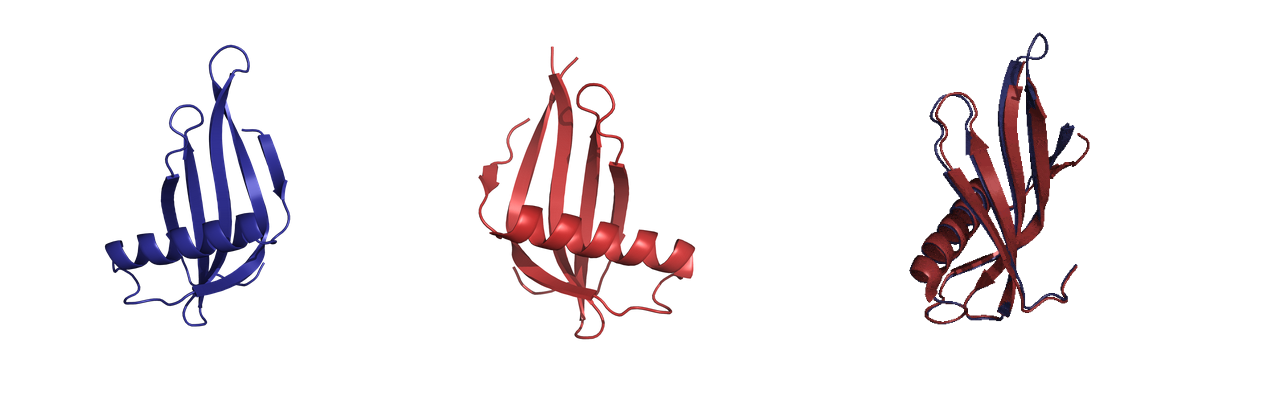
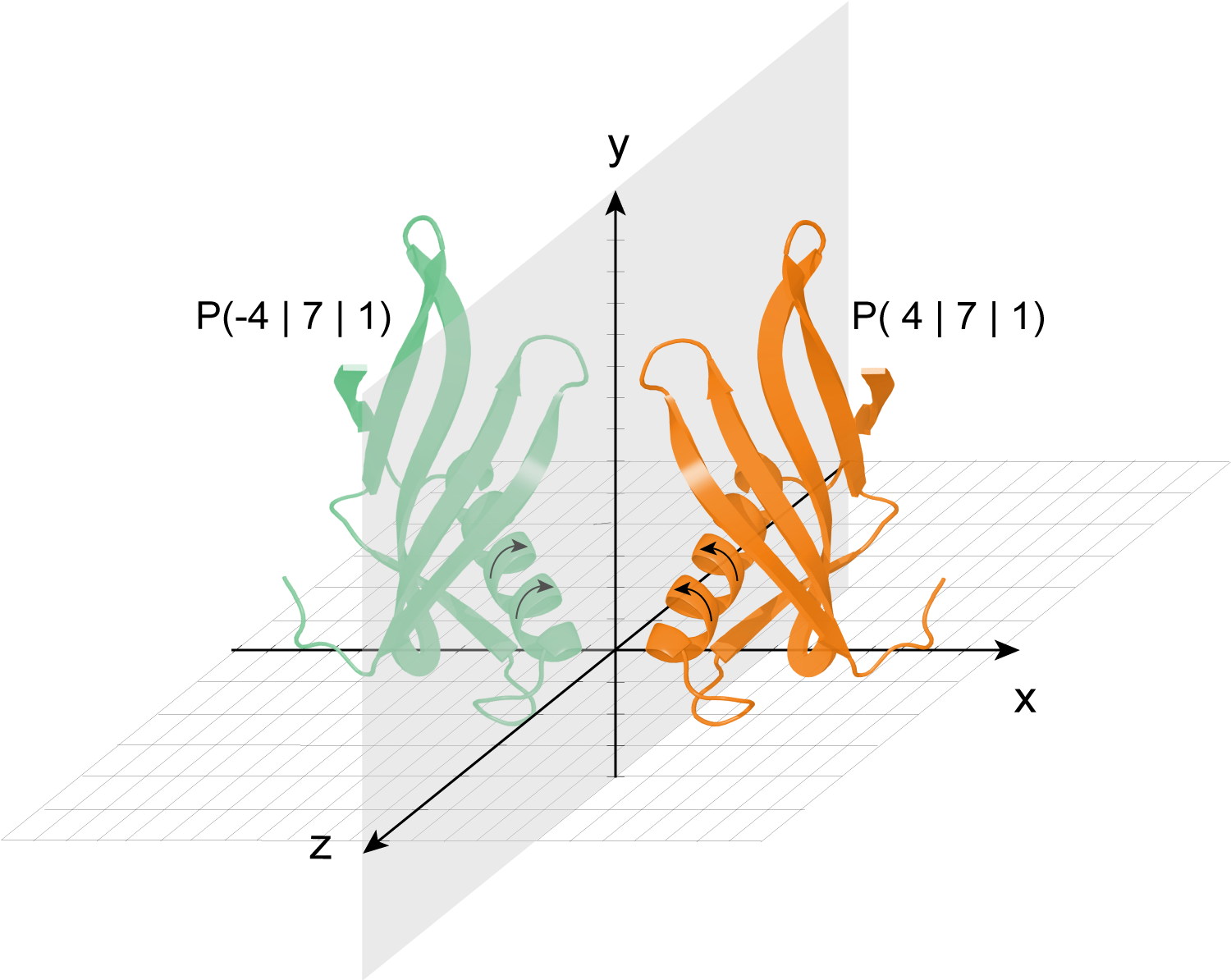
