Engineering Pickering emulsion for Vaccine Delivery System

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Why we need vaccine delivery systems?

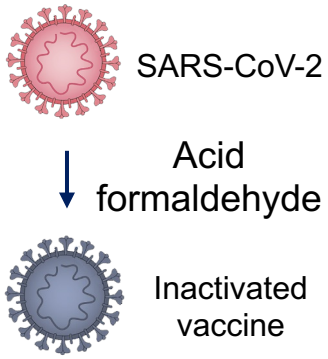
Antigen

- Traditional：Attenuated

  Inactivated（Sinovac）

  - Safety concern:

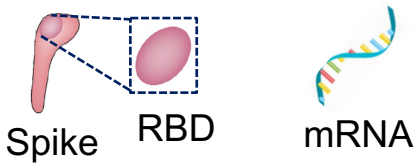
    Large-scale production of viruses



- Subunit：Recombinant proteins

  mRNA、DNA

  - Simpler structure
  - Low immunogenicity



Adjuvant：Specific danger signal

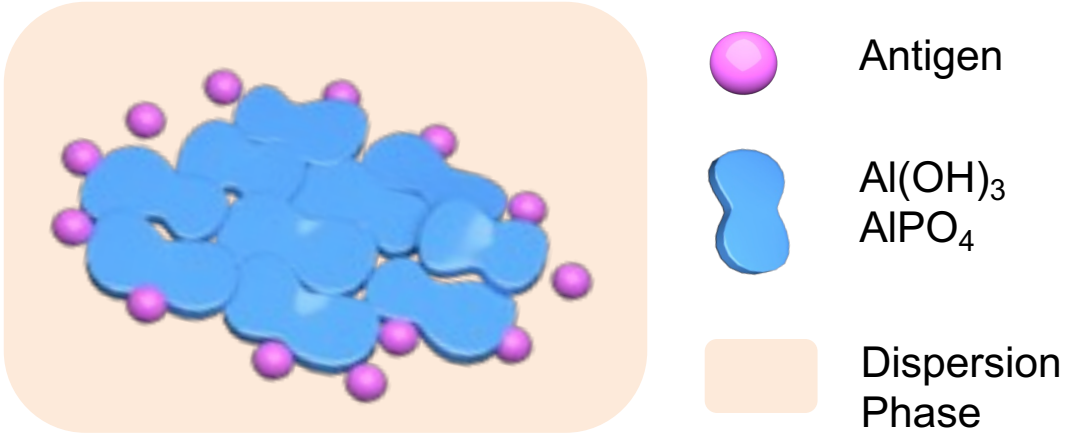
Commercial adjuvant	Target	Challenge
MPLA	TLR4	Hydrophobic
CpG	TLR9	Degradation
QS-21 (saponin)	Capase-1	Toxicity

- Hydrophobicity: MPLA, Imidazoquinoline
- Toxicity：QS-21 (Hemolysis)

Vaccine = (Antigen + Adjuvant) @ Delivery Vehicle

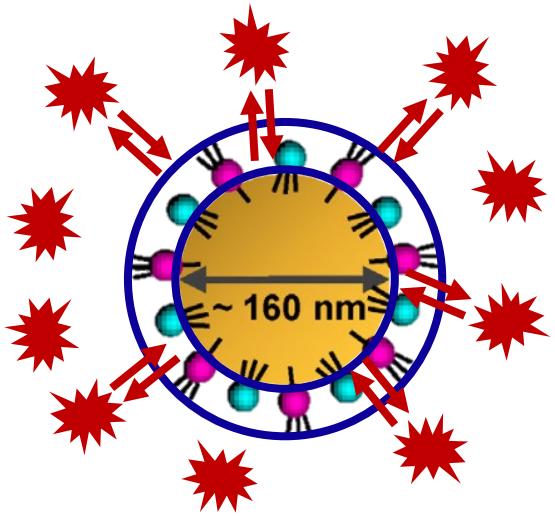
Commercial formulations: Lack of a delivery perspective

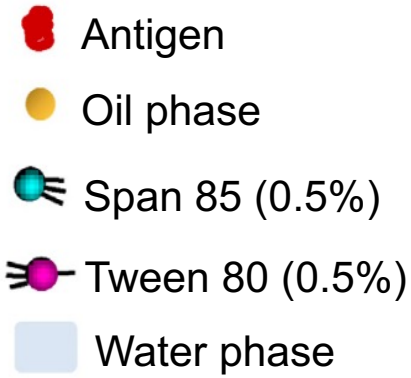
- Alum: aluminum hydrogel



Antigen depot at the injection site

- Surfactant-stabilized O/W emulsion

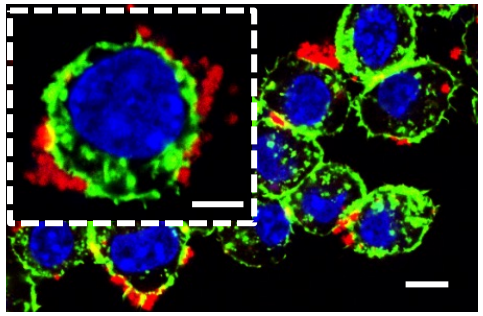




Cell recruitment at the injection site

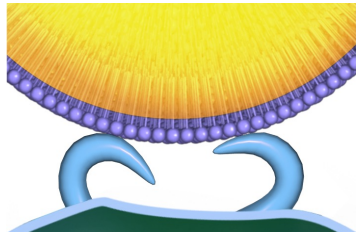
Micro-hydrogel : Large size + hydrophilicity

- Hardly entering the cells with antigens
- Limited cellular immune responses



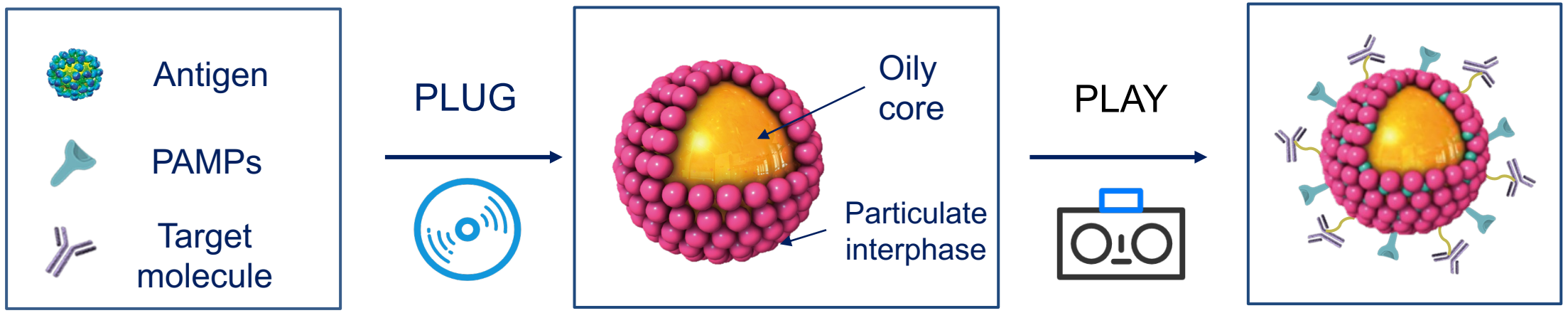
Surface Surfactant : Hydration layer

- Impeding: antigen/cellular interactions
- Low antigen adsorption
- Limited cellular uptake

