Supplementary Information (SI) for Nanoscale.

SUPPORTING INFORMATION

Modeling β-Sheet Breaker Peptides Across Multiple Resolutions: From Neurological Targets to Liposomal Membranes

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Table S1. Binding energy scores of β-sheet breaker peptides obtained from molecular docking using AutoDock CrankPep (ADCP) with a small grid box size of 25 × 25 × 25 Å.

2MXU					2N0A				
Sequence	**ADCP-Trial1**	**ADCP-Trial2**	**ADCP-Trial3**	**ADCP-Avg**	**Sequence**	**ADCP-Trial1**	**ADCP-Trial2**	**ADCP-Trial3**	**ADCP-Avg**
DEEIERQLKALG	-18.9	-18.1	-19.0	-18.7	DEEIERQLKALG	-19.9	-20.3	-18.8	-19.7
RYYAAFFARR	-18.7	-17.6	-17.3	-17.9	HKQLPFYEED	-20.0	-17.7	-18.3	-18.7
HKQLPFYEED	-17.7	-17.7	-17.5	-17.6	HKQLPFFEED	-17.5	-18.1	-18.5	-18.0
HKQLPFFEED	-16.3	-17.9	-18.0	-17.4	QKLVTTAE	-14.2	-13.1	-14.2	-13.8
RTKSGVYLVG	-17.5	-17.7	-16.2	-17.1	KDGIVNGVKA	-14.3	-13.7	-12.0	-13.3
KKLVFFARRRRA	-17.2	-17.8	-16.4	-17.1	AVVTGETAVAQ	-13.3	-12.4	-13.6	-13.1
RPITRLRTHQNR	-16.8	-17.4	-16.9	-17.0	RYYAAFFARR	-13.2	-12.0	-12.2	-12.5
QSHYRHISPAQV	-15.3	-15.7	-17.6	-16.2	DGIVAGVKA	-13.0	-12.2	-11.5	-12.2
RPRTRLHTHRNR	-16.1	-15.4	-16.7	-16.1	QSHYRHISPAQV	-11.4	-12.6	-12.5	-12.2
RGKLVFFGR	-16.7	-15.8	-15.5	-16.0	KEGPVHGVATV	-12.0	-12.5	-11.5	-12.0
GVLYVGSKTR	-16.1	-16.1	-15.6	-15.9	KKLVFFARRRRA	-11.7	-13.0	-11.3	-12.0
KDGIVNGVKA	-16.0	-15.4	-16.3	-15.9	RDLPFFPVPID	-11.5	-11.7	-12.5	-11.9
KEGPVHGVATV	-15.1	-16.4	-15.8	-15.8	RTKSGVYLVG	-11.7	-12.7	-10.8	-11.7
AVVTGGTAVAQ	-14.8	-15.8	-15.3	-15.3	RPITRLRTHQNR	-11.0	-12.9	-11.0	-11.6
KKLVFFA	-15.1	-15.4	-15.4	-15.3	QVTNSGGAVVT	-12.6	-11.6	-10.5	-11.6
QVTNSGGAVVT	-14.6	-15.6	-14.9	-15.0	RDLPFYPVPID	-11.5	-11.5	-11.4	-11.5
VTGVPAVAQK	-14.4	-14.7	-15.3	-14.8	KKLVFFA	-11.6	-11.4	-11.3	-11.4
GAVVKGVTAV	-15.2	-14.4	-14.1	-14.6	LPFFD	-11.6	-11.3	-11.3	-11.4
KFVFFA	-14.1	-14.7	-13.9	-14.2	LPYFD	-11.5	-11.3	-11.0	-11.3
RGGAVVTGR	-14.3	-14.3	-13.9	-14.2	GVLYVGSKTR	-11.7	-11.1	-10.8	-11.2
AVVTGETAVAQ	-15.2	-13.2	-13.8	-14.1	KFVFFA	-11.0	-11.0	-11.3	-11.1
RDLPFFPVPID	-13.1	-13.5	-15.6	-14.1	RGKLVFFGR	-11.1	-11.1	-10.9	-11.0
QKLVFF	-13.7	-14.5	-14.0	-14.1	AVVTGGTAVAQ	-11.4	-10.9	-10.7	-11.0

