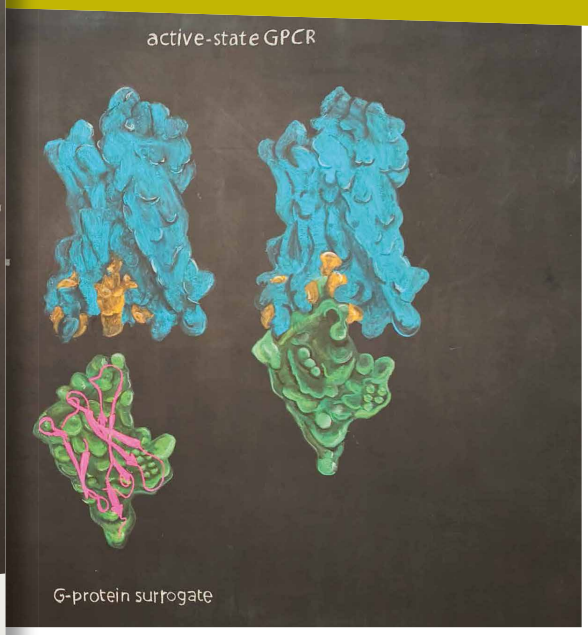

Turning on a GPCR

therapeutics for cancer, inflammation and immune diseases. In 2013 a second spin-off called Agrosavfe spun out from the Nanobody technology. **Agrosavfe** uses Nanobodies that bind to leaves, seeds, fruits, and pests - called Agrobodies - to develop better tools for crop protection, minimizing impact on the environment, growers, processors and consumers.

Because Nanobodies bind conformational epitopes, these antibodies turned out to be exquisite tools for the study of protein structure and function, the expertise of Jan Steyaert's lab.

Structural Biology Brussels

Today, the VUB **Structural Biology Brussels Lab** (SBB), led by Prof. Steyaert, also part of the VIB **Structural Biology Research Centre** (SBRC) unravels the structures and dynamics of the molecular players in biological processes to explain their mode of action. Its integrated approach combines state-of-the-art structural technology with biophysics and biochemistry. Its novel insights enable targeted interventions in health and disease and are translated into biotechnological applications ...

Expertise & Techniques
Key References

The Structural Biology Brussels Lab (SBB), headed by Jan Steyaert, was founded by Lode Wyns in the seventies at the Vrije Universiteit Brussel and is part of one of the Flanders Institute for Biotechnology (VIB) departments, a Flanders-based life sciences research center of excellence.

Situated in Brussels, a multidisciplinary team of international researchers combines extensive expertise in protein chemistry, biophysics and molecular biology. SBB masters technologically advanced techniques such as genetic engineering, protein purification, enzymology, calorimetry, crystallography, surface plasmon resonance, atomic force microscopy, X-ray crystallography and Nuclear Magnetic Resonance (NMR).

Major research interests include Biomedical targets, Structural enzymology, Bacterial adhesion, Toxin-antitoxin systems, Microgravity research and Biomolecular NMR. Translational research is intrinsic to its programs, with possible applications in medicine. The SBB lab was involved in the pioneering work in which Brian Kobilka's research team revealed the structure and inner workings of an important family of G-protein–coupled receptors. This led to two joint publications in "Nature":

- **Structure of a nanobody-stabilized active state of the ß2 adrenoceptor**
  NATURE, 469, 175-80, 2011

- **Crystal structure of the beta2 adrenergic receptor-Gs protein complex**
  NATURE, 477, 549-55, 2011

