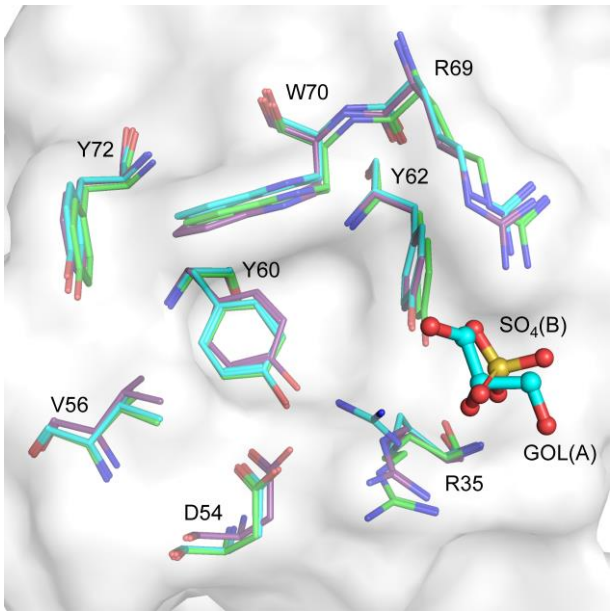
Supplemental material

Supplemental Table S1. Fibulin-5: scores of the 5 top models generated by I-TASSER

Model number	C-Score
1	-2.25
2	-2.62
3	-3.23
4	-3.18
5	-3.16

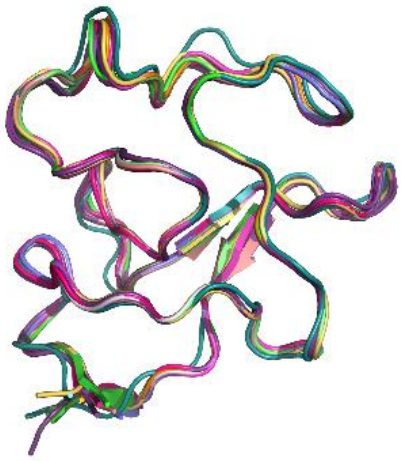
Supplemental Table S2. CONSRANK scores for protein-protein interaction models

	Fibulin-5	**CONSrank score**
1	complex.3.pdb	0.23617
2	complex.6.pdb	0.23535
	Fibronectin	**CONSrank score**
1	complex.6.pdb	0.26607
2	complex.5.pdb	0.26143
	β2GPI	**CONSrank score**
1	complex.8.pdb	0.22286
2	complex.4.pdb	0.21636

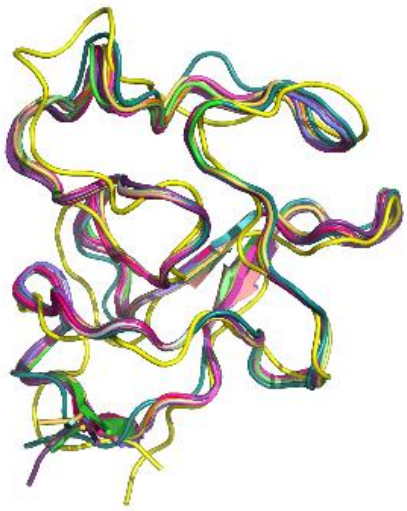


Supplemental Figure 1 Superposition of the three monomers of the asymmetric Unit of KIV-2. Key residues making up each monomer LBS are represented as sticks (chain A in cyan, chain B in green and chain C in purple) and as a surface (grey). The ligands SO_4 and glycerol (GOL) are represented as balls and sticks.

(a)