DGIVAGVKA	-13.8	-14.1	-13.9	-13.9	KLVFFA	-10.7	-11.2	-10.9	-10.9
RDLPFYPVPID	-13.6	-13.5	-14.7	-13.9	RPRTRLHTHRNR	-11.0	-10.6	-11.1	-10.9
QKLVTTAE	-14.3	-13.9	-13.3	-13.8	GAVVKGVTAV	-11.2	-10.4	-10.2	-10.6
GAVVPGVTAV	-13.5	-13.9	-12.8	-13.4	QKLVFF	-10.7	-10.4	-10.5	-10.5
KLVFFA	-13.1	-13.2	-13.9	-13.4	KLVFF	-10.9	-9.9	-10.8	-10.5
PGKLVYA	-13.2	-13.4	-13.5	-13.4	VTGVPAVAQK	-10.0	-9.5	-11.9	-10.5
RGAVVTGR	-13.7	-12.8	-13.4	-13.3	KIVFFA	-9.8	-10.7	-10.6	-10.4
KIVFFA	-13.2	-13.2	-13.3	-13.2	KVVFFA	-10.4	-9.7	-10.3	-10.1
KLVFF	-13.2	-13.0	-12.9	-13.0	PGKLVYA	-10.6	-9.8	-10.0	-10.1
KVVFFA	-13.1	-13.0	-12.7	-12.9	GQTYVLPG	-9.0	-11.0	-10.0	-10.0
VTNSGGAV	-13.6	-12.7	-12.4	-12.9	VTNVPGAVV	-9.4	-9.7	-10.4	-9.8
VTNVPGAVV	-12.4	-12.8	-13.2	-12.8	VTNSGGAV	-8.9	-10.3	-9.7	-9.6
GQTYVLPG	-13.2	-12.3	-12.9	-12.8	GAVVPGVTAV	-9.2	-9.7	-9.5	-9.5
AVVPGVTAV	-12.8	-12.1	-12.8	-12.6	RGGAVVTGR	-8.8	-10.3	-9.2	-9.4
GGAVVTGR	-12.5	-12.3	-12.3	-12.4	AVVPGVTAV	-9.7	-8.5	-10.1	-9.4
KISVRV	-11.9	-12.1	-12.3	-12.1	LPFFN	-9.6	-9.1	-9.5	-9.4
VVPGVTAV	-12.5	-11.5	-12.3	-12.1	RGAVVTGR	-8.7	-9.8	-9.7	-9.4
IGLMVG	-11.5	-11.4	-11.7	-11.5	IGLMVG	-9.2	-9.6	-9.4	-9.4
AVVPGVTA	-11.5	-12.0	-11.0	-11.5	KISVRV	-9.2	-9.0	-9.0	-9.1
LPYFD	-11.5	-11.3	-11.5	-11.4	VVPGVTAV	-9.2	-8.3	-8.6	-8.7
LPFFN	-11.2	-11.4	-11.1	-11.2	AVVPGVTA	-10.1	-7.5	-8.0	-8.5
VTNPGGAV	-11.2	-11.4	-11.1	-11.2	VTNPGGAV	-8.7	-8.3	-8.4	-8.5
LPFFD	-11.4	-10.8	-11.3	-11.2	GGAVVTGR	-8.7	-8.0	-8.6	-8.4
AVVPGVT	-11.2	-11.4	-10.3	-11.0	PGVTAV	-8.2	-8.0	-8.6	-8.3
VPGVTAV	-10.7	-10.8	-10.5	-10.7	VPGVTAV	-8.1	-8.4	-8.1	-8.2
PGVTAV	-10.5	-10.3	-10.5	-10.4	GVVIA	-7.7	-7.9	-8.0	-7.9
GVVIA	-9.5	-9.2	-9.3	-9.3	AVVPGVT	-7.0	-8.6	-7.7	-7.8

Table S2. Binding energy scores of β-sheet breaker peptides obtained from molecular docking using AutoDock CrankPep (ADCP) with a large grid box size of 50 × 50 × 50 Å.