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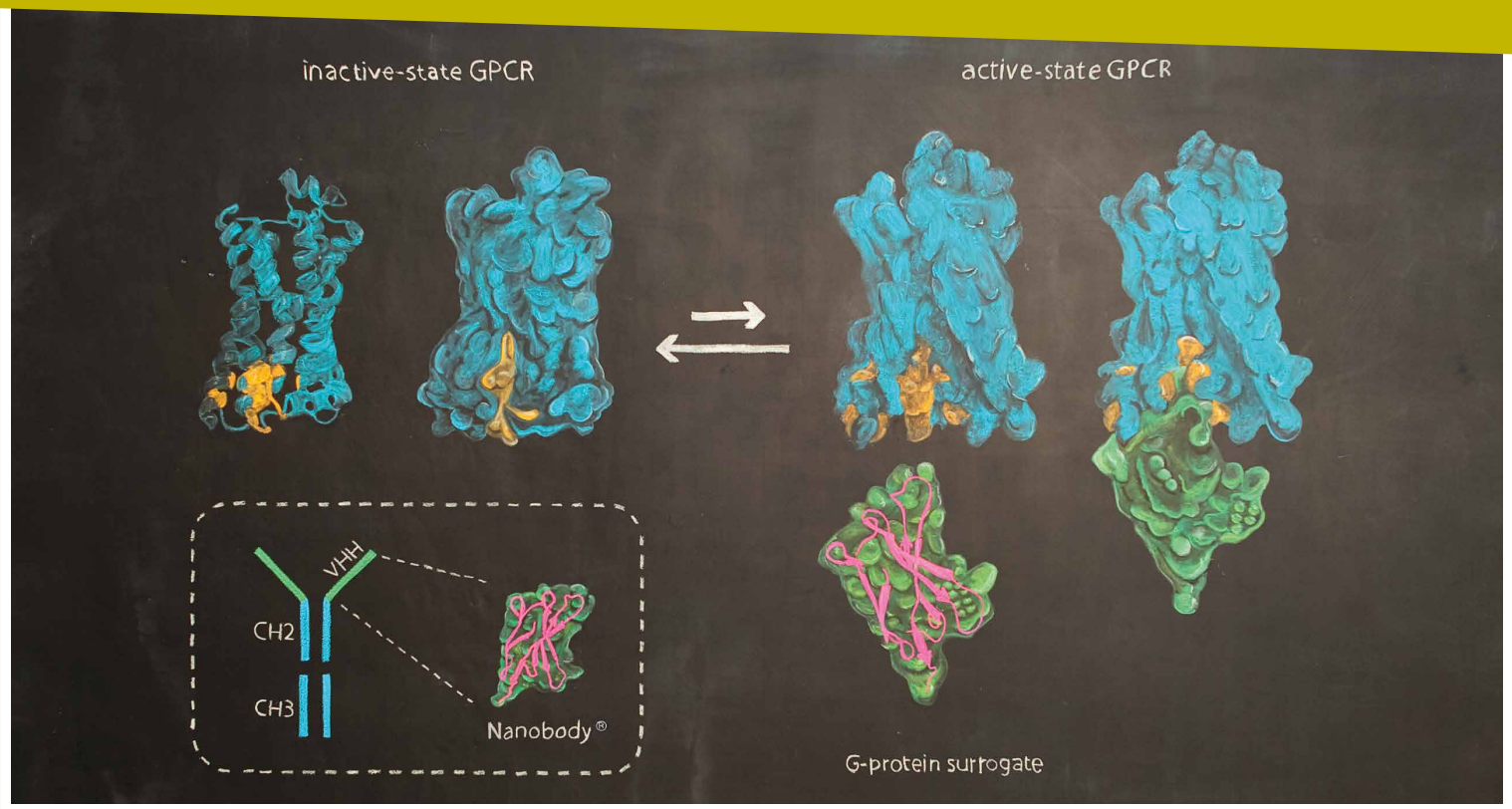

Turning on a GPCR

Proteins: building blocks of life

What does life look like at its smallest scale? And how can we use that knowledge to combat diseases?

It was in 1992 that prof. Hamers' team - while studying the proteins of the immune system - stumbled upon the occurrence of bona fide antibodies devoid of light chains in Camelidae. Over the years, this major discovery has been translated into numerous applications with Serge Muyldermans and Patrick De Baetselier focusing on their use in medicine and Jan Steyaert and Lode Wyns developing them as tools in Structural Biology.

The unique characteristics of single-chain camelid antibodies have strong benefits over conventional antibodies. **Nanobodies®,** the recombinant antigen binding fragments of camelid heavy chain antibodies, are a lot smaller than human antibodies, making it easier to penetrate into organs or tissues. No surprise that antibodies directed against 'disease causing proteins' have found their way into the clinic. The **technology platform** developed at the VIB department of Molecular and Cellular interactions at the Vrije Universiteit Brussel resulted in the successful VIB-VUB spin-off company **Ablynx.** Ablynx translates our scientific work into new Nanobody®-based therapeutics for cancer, inflammation and immune diseases. In 2013 a second spin-off called Agrosavfe spun out from the Nanobody technology. **Agrosavfe** uses Nanobodies that bind to leaves, seeds, fruits, and pests - called Agrobodies - to develop better tools for crop protection, minimizing impact on the environment, growers, processors and consumers.