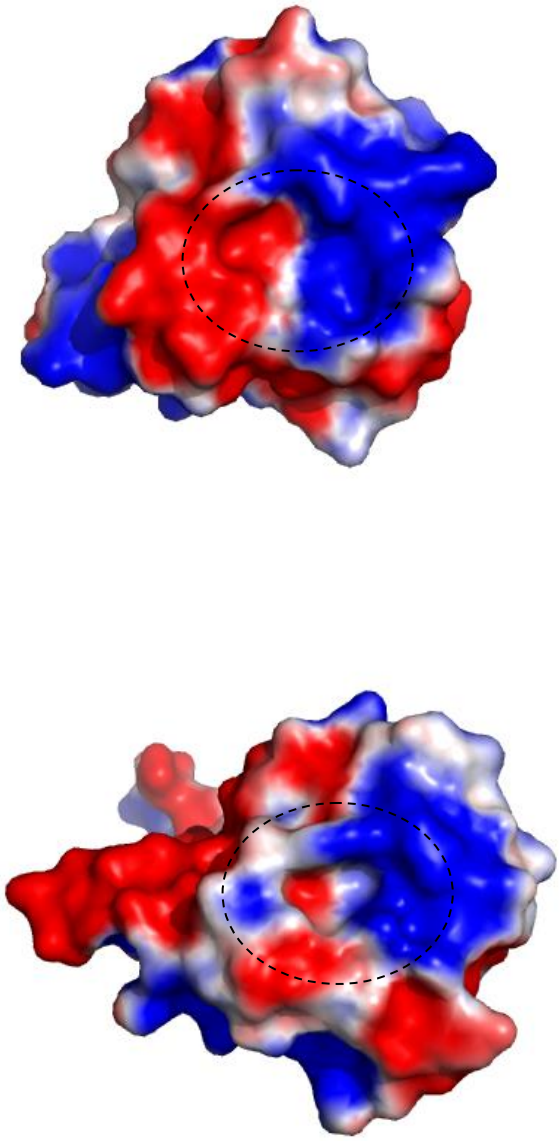


(b)



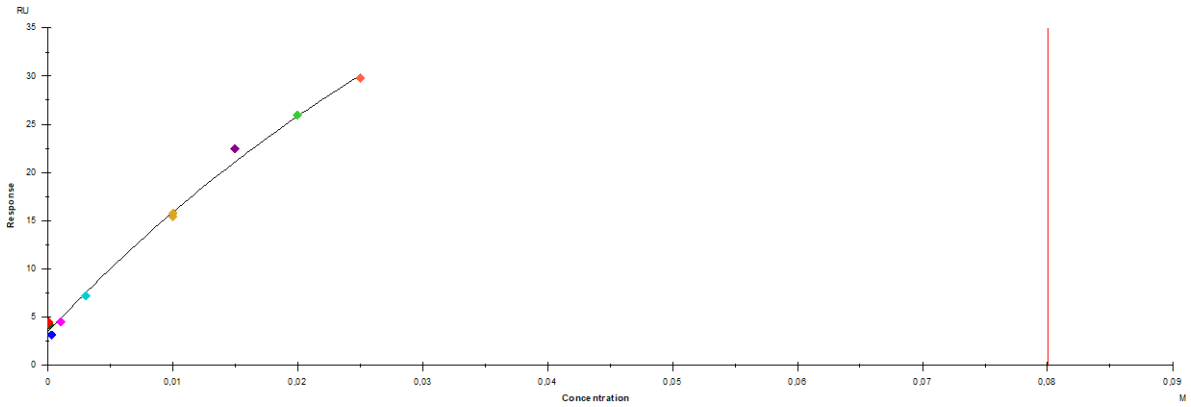
Supplemental Figure 2. Superposition of the structures of KIV-7 (PDB ID: 4BVW, light purple), KIV-8 (PDB ID: 2FEB, yellow), KIV-10 (PDB IDs: 1KIV, 3KIV, 4BVD, 4BVC, 4BV7, in pink, light pink, light green, orange, purple, respectively) and KV (PDB ID: 4BVV, forest green). For KIV-7 and KIV-10, structures both with and without bound ligands are shown. (a) Without KIV-8; (b) with KIV-8 (randomly chosen model from the NMR ensemble, in yellow).

Supplemental Figure 3. Secondary structure of KIV-2, from Stride [1].