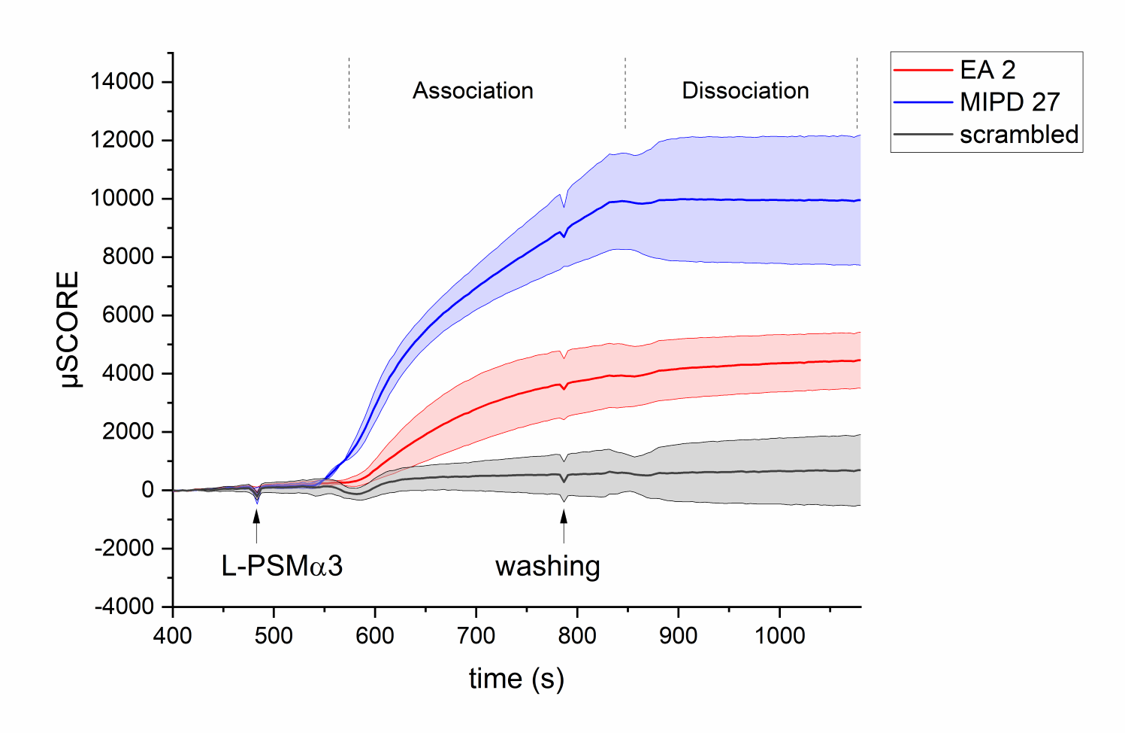
