A comparative molecular dynamics study of bovine antibodies

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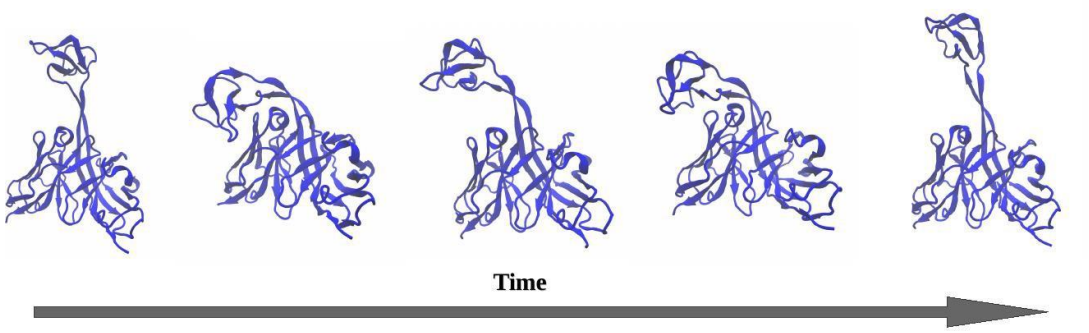

Antibodies are indispensable elements of the adaptive immune system in vertebrates, characterized by their extensive diversity, which enables them to recognize a wide array of antigens. Conventional antibodies are composed of heavy and light chains, each with constant and variable domains. The variable domains, particularly the complementarity-determining regions (CDRs), play a crucial role in antigen recognition. Among these, cow antibodies (CABs) with ultralong CDRH3 regions have shown exceptional ability in binding cryptic viral epitopes, positioning them as promising candidates for antiviral applications [1, 2].

Crystal structures of CABs showed that the ultralong CDRH3s form an elongated stalk and a globular knob at the distal ends of the stalk thus conveying the picture of a rather rigid core-stalk-knob arrangement. However, this finding is questioned by the presence of extensive crystal packing. To gain insight into the dynamics of CABs, we have therefore performed a large-scale comparative molecular dynamics study that included 19 unique CAB structures.

Our data shows that all CABs exhibit high flexibility of their knob domains as exemplified above for CAB BLV1H12 (PDB:4K3D [3]). However, we noted significant differences in the degree of flexibility, the observed knob orientations, and the frequency of the motions. In this context, interactions between the knob of the CDRH3 and the light chain of the CAB seem to play an important role for the stabilizations of distinct knob orientations.

These insights into ultralong CDRH3 antibodies could significantly enhance immunization strategies and antibody engineering, further elucidating their role in the bovine immune response and paving the way for novel antiviral therapies. This work not only underscores the unique capabilities of bovine antibodies but also provides a foundation for future research into their applications across different medical challenges.

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2. Stanfield RL, Berndsen ZT, Huang R, *et al*. Structural basis of broad HIV neutralization by a vaccine-induced cow antibody. *Sci Adv.*, **2020**, *6*, eaba0468..
3. Wang F, Ekiert DC, Ahmad I, *et al*. Reshaping antibody diversity. *Cell*, **2013**, *153*, 1379-1393.