

Tailored Discovery and Engineering of Nano-antibodies (VHHs) Inhibiting Proteases associated with diseases

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VHHs, also referred to as Nanobodies® or nano-antibodies, are single-domain antigen-binding fragments derived from the heavy-chain-only antibodies naturally found in camelids. Owing to their unique structural and biochemical properties — including small size, high solubility, remarkable stability, and the capacity to access cryptic or poorly immunogenic epitopes — VHHs have emerged as powerful tools across a wide range of applications. In particular, they have transformed modern biomedical research and medicine, with growing use in therapeutics, diagnostics, and fundamental studies of protein function.

Within the academic platform AlpaNano, we generate and select VHHs directed against a broad spectrum of targets, including peptides, soluble and membrane proteins, as well as carbohydrates. Selections are performed using biopanning approaches based on phage display, combined with comprehensive screening combining ELISA, biolayer interferometry (BLI), and next-generation sequencing (NGS). These integrated workflows enable the rapid identification of high-affinity and highly specific binders from complex immune and synthetic libraries.

We will present recent work on the development of tailored selection strategies to isolate VHHs efficiently inhibiting proteases associated with diseases including mesothelioma, chronic inflammatory diseases and infectious diseases. In parallel, we will present dedicated pipelines to identify or engineer VHHs that retain binding and functional activity under harsh biochemical conditions characteristic of inflammatory environments, notably in the presence of elevated proteolytic activity, or to target specific tissues.

Together, these developments illustrate the versatility of VHH technology and highlight its potential for generating robust binders adapted to demanding biological contexts, paving the way for innovative applications in both fundamental research and translational settings.