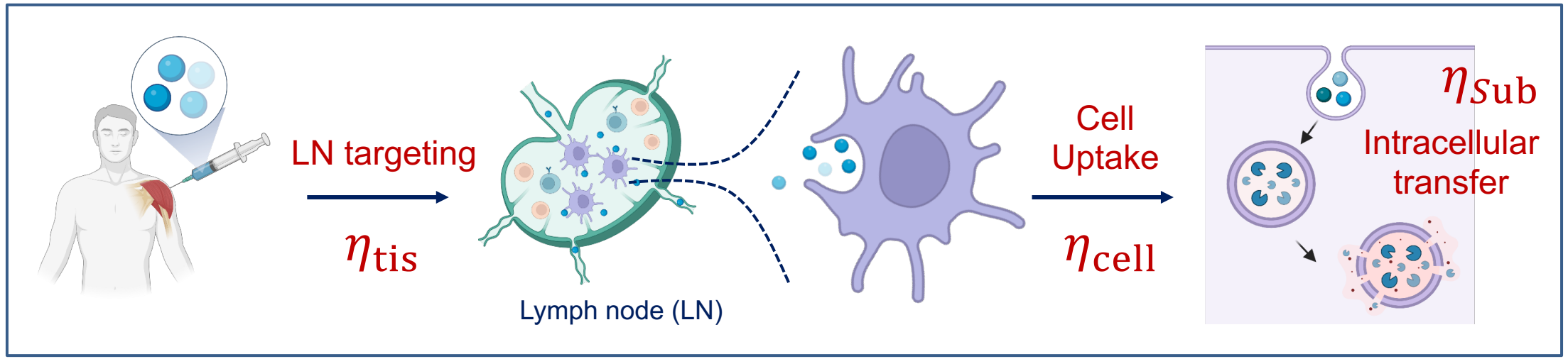


How to improve the vaccine delivery efficacy

- Assembly of vaccine components in a mild & facile way

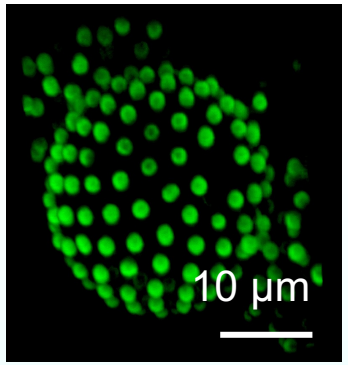


- Breakthrough the multi-scale barrier for the enhanced vaccinations



Pickering emulsion for vaccine delivery system

Pickering emulsion



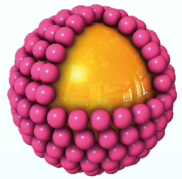
Proposed by *S. Pickering* in *1907*

Employ in cosmetics and petrochemicals

- **Higher bio-compatibility**

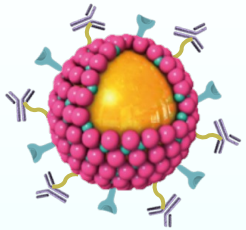
  FDA-approved materials, smaller sizes (0.3-2 μm)