2MXU					**2N0A**				
Sequence	**ADCP-Trial1**	**ADCP-Trial2**	**ADCP-Trial3**	**ADCP-Avg**	**Sequence**	**ADCP-Trial1**	**ADCP-Trial2**	**ADCP-Trial3**	**ADCP-Avg**
KKLVFFARRRRA	-30.0	-25.8	-26.8	-27.5	KKLVFFARRRRA	-25.9	-26.3	-26.9	-26.4
RPRTRLHTHRNR	-24.5	-24.0	-24.3	-24.3	RPRTRLHTHRNR	-23.8	-24.3	-23.3	-23.8
DEEIERQLKALG	-23.9	-23.1	-24.1	-23.7	RPITRLRTHQNR	-22.9	-23.6	-24.3	-23.6
RPITRLRTHQNR	-22.9	-22.4	-24.5	-23.3	DEEIERQLKALG	-21.9	-23.4	-22.4	-22.6
HKQLPFFEED	-20.5	-20.8	-20.5	-20.6	HKQLPFYEED	-22.7	-21.4	-22.4	-22.2
HKQLPFYEED	-20.4	-21.1	-20.2	-20.6	HKQLPFFEED	-21.2	-20.9	-21.3	-21.1
RYYAAFFARR	-20.3	-19.8	-21.3	-20.5	RYYAAFFARR	-20.1	-22.1	-20.3	-20.8
RGKLVFFGR	-20.9	-20.1	-19.8	-20.3	RGKLVFFGR	-19.5	-19.7	-20.1	-19.8

