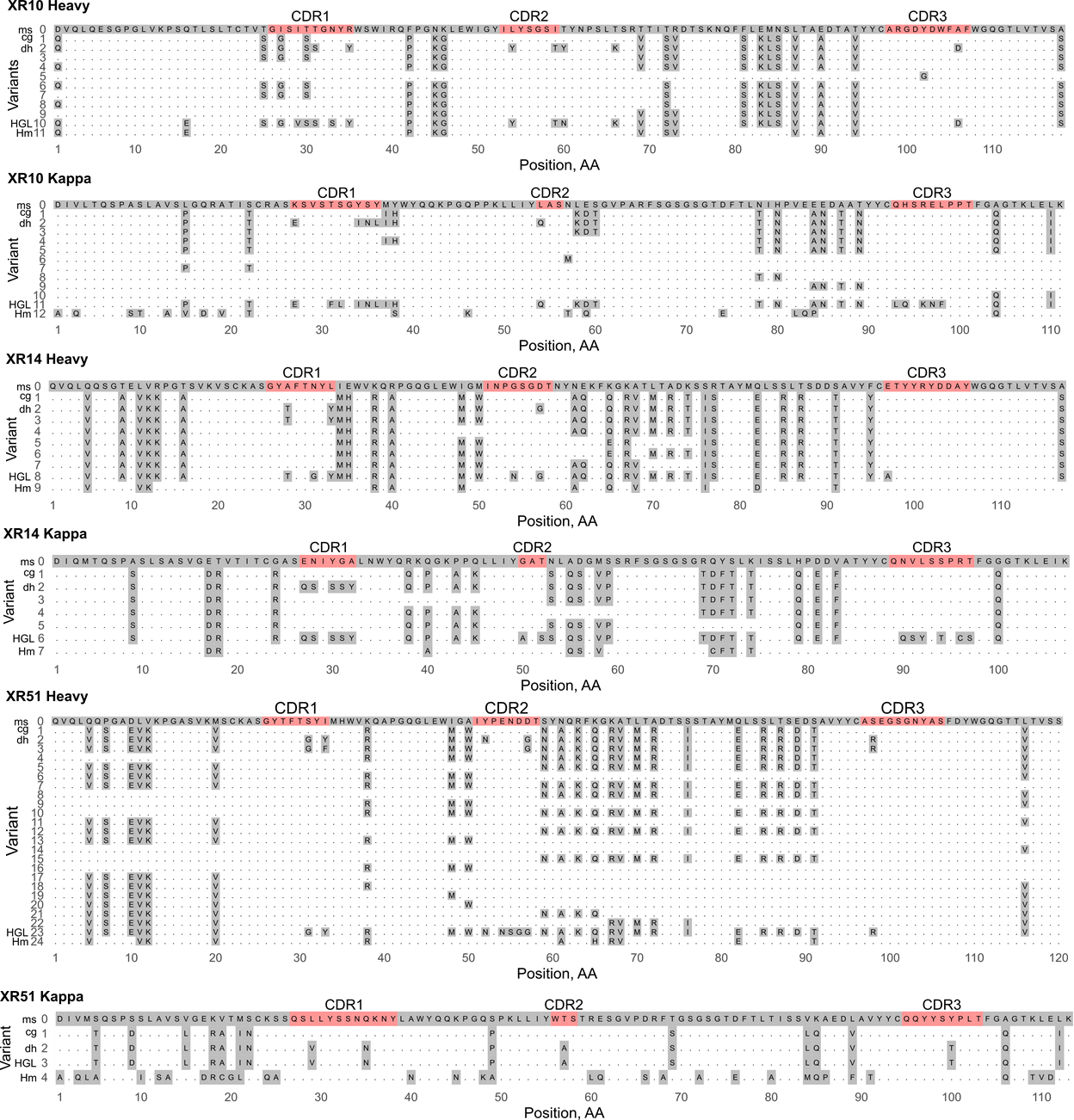
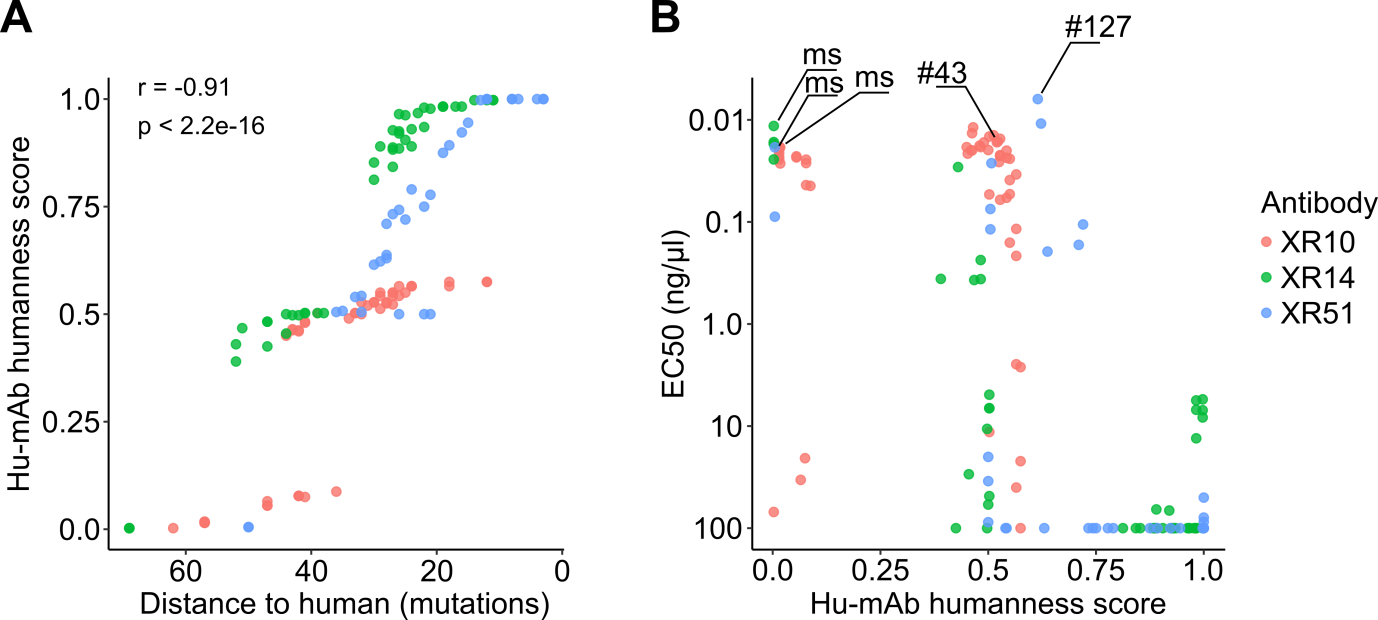
**SUPPLEMENTARY FIGURES**