- **Multi-level structure: "On-demand" assembly**

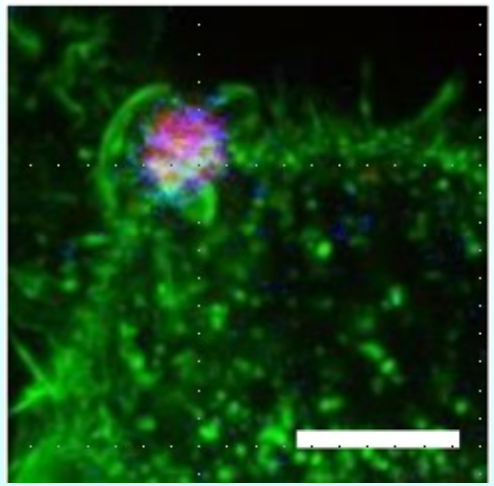


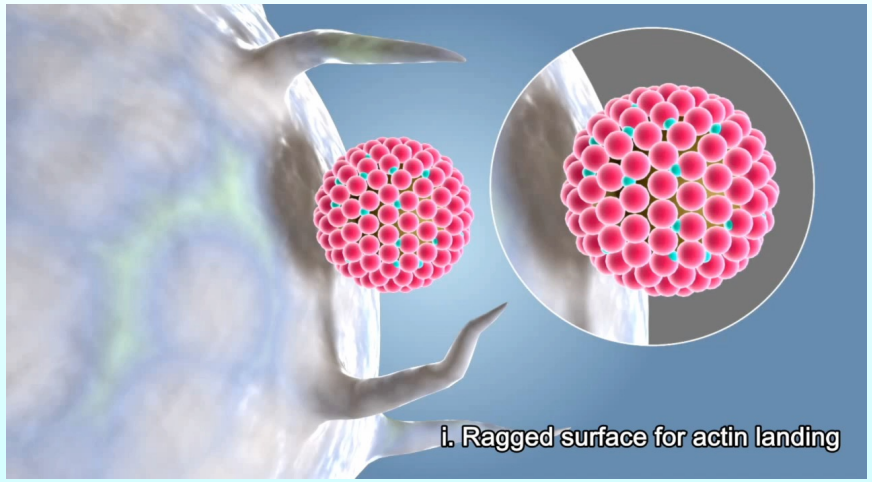
Oil core: Hydrophobic encapsulation

Interparticle gaps: Antigen adsorption



- **Increase the contact zone for higher antigen uptake**



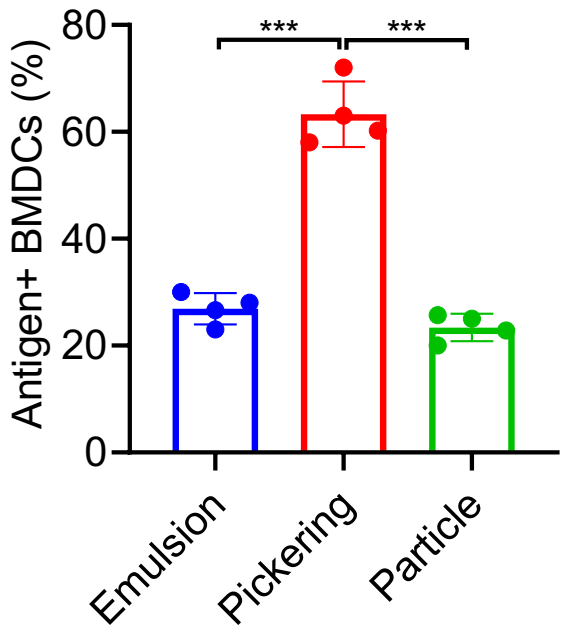


Pickering emulsion for vaccine delivery system

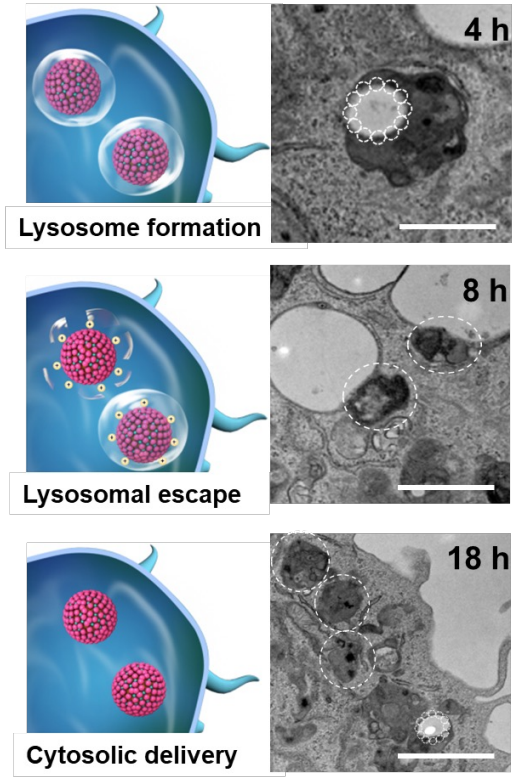
- **Soft contact: Evidently increase the cellular uptake and cross-presentation**

Boost cellular uptake

(~250% increase)

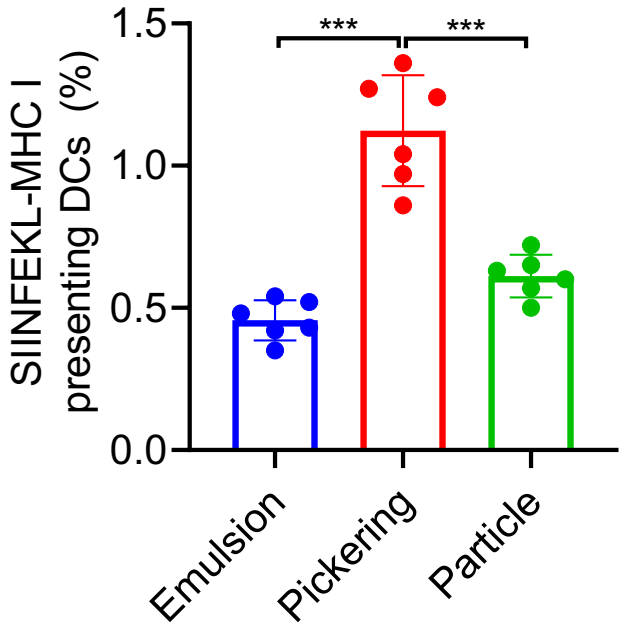


Lysosome escape



MHC I presentation

(> 2-fold increase)



Nature Materials, 2018, 17(2): 187-194

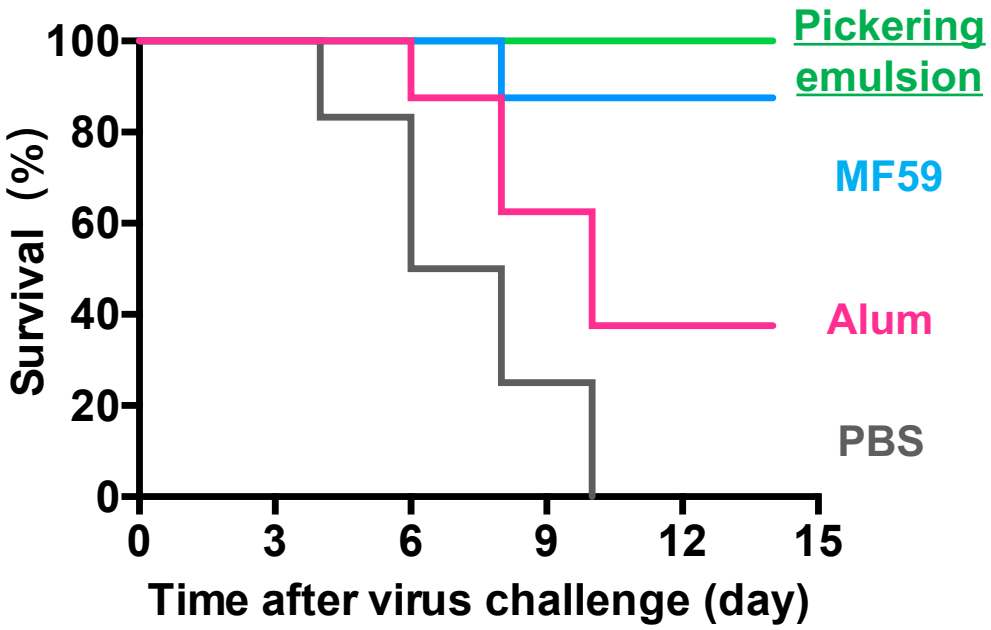
CN201410272743 (Authorized) , JP6434995 (Authorized)