RTKSGVYLVG	-19.8	-19.1	-19.2	-19.4	RTKSGVYLVG	-19.6	-19.4	-19.2	-19.4
KDGIVNGVKA	-18.7	-18.9	-19.1	-18.9	KDGIVNGVKA	-19.6	-19.0	-19.4	-19.3
KKLVFFA	-18.6	-18.8	-17.4	-18.3	KKLVFFA	-18.3	-18.0	-18.7	-18.3
GVLYVGSKTR	-16.8	-18.2	-19.1	-18.0	GVLYVGSKTR	-17.7	-17.0	-17.1	-17.3
QSHYRHISPAQV	-17.0	-18.3	-17.0	-17.4	KISVRV	-16.8	-16.6	-16.9	-16.8
QKLVTTAE	-16.7	-16.4	-15.8	-16.3	KEGPVHGVATV	-16.3	-16.7	-16.9	-16.6
KEGPVHGVATV	-15.8	-15.2	-17.8	-16.3	RGGAVVTGR	-16.5	-16.1	-17.0	-16.5
RDLPFYPVPID	-15.1	-16.8	-16.9	-16.3	RDLPFYPVPID	-16.2	-16.7	-16.6	-16.5
RGAVVTGR	-17.7	-16.1	-15.0	-16.3	QSHYRHISPAQV	-16.7	-15.8	-16.7	-16.4
AVVTGGTAVAQ	-18.0	-14.6	-16.1	-16.2	QKLVTTAE	-16.4	-15.9	-15.5	-15.9
RGGAVVTGR	-17.0	-15.8	-15.5	-16.1	DGIVAGVKA	-15.1	-16.2	-15.9	-15.7
RDLPFFPVPID	-16.6	-15.5	-15.0	-15.7	AVVTGETAVAQ	-15.8	-15.9	-14.1	-15.3
KISVRV	-15.4	-15.4	-15.6	-15.5	RDLPFFPVPID	-15.3	-14.7	-15.6	-15.2
QVTNSGGAVVT	-14.9	-16.4	-14.9	-15.4	GAVVKGVTAV	-14.8	-14.9	-15.8	-15.2
QKLVFF	-14.8	-15.8	-15.4	-15.3	RGAVVTGR	-15.5	-14.8	-15.0	-15.1
GAVVKGVTAV	-15.3	-15.6	-14.9	-15.3	KFVFFA	-14.6	-14.8	-15.6	-15.0
AVVTGETAVAQ	-14.2	-15.0	-16.3	-15.2	KIVFFA	-15.0	-15.4	-14.6	-15.0
VTGVPAVAQK	-14.8	-15.4	-15.2	-15.1	PGKLVYA	-14.7	-15.5	-14.6	-14.9
DGIVAGVKA	-15.3	-14.8	-15.1	-15.1	KVVFFA	-14.5	-15.9	-14.2	-14.9
PGKLVYA	-14.3	-14.5	-16.4	-15.1	QKLVFF	-14.4	-14.8	-15.2	-14.8
KFVFFA	-14.7	-14.5	-15.1	-14.8	VTGVPAVAQK	-15.1	-14.5	-14.0	-14.5
KVVFFA	-14.5	-15.1	-14.2	-14.6	QVTNSGGAVVT	-15.1	-13.8	-14.6	-14.5
KLVFFA	-14.4	-14.2	-14.2	-14.3	KLVFFA	-15.3	-13.8	-14.3	-14.5
LPFFD	-14.5	-13.7	-14.6	-14.3	LPYFD	-14.8	-15.0	-13.5	-14.4
KIVFFA	-14.8	-14.0	-13.8	-14.2	KLVFF	-14.4	-14.5	-14.0	-14.3
VTNVPGAVV	-15.1	-12.6	-14.9	-14.2	LPFFD	-13.9	-14.3	-13.9	-14.0
KLVFF	-14.0	-14.0	-13.9	-14.0	AVVTGGTAVAQ	-13.5	-13.6	-13.5	-13.5
LPYFD	-13.8	-13.9	-13.6	-13.8	GQTYVLPG	-13.5	-12.8	-13.0	-13.1
AVVPGVTAV	-12.5	-12.2	-14.5	-13.1	VTNPGGAV	-13.7	-12.7	-11.9	-12.8
GQTYVLPG	-12.5	-13.4	-13.3	-13.1	GGAVVTGR	-12.6	-12.4	-12.6	-12.5
VTNSGGAV	-13.7	-12.8	-12.4	-13.0	GAVVPGVTAV	-12.5	-12.3	-12.6	-12.5
GAVVPGVTAV	-13.7	-13.3	-11.8	-12.9	AVVPGVTAV	-13.1	-12.6	-11.3	-12.3
IGLMVG	-12.9	-12.8	-12.9	-12.9	IGLMVG	-11.8	-12.3	-12.8	-12.3
GGAVVTGR	-13.3	-12.4	-12.5	-12.7	LPFFN	-12.4	-12.6	-11.8	-12.3
LPFFN	-12.0	-12.4	-12.2	-12.2	VTNSGGAV	-11.9	-11.9	-12.2	-12.0
VVPGVTAV	-12.2	-11.9	-12.1	-12.1	VTNVPGAVV	-11.9	-11.8	-11.3	-11.7
AVVPGVT	-11.0	-12.3	-12.7	-12.0	VVPGVTAV	-11.7	-10.9	-12.0	-11.5
VTNPGGAV	-11.7	-11.8	-12.0	-11.8	AVVPGVTA	-11.4	-11.6	-10.7	-11.2
AVVPGVTA	-11.7	-11.4	-11.6	-11.6	VPGVTAV	-10.8	-11.1	-11.1	-11.0
VPGVTAV	-12.0	-10.8	-11.6	-11.5	AVVPGVT	-10.6	-11.0	-10.5	-10.7
PGVTAV	-11.6	-11.0	-11.2	-11.3	PGVTAV	-10.3	-10.8	-10.0	-10.4
GVVIA	-10.0	-10.0	-10.3	-10.1	GVVIA	-9.8	-9.5	-9.7	-9.7

