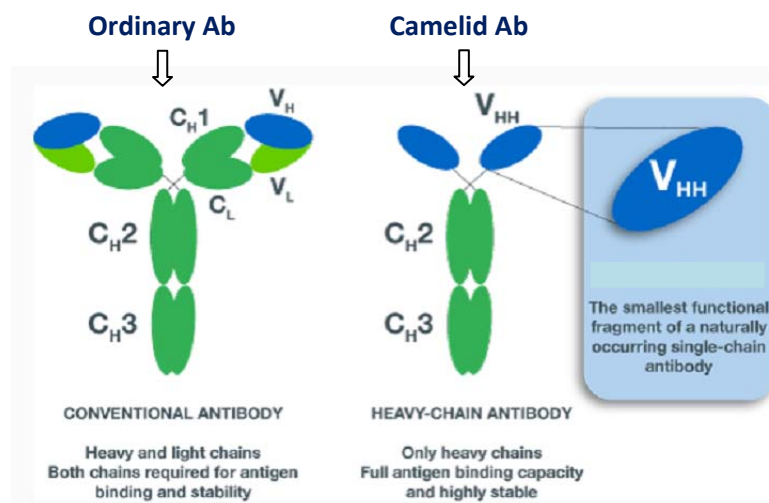


Nanobodies – Valuable Tools From Desert

What is a Nanobody?

Nanobodies (V_{HH}) are a type of antibodies derived from **camelids** (members of the biological family Camelidae. Examples: Camels, alpacas etc) and are much smaller than traditional antibodies. Standard antibodies are giants molecular structures, since each one consist of two heavy protein chains and two light chains, intricately folded and garnished with elaborate sugars. Nanobodies, however, are relatively simple proteins about a tenth the size of human antibodies and just a few nanometers in length. **They are fully functional antibodies that lack light chains. They also lack constant heavy chain domain 1 (C_{H1})**. It is shown that, at least 50% of circulating Abs in camelids lack light chains. Why species in the camel family differ from all other mammals in this respect remains a mystery!

The structure of Nanobody:



As shown in figure, **the variable domain of heavy chain (V_{HH}) alone is sufficient enough, to bind to an Ag**. Equally surprising, these "incomplete" antibodies are able to grasp their targets just as firmly as normal antibodies do, despite having only half as many CDRs (Complementarity determining regions). Hence, the isolated and cloned V_{HH} domain is a **perfectly stable polypeptide harbouring the full antigen-binding capacity of the original heavy-chain antibody, making it the smallest host factor in the world, that specifically binds to an Ag**.

Discovery: Antibodies lacking light chains were first discovered by a group of biologist led by **Raymond Hamers** at Free University (Brussels, Belgium) in **1989**. During one of their tests for antibodies in the camelid blood showed an error: instead of normal four-chain antibodies it indicated the presence of simpler antibodies composed solely of a pair of heavy chains. After several years of investigation, Hamers and his colleagues published their discovery in Nature in 1993, entitled "Naturally occurring antibodies devoid of light chains" [Jun 3; 363(6428):446-8; Pubmed ID: 8502296].

Nanobodies from microbes:

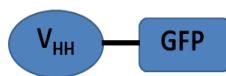
Because nanobodies are so much simpler than antibodies in chemical composition and shape, they can be encoded by a single gene and are easier for microbes to synthesize. In 2002 biologists at Unilever Research in the Netherlands brewed more than a kilogram of nanobodies from a standard

15,000-liter tank of yeast (a yield of 67 milligrams per liter). Today, a Belgian biotech company named **Ablynx**, has developed and patented nanobody production for wide range of biological and therapeutic applications. It was their discovery that, V_{HH} domains have unique structural and functional properties and forms the basis of a new generation of therapeutic antibodies, which Ablynx has named 'nanobodies'.

How does a Nanobody become "Chromobody"?

Nanobodies have numerous applications in biology, among which one of the most important application is the use of nanobodies as chromobodies.

Chromobodies are formed by fusing the V_{HH} (nanobody) with fluorescent proteins to generate "**fluorescent, antigen-binding nanobodies**"; as shown below.



The interesting fact is that, **they can be expressed in living cells**. Chromobodies were first developed by group led by **Heinrich Leonhardt** of Ludwig Maximilians University Munich, Germany in **2006**, as published in Nature Methods, entitled, "Targeting and tracing antigens in live cells with fluorescent nanobodies" [Nov;3(11):887-9, Pubmed ID: 17060912]. They demonstrated that chromobodies can recognize and trace antigens in different subcellular compartments. Chromobodies thus became a powerful tool that enables new functional studies; as **potentially any antigenic structure can be targeted and traced in living cells in this fashion!**

Nanobodies as small molecule drugs:

Like conventional antibodies, Nanobodies show;

- High target specificity,
- High affinity for their target &
- Low inherent toxicity.

Ablynx's have combined these advantages of Nanobodies with important features of small molecule drugs. It's shown that like small molecule drugs, nanobodies have the opportunity to inhibit enzymes and readily access receptor clefts. Furthermore, Nanobodies:

- are extremely stable
- have the potential to be administered by means other than injection
- are easy to manufacture.

Moreover, nanobodies have a high homology with the V_H domains of human antibodies and can be further humanised without any loss of activity. Importantly, Nanobodies have a low immunogenic potential, which has been confirmed in primate studies with Nanobody lead compounds.

A day, where 'nanobody based therapy' is not far!...

Fantastic 4