Pickering emulsion for vaccine delivery system

- **Solid → Soft : Stimulating the prophylactic and therapeutic effects**

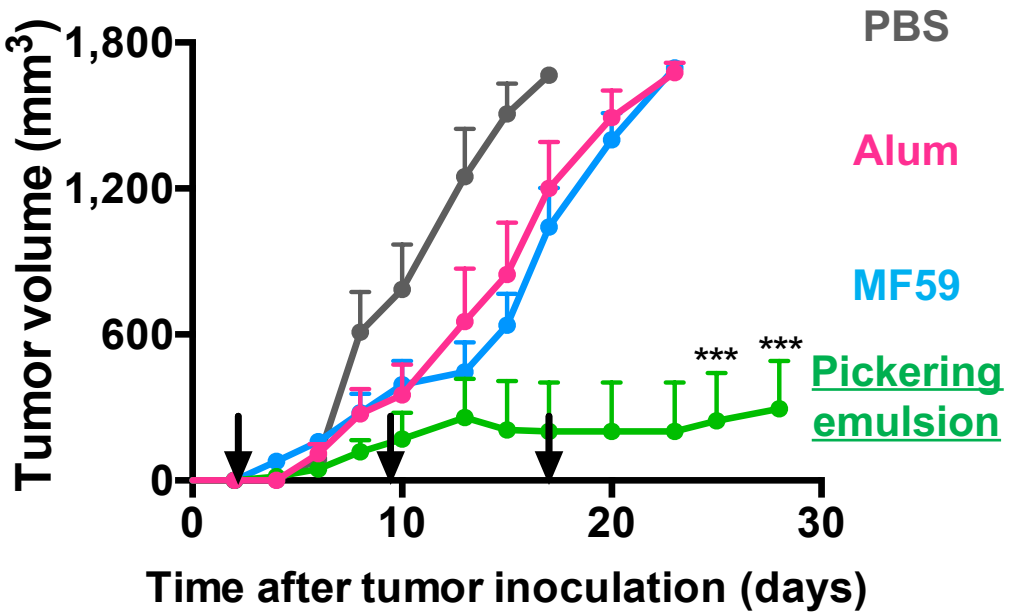
☐ H1N1 influenza vaccine:

100% survival rates



☐ MUC1-peptide vaccine:

Melanoma regression



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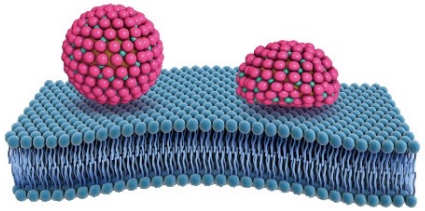
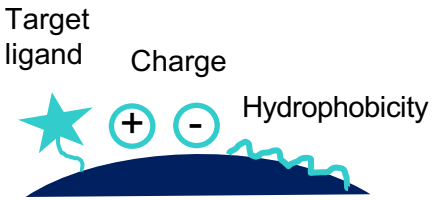
Dig deeper: Physiochemical property & bio-effects

Physiochemical property

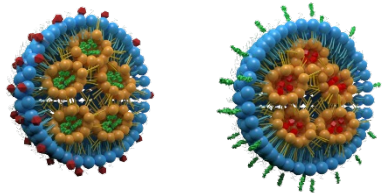
Softness



Surface Property

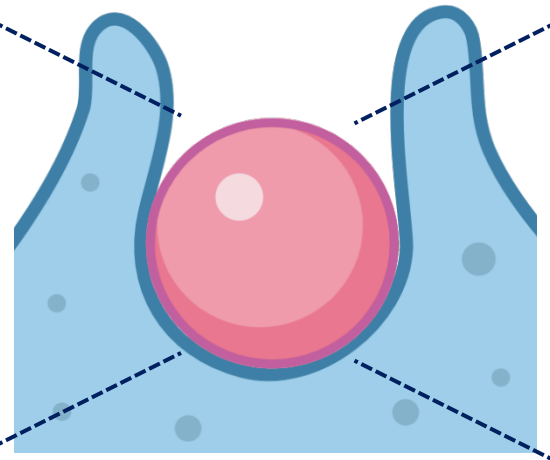


Assembly Strategy



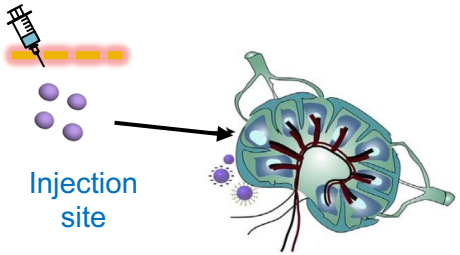
Particle/Membrane

Interfacial interaction

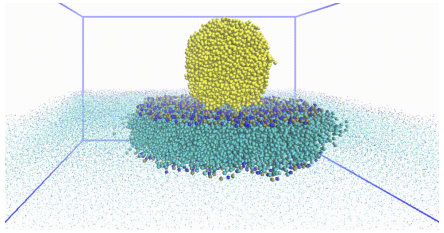


Delivery efficiency

Tissue Level



Cell uptake



Immune response

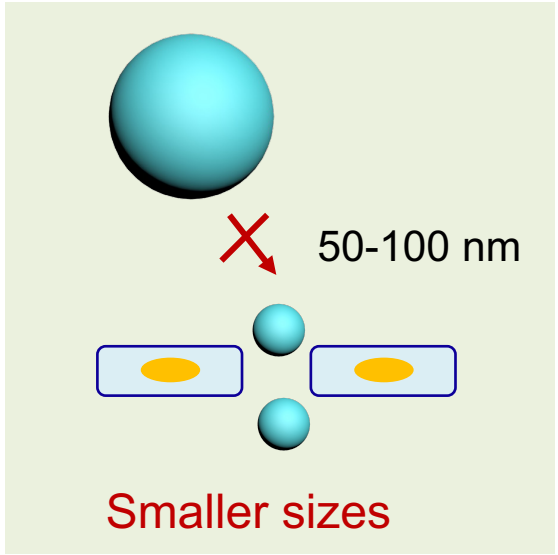
IgG

T cell

1. Softness： deformability for the enhanced bio-distribution

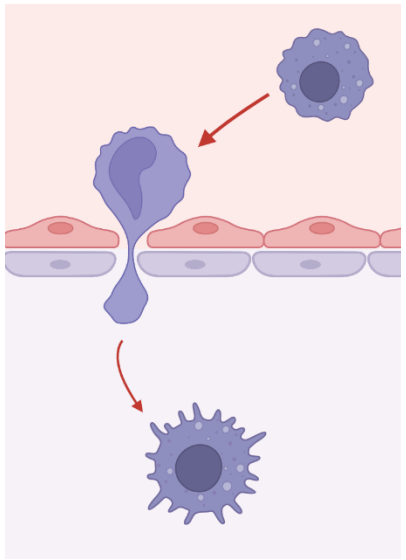
- Deform & pass through the cellular gap: Higher LN accumulation of antigens