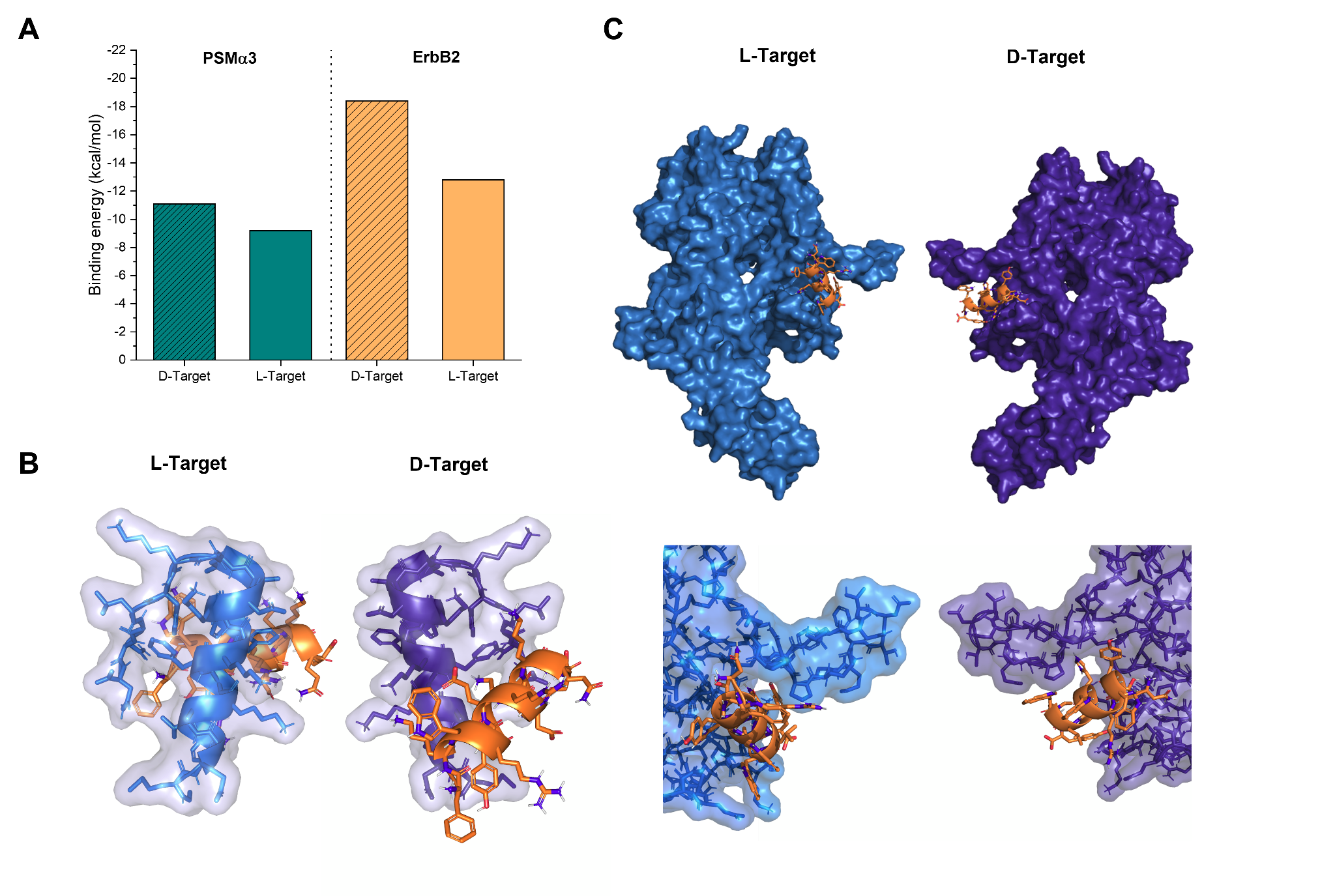
Supplementary information