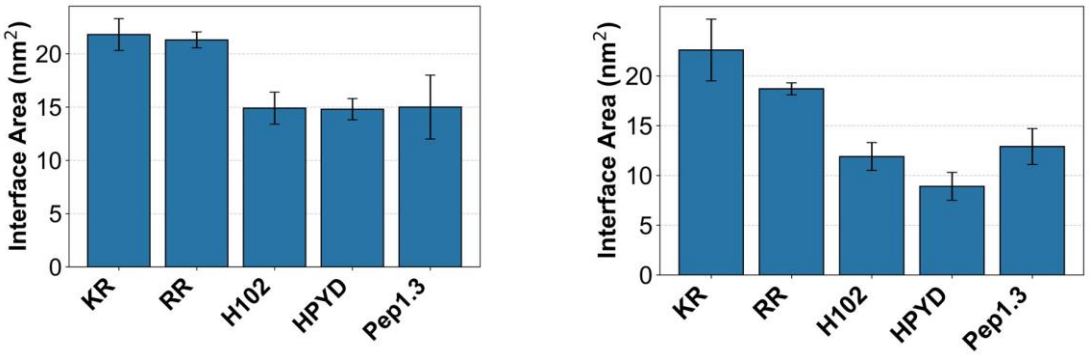

Figure S1. The average protein-peptide interface area values for 2MXU (left) and 2N0A (right) with standard deviations calculated from three independent runs.

Table S3. HPEPDOCK blind docking results of selected five peptides for stability tests.

	2MXU		2N0A	
Peptide Name	**Sequence**	**Binding Score**	**Sequence**	**Binding Score**
RR	RYYAAFFARR	-299.7	RYYAAFFARR	-232.9
KR	KKLVFFARRRRA	-265.4	KKLVFFARRRRA	-216.3
H102	HKQLPFFEED	-235.0	HKQLPFFEED	-165.6
HPYD	HKQLPFYEED	-209.8	HKQLPFYEED	-174.9
Pep1.3	DEEIERQLKALG	-186.7	DEEIERQLKALG	-135.2

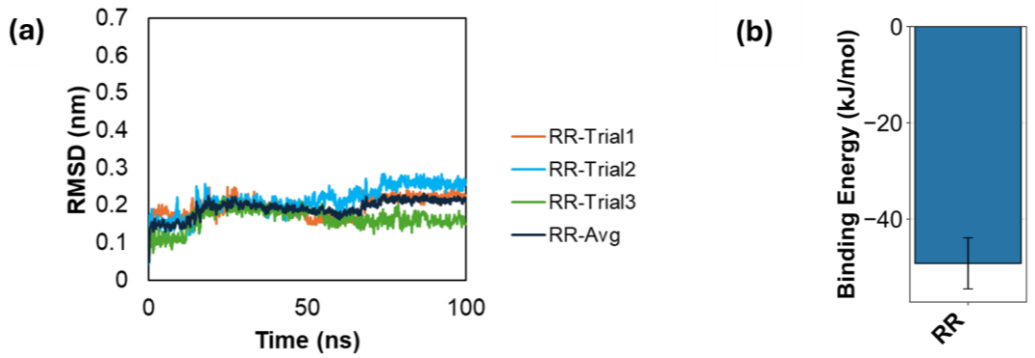

Figure S2. RMSD plots for RR peptide in complex with 2MXU **(a)**, where initial configuration was obtained from ADCP docking calculations. The average binding free energy of RR calculated using MMPBSA based on three independent simulation runs **(b)**.