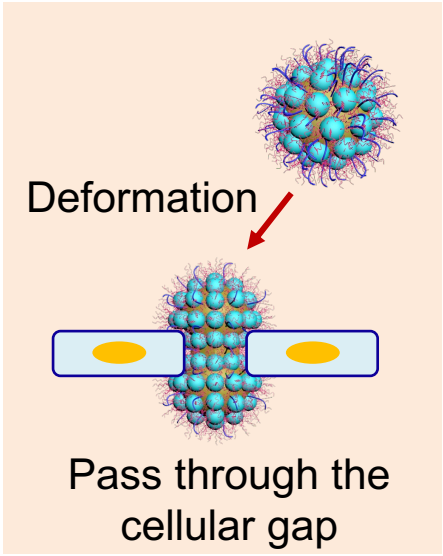
Solid particle

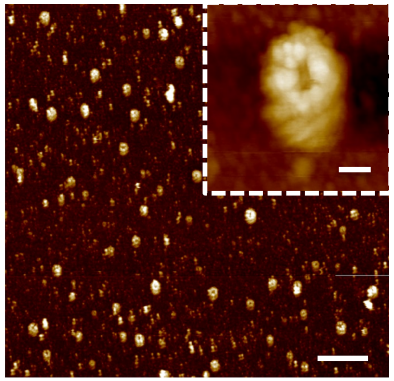


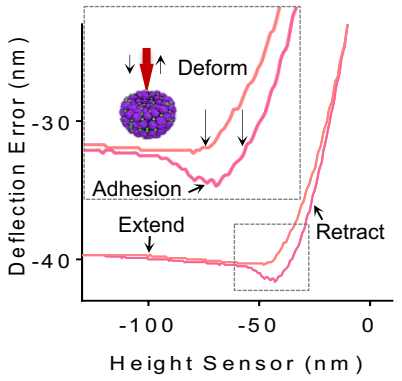
- ☐ Hard to manufacture
- ☐ Limited loading capability

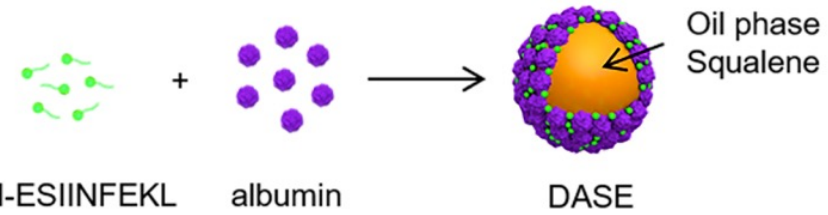
Pickering emulsion: cell-mimic deformation