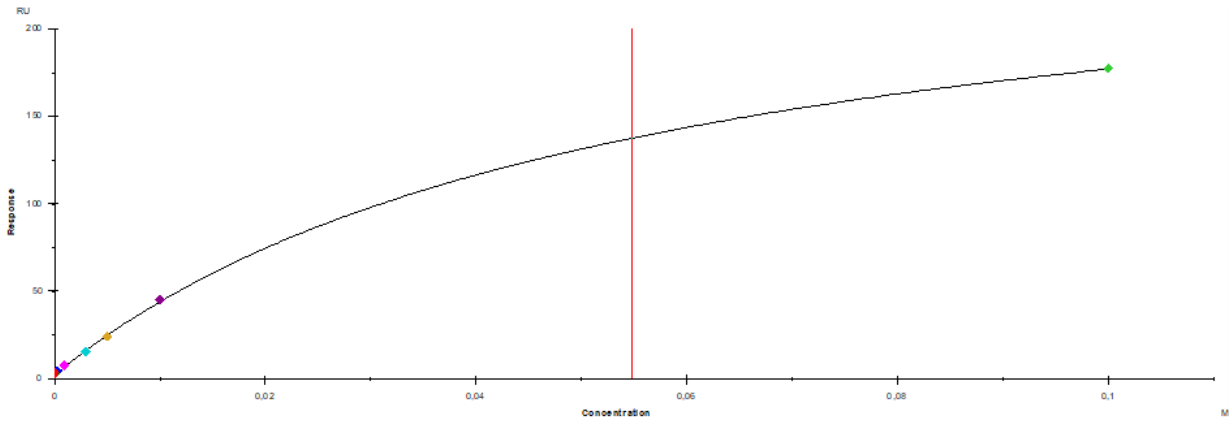


Supplemental Figure 4 Electrostatic potentials generated by PyMol: KIV-10 (top, PDB ID: 1KIV) and KIV-2 (bottom, PDB ID: 6RX7, chain A). Encircled with a dashed line is the LBS. Red: negatively charged surface. Blue: positively charged surface.

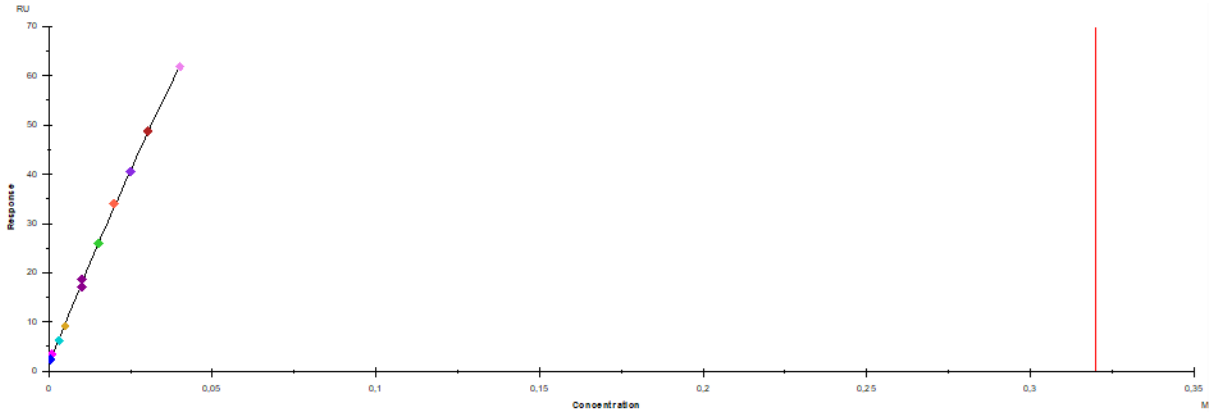
(a)



