

EXTRACELLULAR VESICLE-BASED NATIVE MEMBRANE PROTEIN DISPLAY

A dual platform for nanobody discovery and direct binding kinetics measurements

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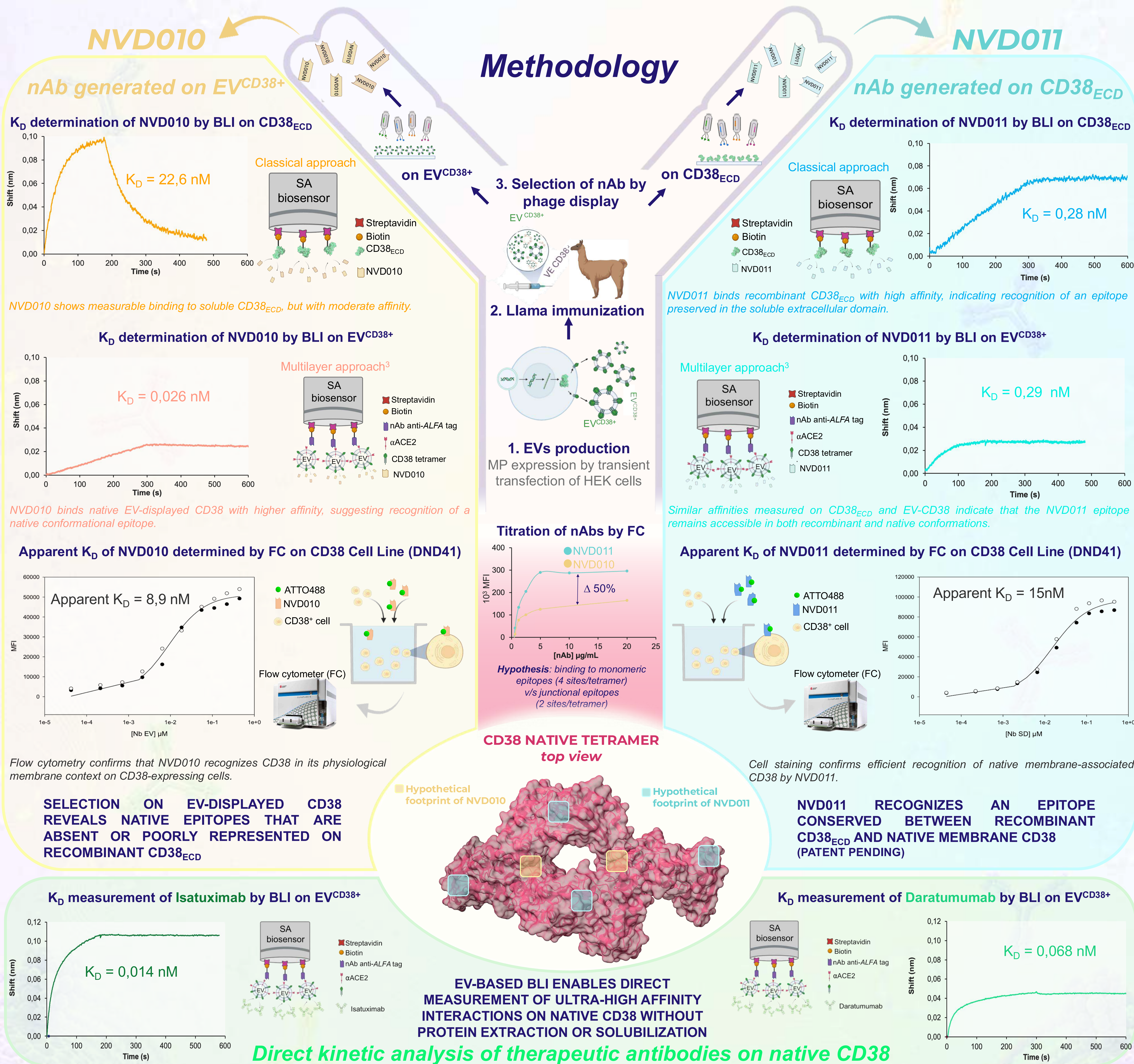
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Context

Membrane proteins (MPs) are major therapeutic and diagnostic targets, yet antibodies and nano-antibodies (nAbs) are generally generated against recombinant soluble extracellular domains (ECDs). Such approaches may alter the native oligomerization state and conformational profile of MPs, potentially masking physiologically relevant epitopes¹. NVDIAG technology exploits extracellular vesicles (EVs) displaying MPs in their native lipid bilayer environment to preserve their structural organization^{2,3}.

CD38 is a biomarker of multiple myeloma and is thought to form tetramers at the cell surface, whereas recombinant CD38_{ECD} is monomeric in solution⁴. Using this model target, we investigated whether EV-based antigen presentation enables the discovery of nAbs recognizing native epitopes absent on soluble CD38_{ECD}. We further show that EVs provide a platform for direct BioLayer Interferometry (BLI), enabling kinetic characterization of antibodies on native MPs without extraction or solubilization.



Conclusion

This study demonstrates that extracellular vesicle-based antigen native membrane protein profoundly influences nano-antibody discovery outcomes. Selection performed on EV-displayed CD38 revealed nano-antibodies recognizing native conformational or oligomerization-dependent epitopes that are not fully preserved or even absent in recombinant soluble CD38_{ECD}. In parallel, EV-based BioLayer Interferometry enabled direct kinetic characterization of nano-antibodies and therapeutic antibodies on native membrane proteins, yielding affinity measurements consistent with their physiological membrane context. Together, these results establish EVs as a powerful platform for both binder discovery and functional characterization of membrane protein targets, with potential applications in therapeutic antibody development and companion diagnostics.



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