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## Preface

The development of the hybridoma technology created the possibility to obtain unlimited amounts of monoclonal antibodies (mAb) with high specificity and affinity for any target and to introduce mAbs in a wide range of applications. Examples of antibody-based drugs in therapeutic settings and antibody-based probes in diagnostics are infinite. However, the bulky size of mAbs, costly production, and cumbersome engineering retarded or hampered regularly their streamlined development in some applications. Consequently, mAbs became the focus of many attempts to minimize the size and complexity of their antigen-binding fragments. Eventually, these efforts led to the recombinant production of smaller antigen-binding fragments such as Fab or scFv (where a synthetic linker connects the variable domains of heavy and light chain, i.e., VH and VL), and even sdAbs (single domain antibodies derived mostly of the VH). Although the first set of sdAbs offered significant advantages, they also suffered from multiple shortcomings, all of which have been remediated by elegant engineering. Interestingly, while scientists were designing, engineering, and shaping the ideal sdAb, a serendipitous discovery showed that a similar engineering occurred already in nature in the camelids, and later on, it was found that cartilaginous fish antibodies performed the exercise even earlier on in evolution. These animals have in their blood functional antibody isotype composed of heavy chains—only that lack light chains, in addition to the classical antibodies containing two heavy and two light chains. These heavy-chain antibodies (HCAbs) recognize the antigen via a single variable domain, referred to as VHH or V-NAR. The VHH or V-NAR is the smallest intact antigen-binding fragment that can be produced recombinantly at low cost.

The valuable properties of man-made sdAbs, VHHs, and V-NARs including solubility and stability, high affinity and specificity for their cognate antigen, small size and strict monomeric behavior offer many opportunities. As a result, several spin-off companies have been founded in Australia, Belgium, England, Germany, Netherlands, and Scotland that introduced these proteins successfully in a wide range of applications to cover a special need in research or even to produce next-generation therapeutics in the clinic.

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