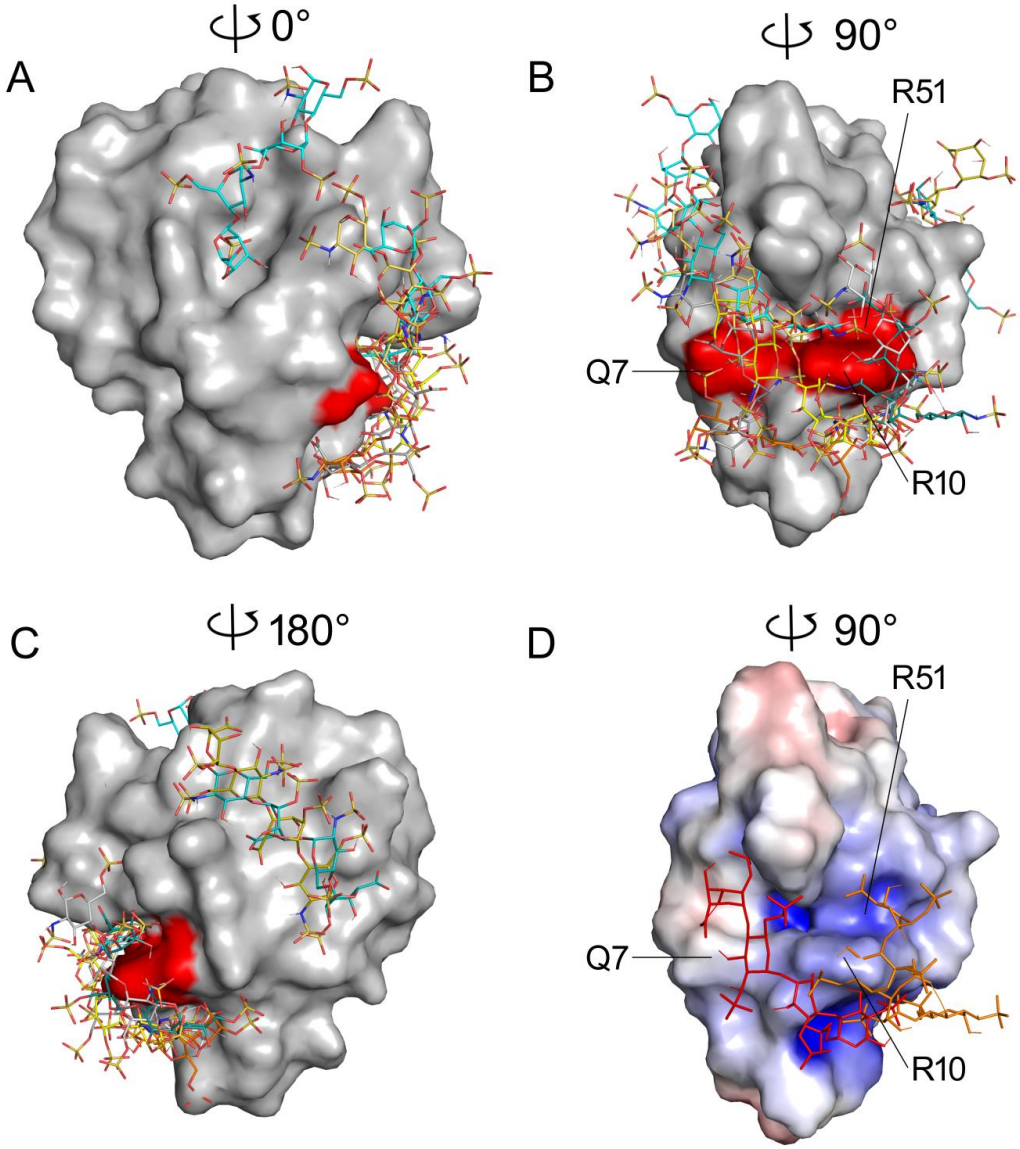
(b)



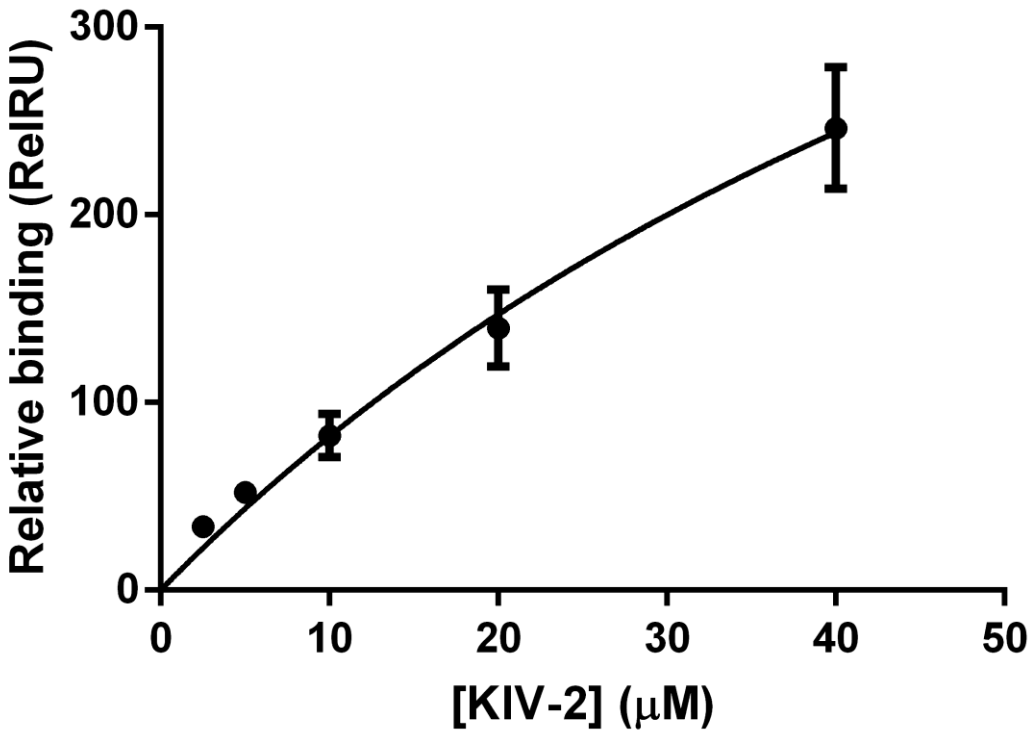
(c)