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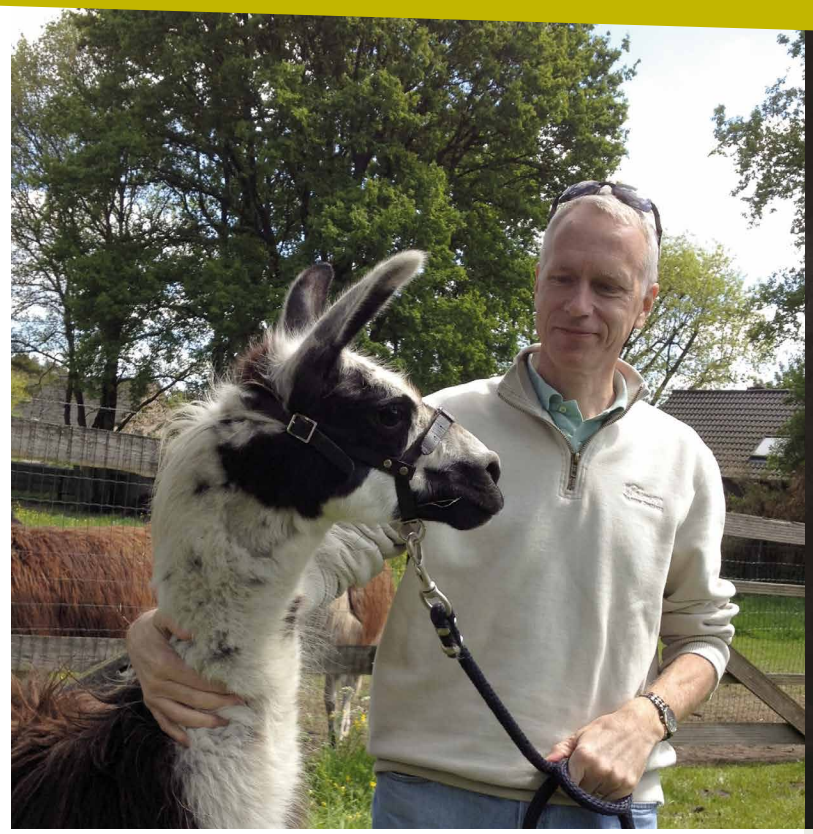
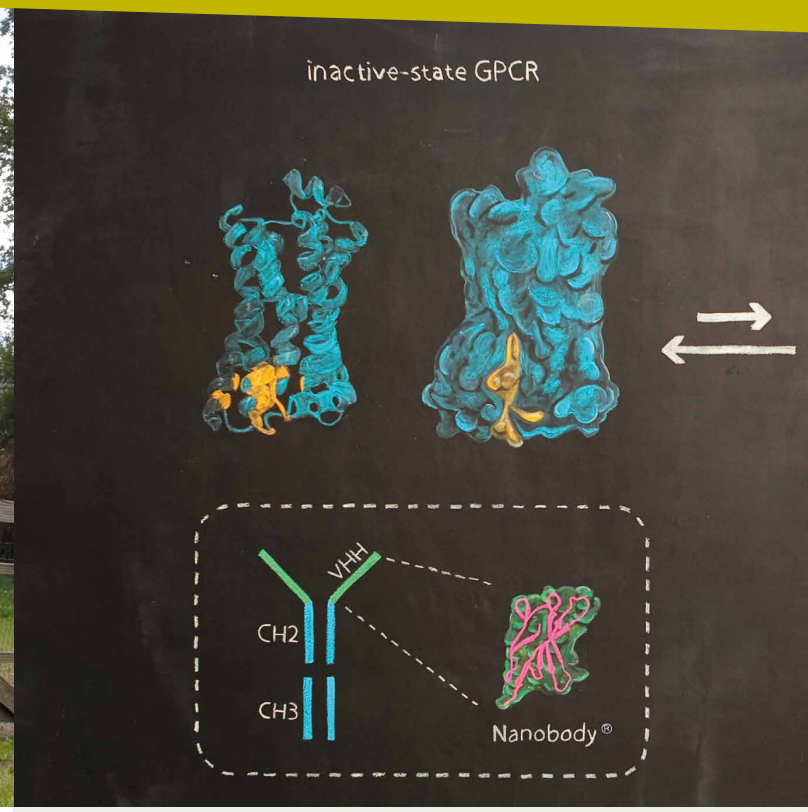
Xaperones
Nanobodies® as crystallization chaperones

In recent years, the Steyaert lab proved that Nanobodies can be successfully used as crystallization chaperones for the structure determination of the most challenging proteins including intrinsically disordered proteins, proteins from larger molecular complexes, aggregating proteins, oligomerizing proteins and membrane proteins that would prove unsolvable using more conventional strategies. Recent highlights include the elucidation of the first GPCR structure in its active state using a conformational selective Nanobody (Nature 469, 175-180, 2011) and the structural investigation of the GPCR-G protein complex by Xaperone-assisted X-ray crystallography (Nature 477, 549–555, 2011). With this groundbreaking work, **the Steyaert lab contributed to the Nobel Prize in Chemistry** that was awarded to Prof. Brian Kobilka and Prof. Robert Lefkowitz in 2012 for **the discovery of G-protein-coupled receptors.**

Based on Nanobody-assisted X-ray crystallography, the Steyaert lab developed a new Business unit, **Xaperones**, to produce Xaperones for the pharmaceutical Industry. The applications of Xaperones in structural biology are numerous. Xaperones increase the hydrophilic surface of integral membrane proteins, reduce their conformational heterogeneity and can trap unstable structural intermediates along the fibrillation pathway of amyloidogenic proteins. A multidomain protein is more rigid in a complex with a Xaperone than the multidomain protein by itself. In complex with a Xaperone, the total amount of structured polypeptide increases, providing a much better starting point for the crystallization of intrinsically unfolded proteins. Xaperones are suitable to stabilize the protomers of larger protein assemblies in one-to-one heterodimers or transient protein complexes.



Brian Kobilka and the llama that produced the Nobel Nanobodies. Kobilka received the Noble Prize in Chemistry 2012 for studies of G-protein-coupled receptors.



With the IOF funding, Structural Biology Brussels aims to translate the structural biology services of the current Business unit Xaperones into an intergrated company focusing on Xaperone-assisted drug discovery.

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