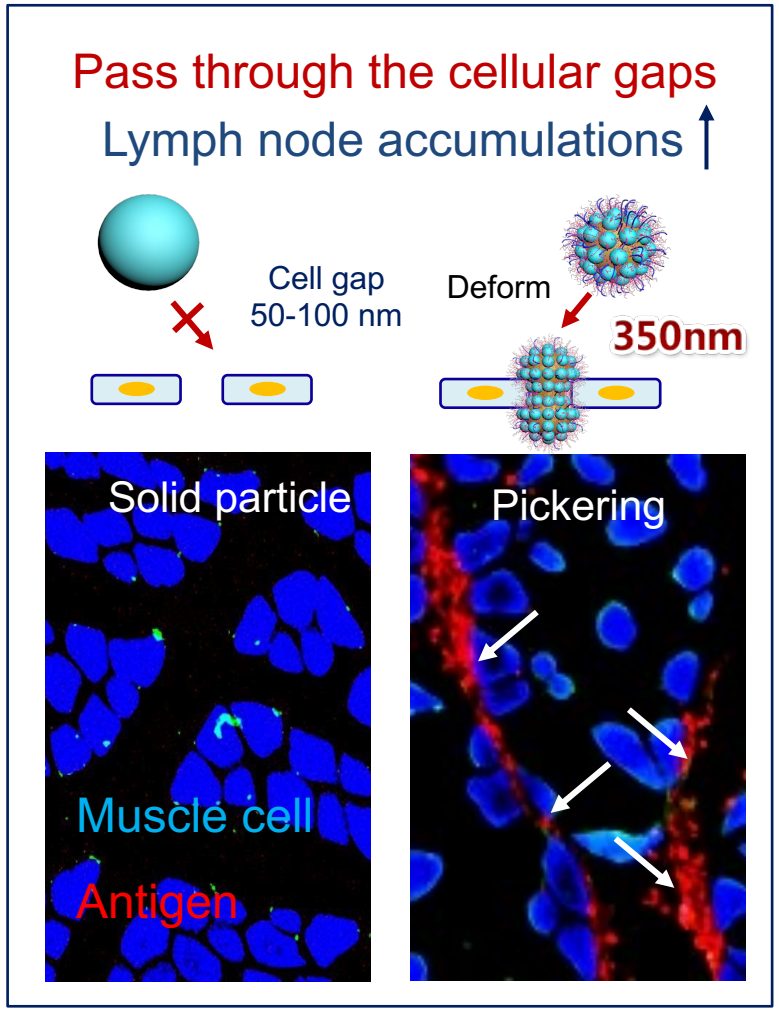


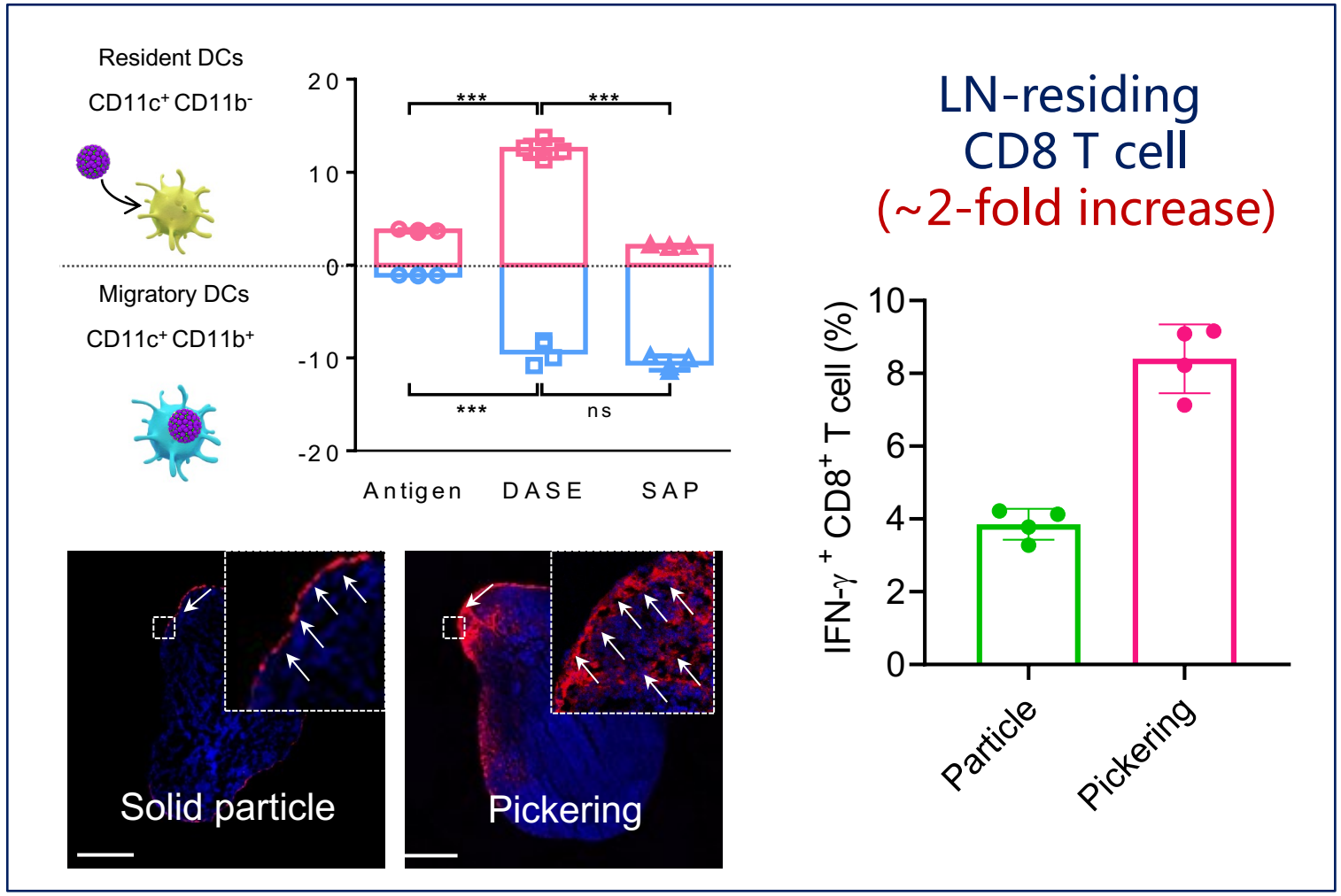


Advanced Materials, 2021, 33, 2100106；CN202110282117（Authorized）

1. Softness： deformability for the enhanced bio-distribution

- **Deform & pass through the cellular gap: Higher LN accumulation of antigens**



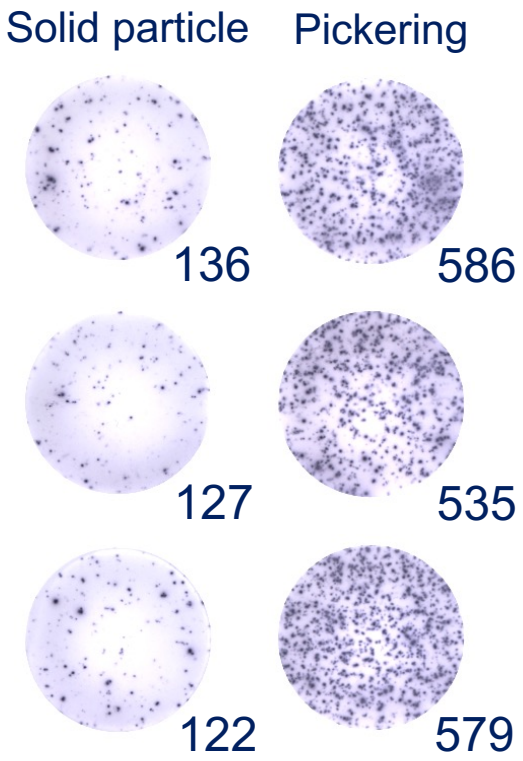


Advanced Materials, 2021, 33, 2100106； CN202110282117（Authorized）

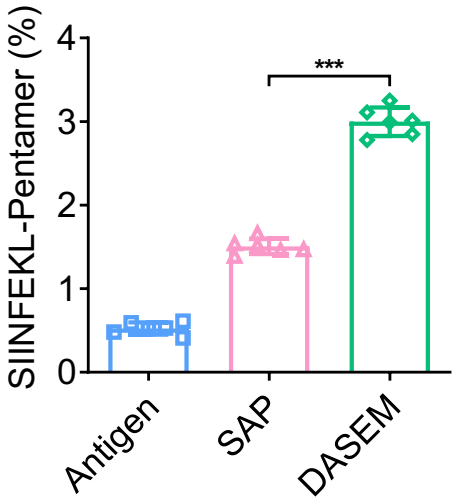
1. Softness： deformability for the enhanced bio-distribution