Supplemental Figure 5 Kinetic profiles of EACA (a), t-AMCHA (b) and NAG (c) on KIV-2. On the y axis the Response in RUs, on the x axis the analyte concentration.

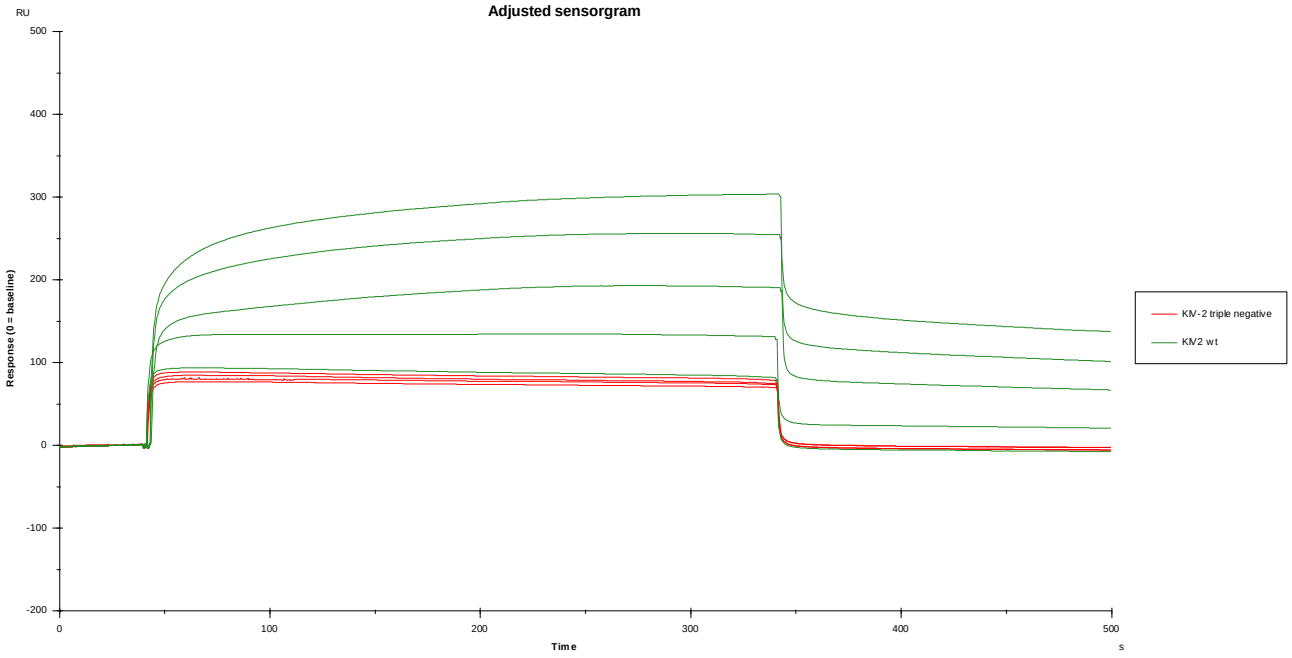


Supplemental Figure. 6 Prediction of heparin binding to KIV-2. Panels A to C: The top 10 models obtained by ClusPro prediction are reported. KIV-2 is shown as surface (grey) and different heparin molecules are shown as sticks of different colors. In red: Q7, R10 and R51 residues replaced by Glu in the KIV2 triple negative mutant. Panel D: the top 2 models obtained by CONSRank are represented as sticks, KIV2 is colored by surface charge, with blue indicating a positive surface charge. The mutated residues Q7, R10 and R51 are labelled.