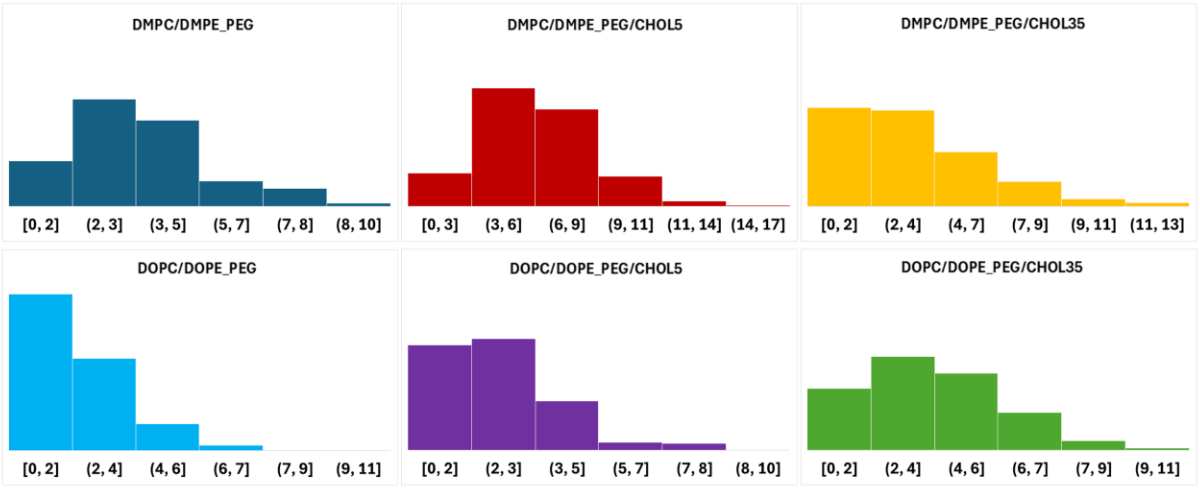

Figure S3. The distribution of hydrogen bonds between the RR peptide and PEG chains in different membrane models during the last 100 ns of the simulations.

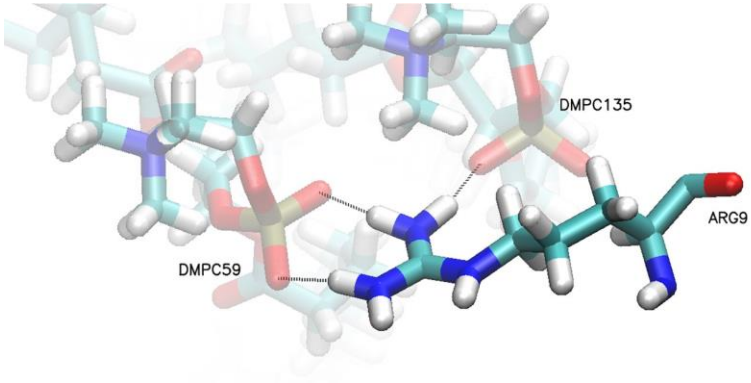

Figure S4. Multidentate hydrogen-bonding behavior of arginine (Arg) residues showing interactions between the NH groups of Arg side chains and the oxygen atoms of phosphate groups in DMPC lipids. The snapshot was taken from the DMPC/DMPE_PEG system at t = 400 ns.

Table S4. Time-averaged center-of-mass (COM) distance of RR peptides from the membrane COM during the last 100 ns of the trajectories.