- **Direct LN activation for robust IFN-γ⁺ T cell immune responses**

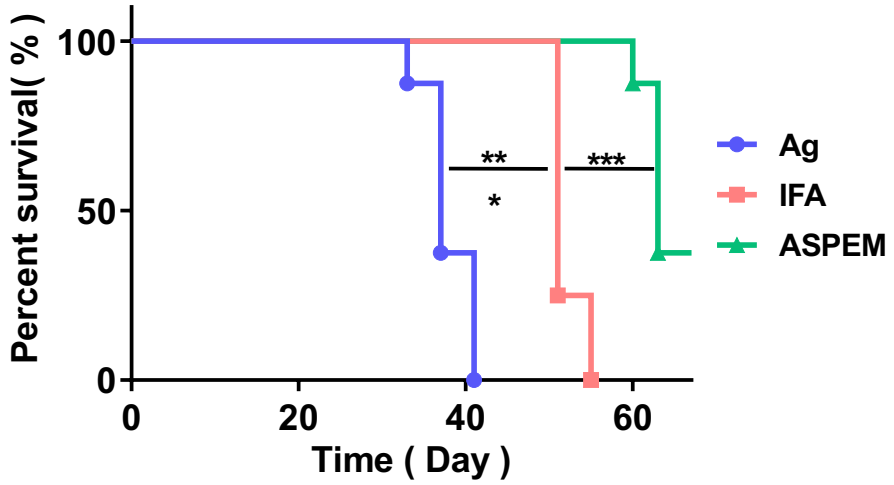
IFN-γ⁺ T cell

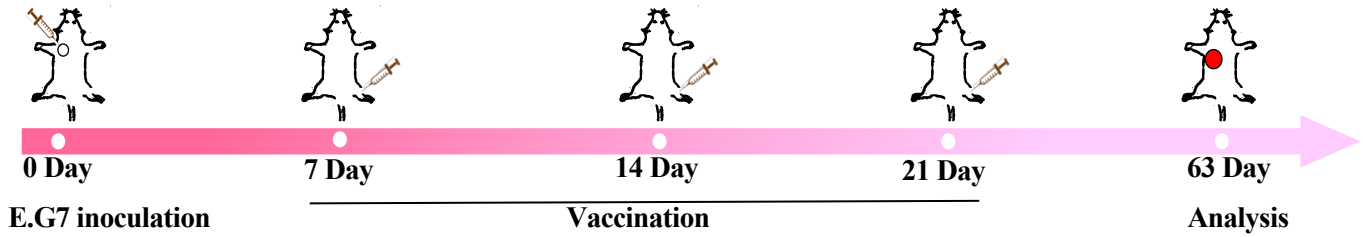


CTL responses



Increase survival rate of tumor-bearing mice



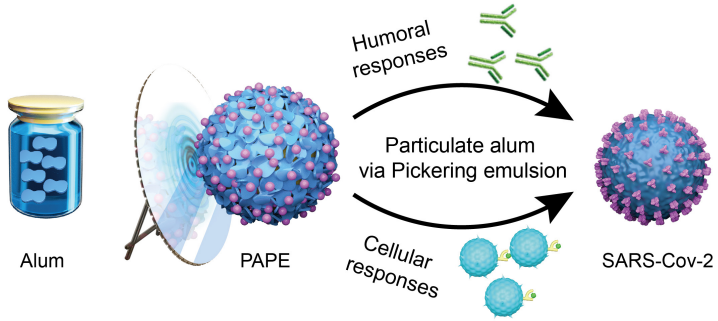


Advanced Materials, 2021, 33, 2100106；CN202110282117（Authorized）

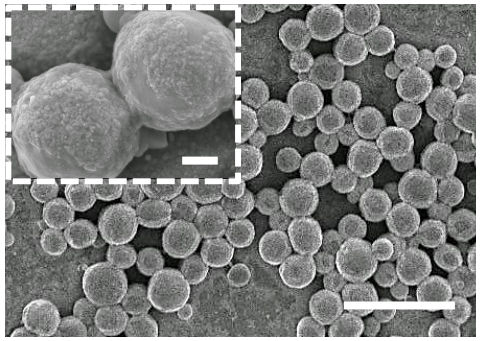
2.Hydrophobicity: Boost cellular uptake

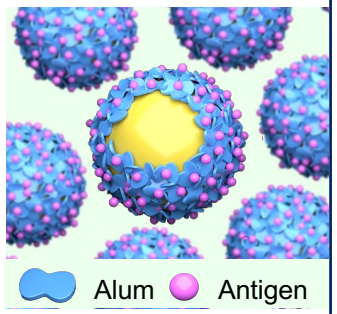
- **Interparticle gap: Membrane affinity ↑ Antigen uptake ↑**

Alum-Pickering emulsion Packing alum on the interphase

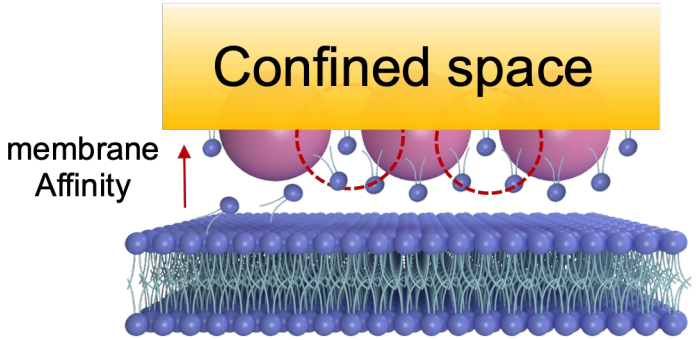


Clinically abundant alum
+ squalene (oil phase for MF59)