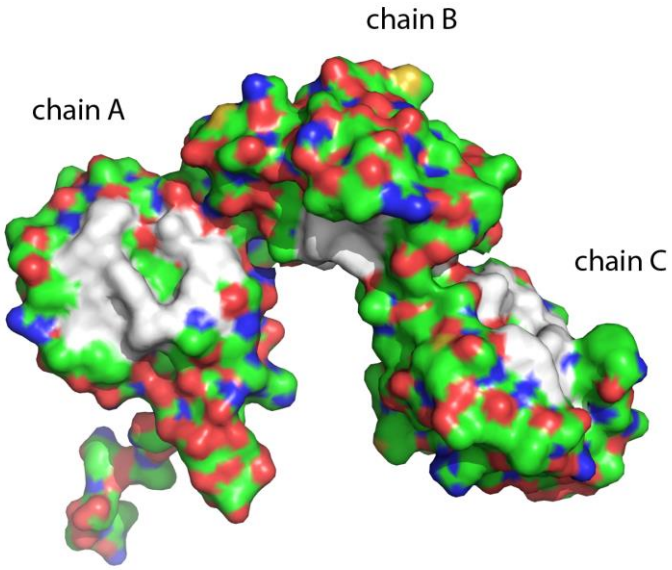
(a)

(b)

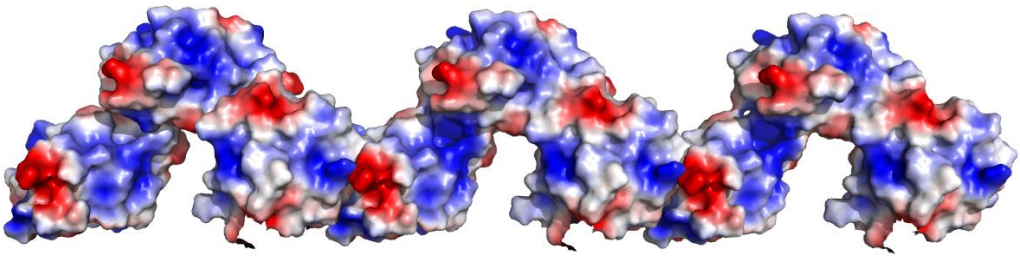


Supplemental Figure 7 KIV2 affinity for heparin: (a) KD determination for KIV-2 wild-type and (b) SPR sensorgrams of KIV-2 wt (green) versus KIV-2 triple mutant (red).