Lipid Composition	Distance (nm)
DMPC/DMPE_PEG	2.62 ± 0.17
DMPC/DMPE_PEG/CHOL5	3.07 ± 0.15
DMPC/DMPE_PEG/CHOL35	3.07 ± 0.10
DOPC/DOPE_PEG	2.36 ± 0.14
DOPC/DOPE_PEG/CHOL5	2.43 ± 0.14
DOPC/DOPE_PEG/CHOL35	2.82 ± 0.16

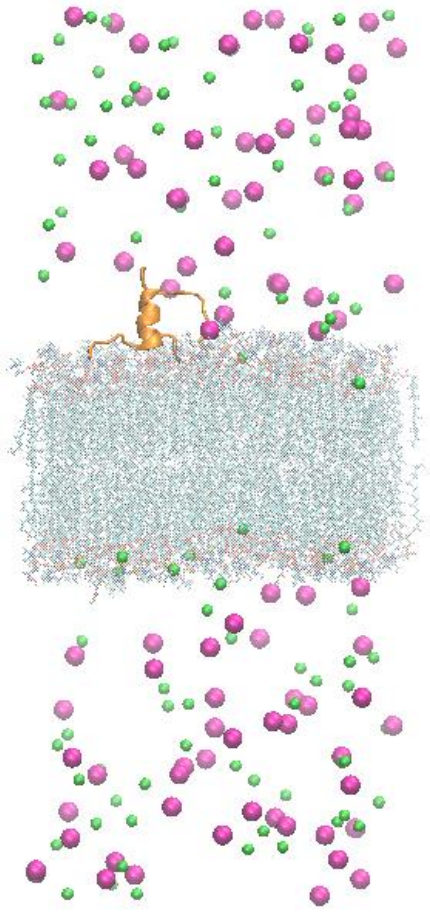

Figure S5. Spatial distribution of sodium (green) and chloride (pink) ions in the DMPC/DMPE_PEG/CHOL35 membrane system. Peptides are shown in orange cartoon representation.

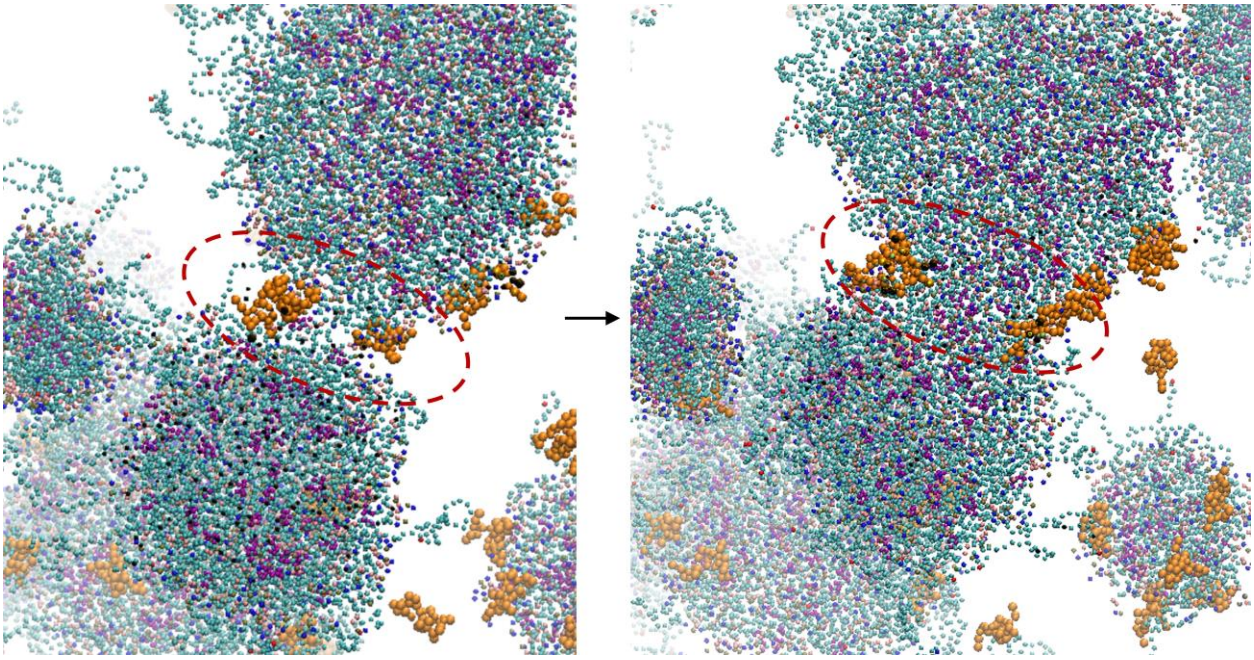

Figure S6. A self-assembly snapshot illustrating the bridging potential of peptides in the DLPC/DLPE_PEG/CHOL15 system.

