Supplementary data for

Why the Synthetic Virus-like Nanoparticles can Achieve Higher Cellular Uptake Efficiency?

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I. Simulation Procedure and Interaction Parameters

Based on the previous simulation studies,[1,2] we set the interaction parameter α_{ij}, and the detailed values are shown in Table S1. Previous studies have demonstrated that the interaction parameters are convincing. In this table, W stands for water bead, H stands for hydrophilic bead of lipid, T stands for hydrophobic bead of lipid, P stands for bead of nanoparticle.

Table S1 Interaction parameters of bead–bead pairs α_{ij}

α_{ij}	W	H	T	P
W	25	25	100	25
H	25	25	100	25
T	100	100	25	100
P	25	25	100	25

II. Verification of forced translocation approach

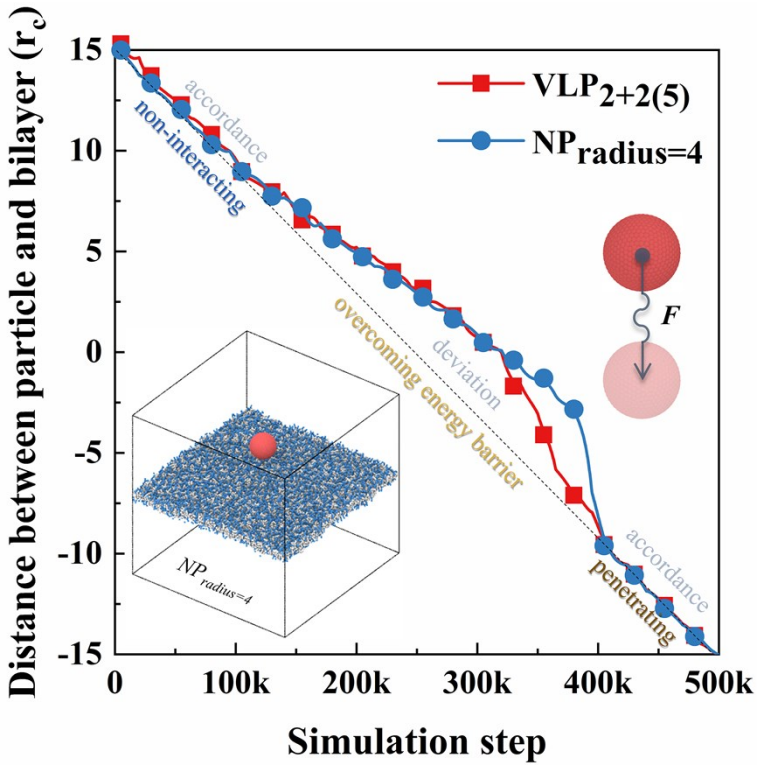

Fig. S1 Evolution of particle position as a function of simulation step.

In this study, by adopting forced translocation approach, the complete internalization pathway of particle is investigated. This approach also allows us to properly analyze the critical penetration force of NPs across lipid bilayer membrane. Here, the $VLP_{2+2(5)}$ and $NP_{radius=4}$ systems are chosen as example to illustrate the forced translocation process. As shown in Fig. S1, particle starts to approach bilayer from $15r_c$ above bilayer. At the beginning, the motion of particle is accordance with the linear equation of spring force, indicating the interactions between particle and bilayer is weak. With the decrease of distance between particle and bilayer, the motion of

particle is deviated from linear equation. After the force on the imaginary spring builds up until it is sufficient to cross bilayer, the force on particle abruptly unloaded, and the motion of particle back to accordance with the linear equation again. The forced translocation process can be divided into three parts, as discussed in manuscript. The evolution of particle position as a function of simulation step also demonstrate that the $VLP_{2+2(5)}$ has higher transmembrane capability than $NP_{radius=4}$.

III. Building of Coarse-grained Model of Nanoparticle

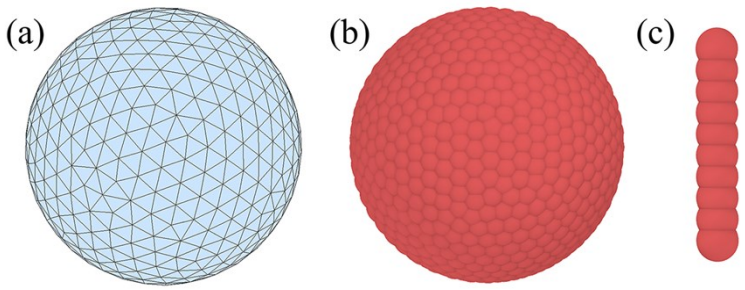

Fig. S2 (a) The triangular packing of surface beads. (b) The coarse-grained model of spherical core. (c) The coarse-grained model of spike.

In order to clarify the effect of spike number and spike length on the interactions between VLP and bilayer, 50 coarse-grained VLP models with different spike length and spike number are built. The triangular packing was adopted to build the smooth spherical inner core of VLP, as shown in Fig. S2, and we have verified that the triangular packing of surface beads is sufficient to prevent solvent beads from penetrating into the inner core. To obtain VLP models with same influencing radius, the spherical cores with different radius were built. Meanwhile, beads were linear connected with interval of $0.2r_c$ to model the spikes of VLPs, and these spikes were evenly grafted onto the surface of spherical inner core base on the mass center. The beads in the particles were restricted to move together as an intact rigid body. In addition, it should be noted that the modelling of VLPs in this study is based on the silica VLPs in experiments, not another type of VLPs which resembles viruses (do not contain any genetic material so that they are not infectious),[3] because the length[4] and distribution[5] of spikes of silicon-based VLPs can be delicately tailored.

IV. Structure of Lipid Bilayer in Equilibrium State

To obtain the rational structure of bilayer, the lipid bilayer system is first simulated. The bilayer under zero tension in equilibrium is flat and complete. The density profiles of hydrophobic interior and hydrophilic corona in equilibrium demonstrate that the interior and exterior force of the lipid bilayer are balanced, as shown in Fig. S3.

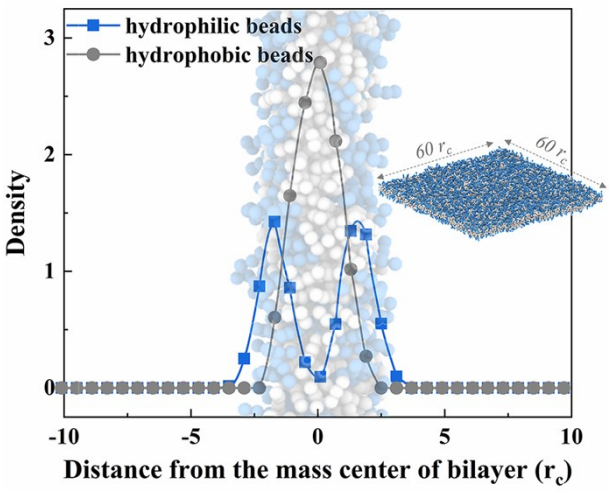

Fig. S3 Density profile of hydrophilic/hydrophobic beads of lipid bilayer in equilibrium state.

Reference

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