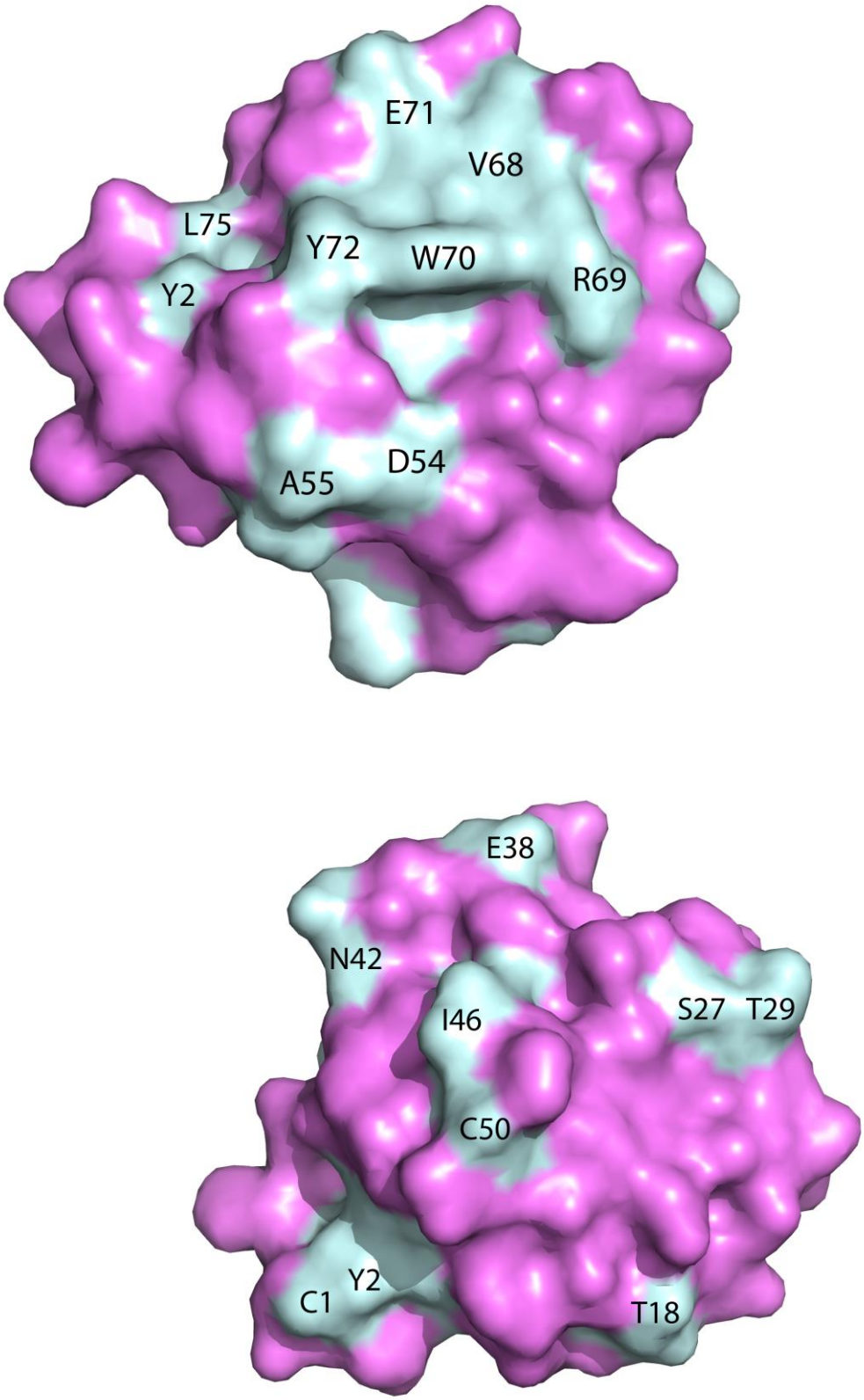
(a)



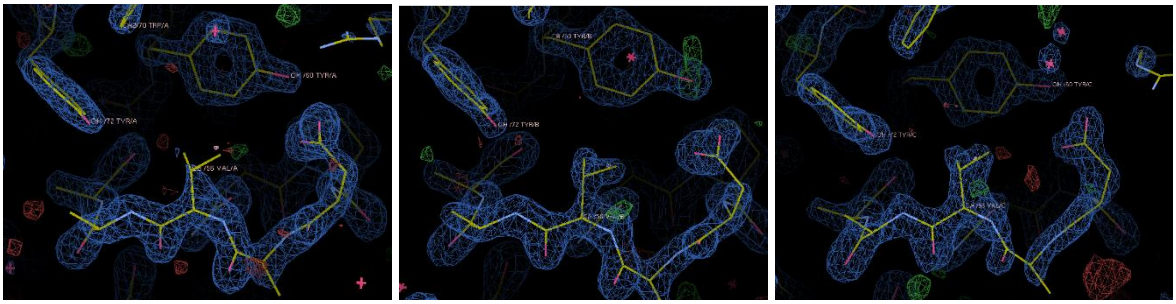
(b)



Supplemental Figure 8 Surface representation of the trimeric asymmetric unit of KIV-2 (a, in white: LBS) and of the KIV-2 tandem repeat protein chain (b, electrostatic charges) generated by crystal contacts (three asymmetric units are represented, linker regions were removed for clarity).



Supplemental Figure 9 Front and rear view of the absolutely conserved (light blue, labelled) and variable (purple) residues in KIV-2 [2].



Supplemental Figure 10 Electron density of Val56. From left to right: chains A, B and C of KIV-2.

References

1. Heinig, M. and D. Frishman, *STRIDE: a web server for secondary structure assignment from known atomic coordinates of proteins.* Nucleic Acids Res, 2004. **32**(Web Server issue): p. W500-2.
2. Coassin, S., et al., *A comprehensive map of single-base polymorphisms in the hypervariable LPA kringle IV type 2 copy number variation region.* J Lipid Res, 2019. **60**(1): p. 186-199.