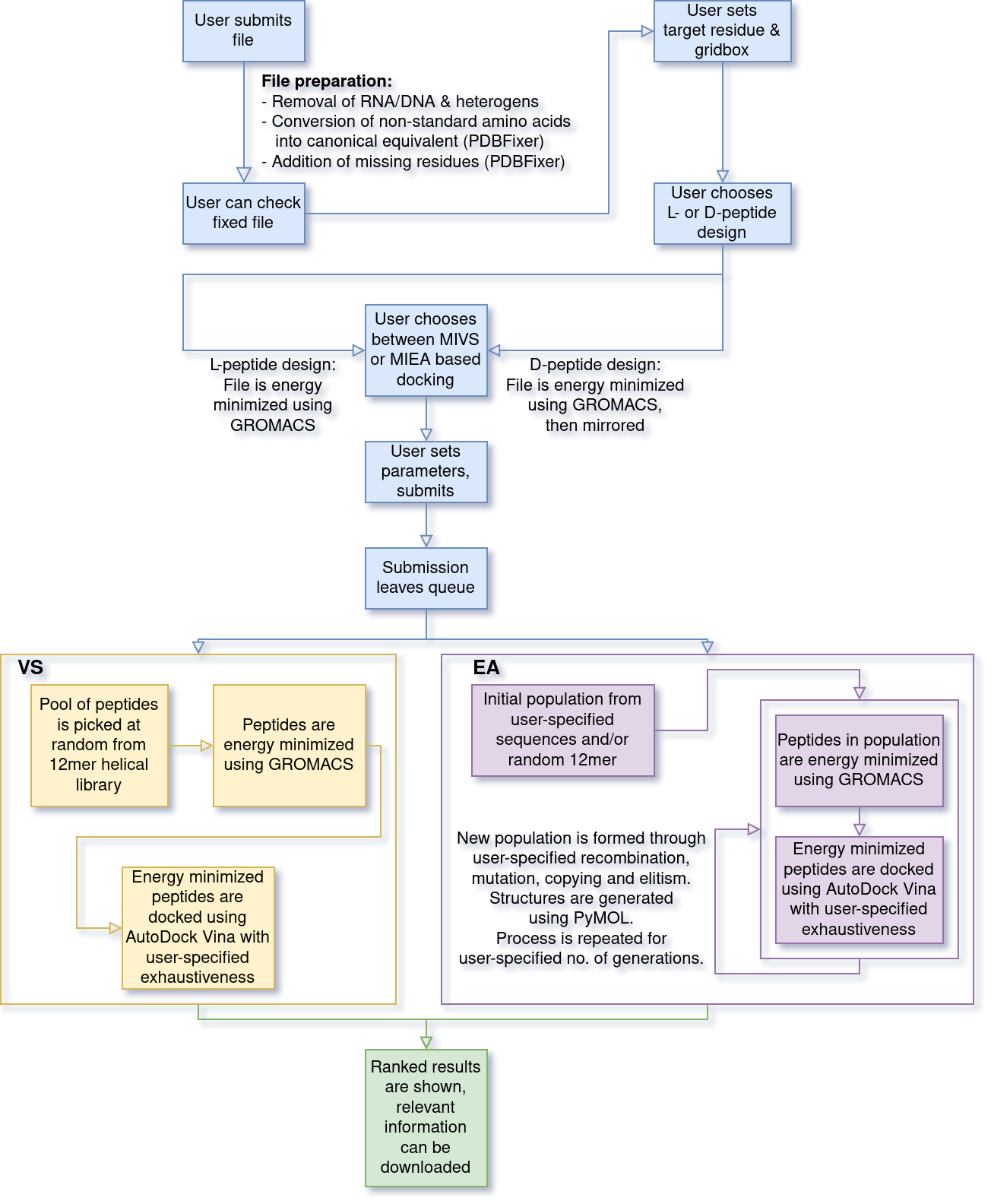
***Supplementary Figure 1: L-to-D conversion of protein structures.*** *A: L-Monellin crystal structure PDB ID: 1MOL (orange) and structure prediction of its mirror-image D-analogue (light green) by inversion of the X-coordinates of all atoms. B: Alignment of two D-Monellin structures with Pymol: D-Monellin crystal structure PDB ID: 2Q33 (red) and D-Monellin model predicted by L-to-D conversion (blue).*