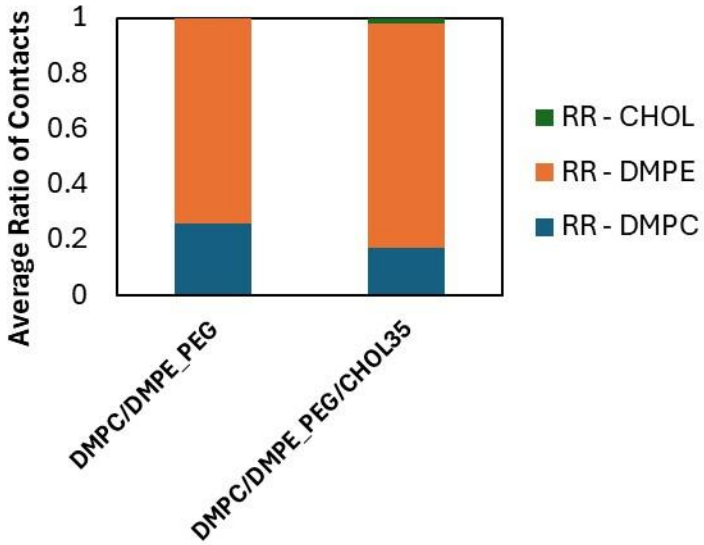

Figure S7. Average normalized contact ratios of RR peptides with lipid molecules within 0.4 nm distance in DMPC/DMPE_PEG and DMPC/DMPE_PEG/CHOL35 atomistic membrane systems.

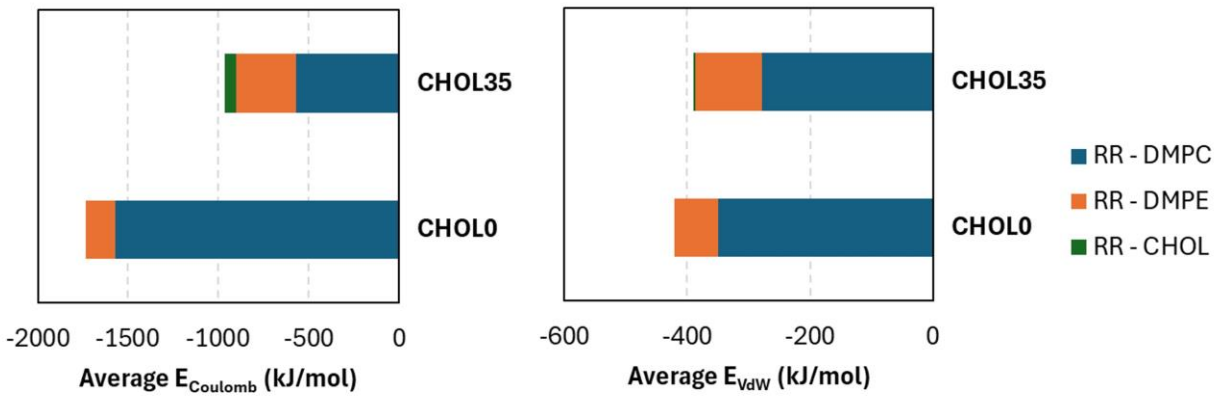

Figure S8. Average short-range non-bonded interaction energies between RR peptides and lipid components in DMPC/DMPE_PEG and DMPC/DMPE_PEG/CHOL35 atomistic membrane systems.