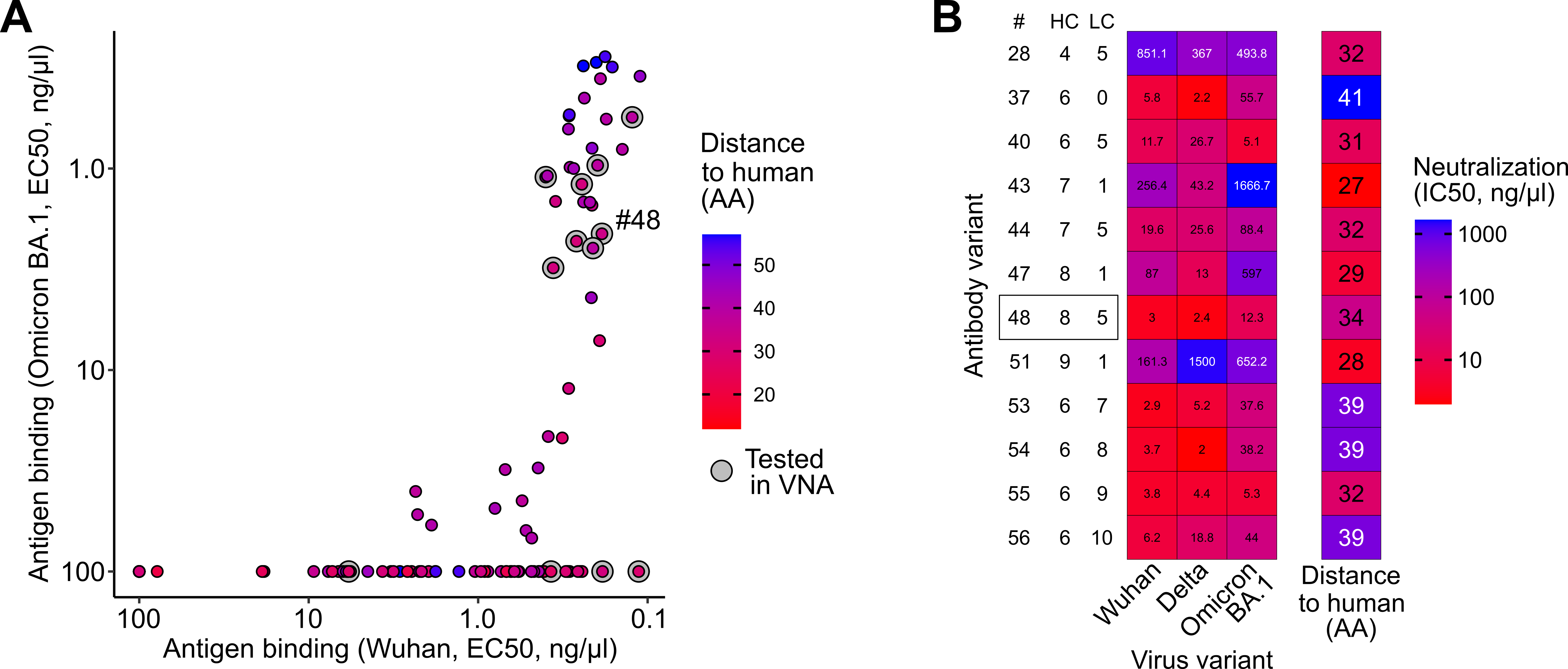
**Figure S1. Multiple alignment of the XR amino acid sequences**. ms – original mouse mAb sequence, cg – CDR grafted version, dh – deeply humanized version, HGL – germline human sequence, Hm - sequence humanized by Hu-mAbs.