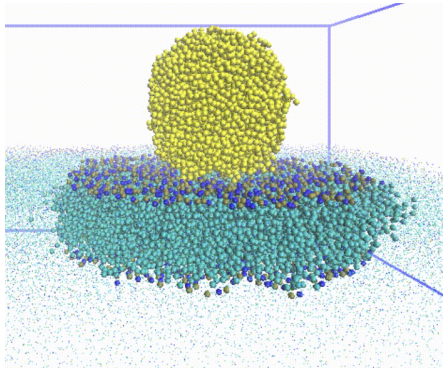


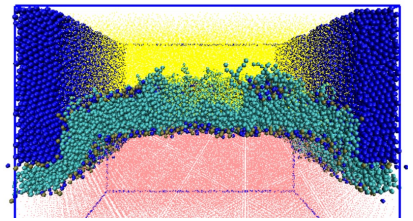


Adsorb membrane lipid Facilitate trans-membrane delivery



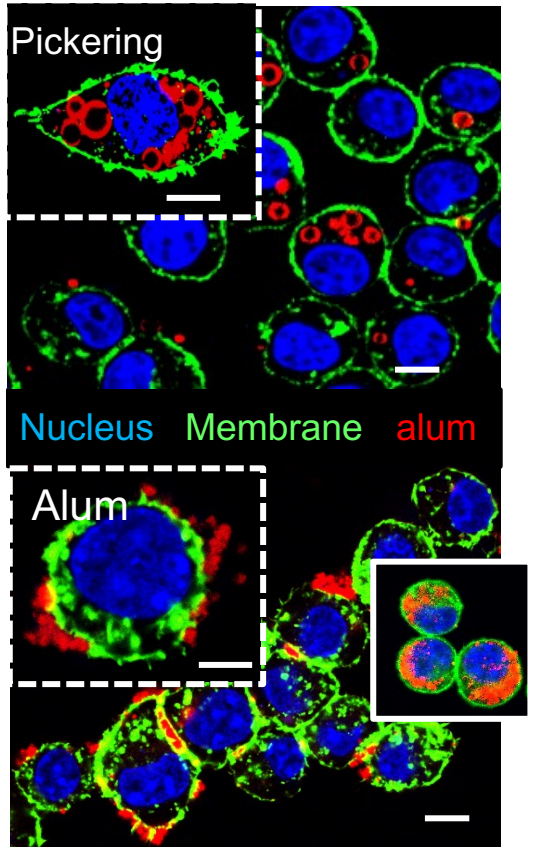
Hydrophobicity + surface tension





Lipid tail flipping

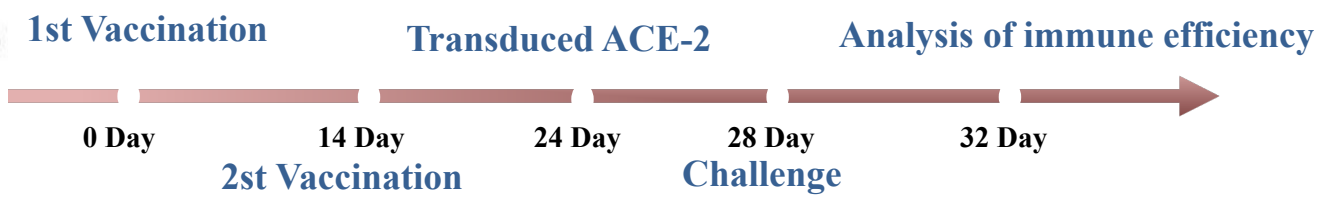
Potent cellular uptake



Alum hardly enter the cell

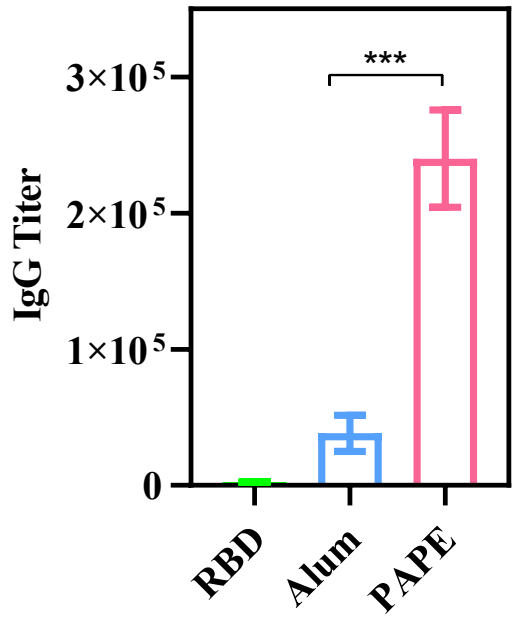
Advanced Materials, 2020, 32, 2004210（Cover）

2.Hydrophobicity: Boost cellular uptake



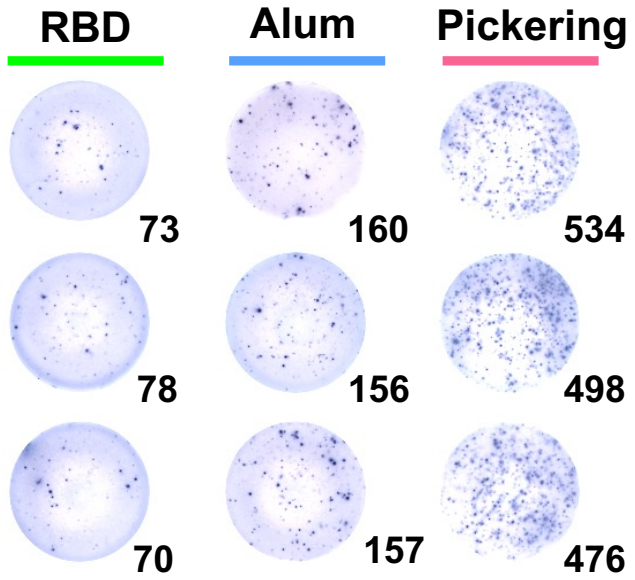
- RBD-specific IgG

  (6-fold increase)



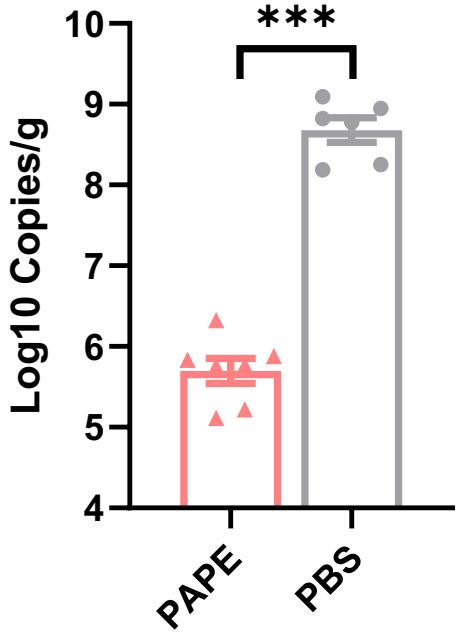
- Cellular immune response

  IFN-r+ cells (~300% increase)



- Protection against

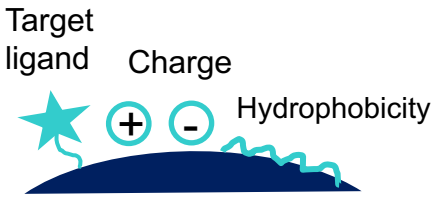
  SARS-CoV-2 challenge



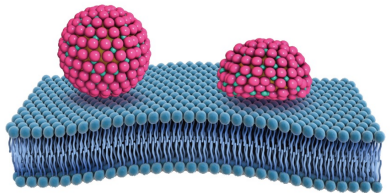
Advanced Materials, 2020, 32, 2004210（Cover）

Take-home message: Delivery matters

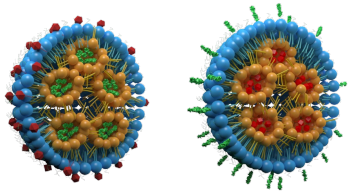
Surface properties

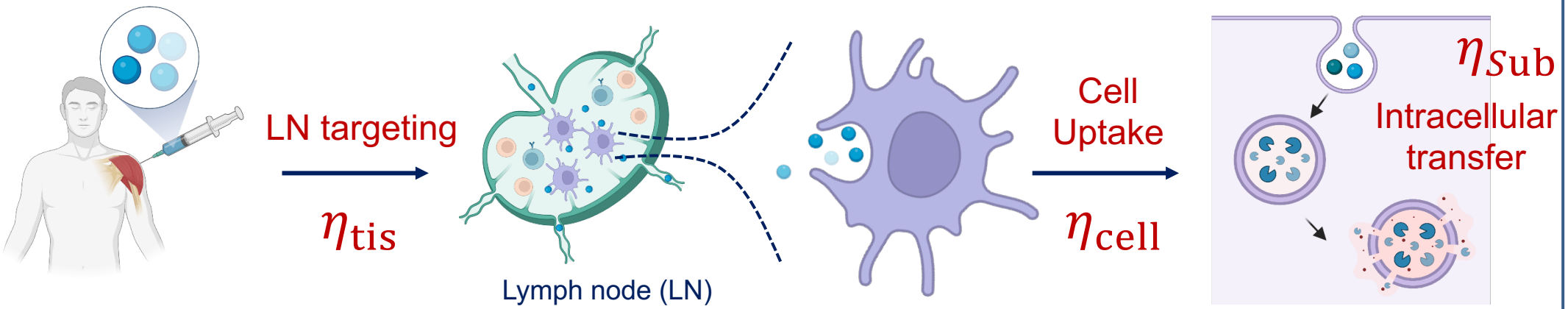


Softness



Loading strategy





Channeling the delivery process $\eta_{del} = \eta_{tis} \times \eta_{reg} \times \eta_{cell} \times \eta_{sub}$

Ideal Vaccine = (Antigen + Adjuvant) @ Delivery Vehicle

Thanks

Prof. Guanghui Ma

Prof. Wei Ge

Prof. Lianpan Dai

Prof. Xiangxi Wang

NSFC

SINOVAC 科兴

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