***Supplementary Figure 2:******SCORE binding assay of MIPD- and MIEA-derived L-peptide ligands to L-PSMα3.*** *The mean intensities of four spots (EA2) and 2 spots (scrambled, MIPD27) with standard deviation are depicted. Two spots of MIPD27 were excluded due to potential immobilization issues.*



***Supplementary Figure 3: In silico docking-based assessment of ligand stereospecificity.*** *The ligand L-EA2 was docked to D-PSMα3 and L-PSMα3 and the ligand L-DNRGSHFWLTKF was docked to D-ErbB2/L-ErbB2 using a gridbox, centered on the ErbB2 binding cleft area as used in Figures 8 E and F. A: Binding energies obtained from docking simulations are given in kcal/mol B: Predicted binding poses of L-EA2 (orange) to D-PSMα3 (blue) and L-PSMα3 (violet). C: Predicted binding poses of L-DNRGSHFWLTKF (orange) to D-ErbB2 (blue) and L-ErbB2 (violet), gridbox not shown. Top: whole molecule view, Bottom: Zoom-in on ErbB2 binding cleft.*



***Supplementary Figure 4: finDr workflow.*** *User uploads the target structure. The structure is prepared for further analysis by removal of DNA and RNA atoms, conversion of non-standard amino acids into their canonical equivalent and adding of missing residues. Then, the user sets a target residue and gridbox, before deciding between L- or D- peptide drug design. User finally chooses MIVS or MIEA and sets the according docking simulation parameters. When computing power is available, either MIVS or MIEA is performed. Finally, the user gets notified about the completion of the job and can view results online as well as be able to download relevant data.*

**Supplementary Table 1:** Formylmethionine (Fme) forcefield parameters in Gromacs format

**[ NFME ]**

**[ atoms ]**

**N N -0.572522 1**

**H H 0.322879 2**

**CA CT -0.017921 3**

**CN C 0.662279 18**

**HF H5 0.034579 19**

**OF O -0.607721 20**

**HA H1 0.105079 4**

**CB CT 0.028048 5**

**HB1 HC 0.02410 6**

**HB2 HC 0.02410 7**

**CG CT 0.00180 8**

**HG1 H1 0.04400 9**

**HG2 H1 0.04400 10**

**SD S -0.27370 11**

**CE CT -0.05360 12**

**HE1 H1 0.06840 13**

**HE2 H1 0.06840 14**

**HE3 H1 0.06840 15**

**C C 0.59730 16**

**O O -0.56790 17**

**[ bonds ]**

**N CN**

**N H**

**N CA**

**CN OF**

**CN HF**

**CA HA**

**CA CB**

**CA C**

**CB HB1**

**CB HB2**

**CB CG**

**CG HG1**

**CG HG2**

**CG SD**

**SD CE**

**CE HE1**

**CE HE2**

**CE HE3**

**C O**

**[ impropers ]**

**HF CN OF N**

**CA H N CN**

**CA +N C O**

**N CA C +N 105.4 0.75 1**

**Supplementary Table 2:** *Sequences of PSMa3-binding L-peptide ligands identified in MIPD and phage ELISA against D-PSMa3.*

|  |  |  |  |
| --- | --- | --- | --- |
| **Name** | **Sequence** | **m/z (calculated)** | **m/z (observed)** |
| MIPD 8 | KHLHYHSSVRYG | 1483.75 | 1483.7 |
| MIPD 11 | KHVQITSTFGVI | 1329.74 | 1329.55 |
| MIPD 27 | MPMFKHRMFHTH | 1599.95 | 791.36 |
| scrambled control | LPSSHHIPPMHI | 1365.60 | 1365.50 |
| EA2 | FKWRYERDKKQS | 1670.86 | 835.79 |
| MIPD 3 | WDMWPSMDWKAE | not synthesized | not synthesized |