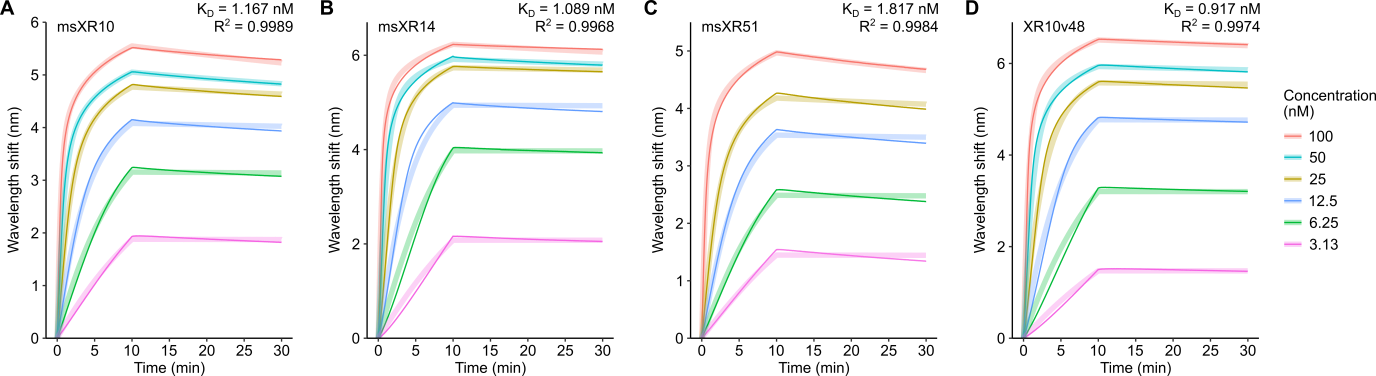
**Figure S2. Experimentally-driven mAb humanization procedure outline.** The first step entails alignment to human (or target organism) germline segment library to select the framework regions of the highest homology. CDRs are then grafted in the human frameworks. Chain and framework reshuffling is used to locate the binding-affecting mutations introduced through humanization. Final step is performed on individual amino acid residues level.



**Figure S3. Variants evaluation by Hu-mAbs software. (A)** Humanization extent estimated by Hu-mAb humanness score and DtH. Correlation is calculated with Spearman’s rank test. **(B)** Antibody binding (EC50) to Wuhan RBD against Hu-mAb humanness score. ms - original mouse mAb variant.



**Figure S4. Subset of XR10 variants characterization.** **(A)** Binding of all XR10 variants to Wuhan and Omicron BA.1 RBD with the further tested subset highlighted. **(B)** Neutralization of Wuhan, Delta, and Omicron BA.1 viruses by the selected XR10 antibodies. XR10v48 is selected for hamster challenge tests.



**Figure S5. Biolayer interferometry analysis.** Kd calculated using the global fit of the association/dissociation curves received from wavelength shift measurement. R2 – determination coefficient.