An Inhalable Hybrid Biomimetic Nanoplatform for Acute Lung Injury Treatment

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THE FUTURE OF DELIVERY SCIENCE

Personal Profile

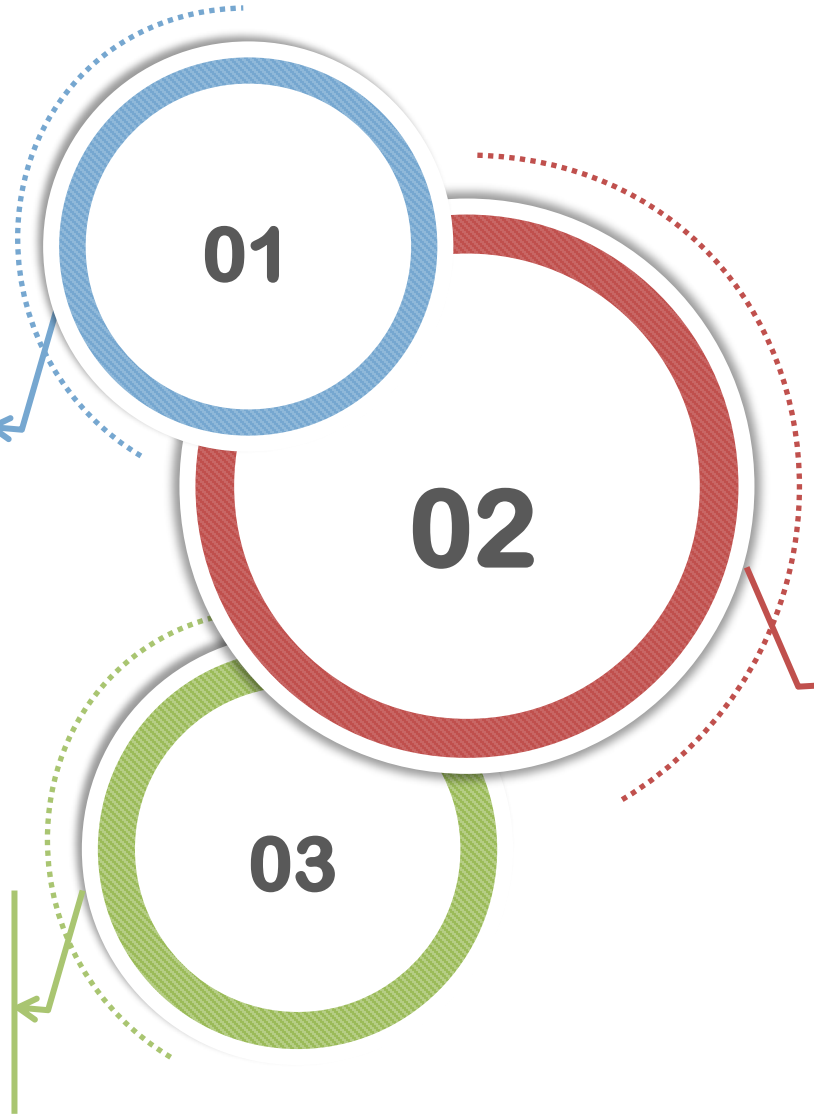
LIU Chang

PhD candidate., University of Macau
Major: Biomedical Sciences

Research Interests

- Inhaled nanomedicines and pulmonary disease
- Developing lipid-based particles for pulmonary drug delivery
- Polymeric particle-based therapies for acute inflammatory diseases

Outline



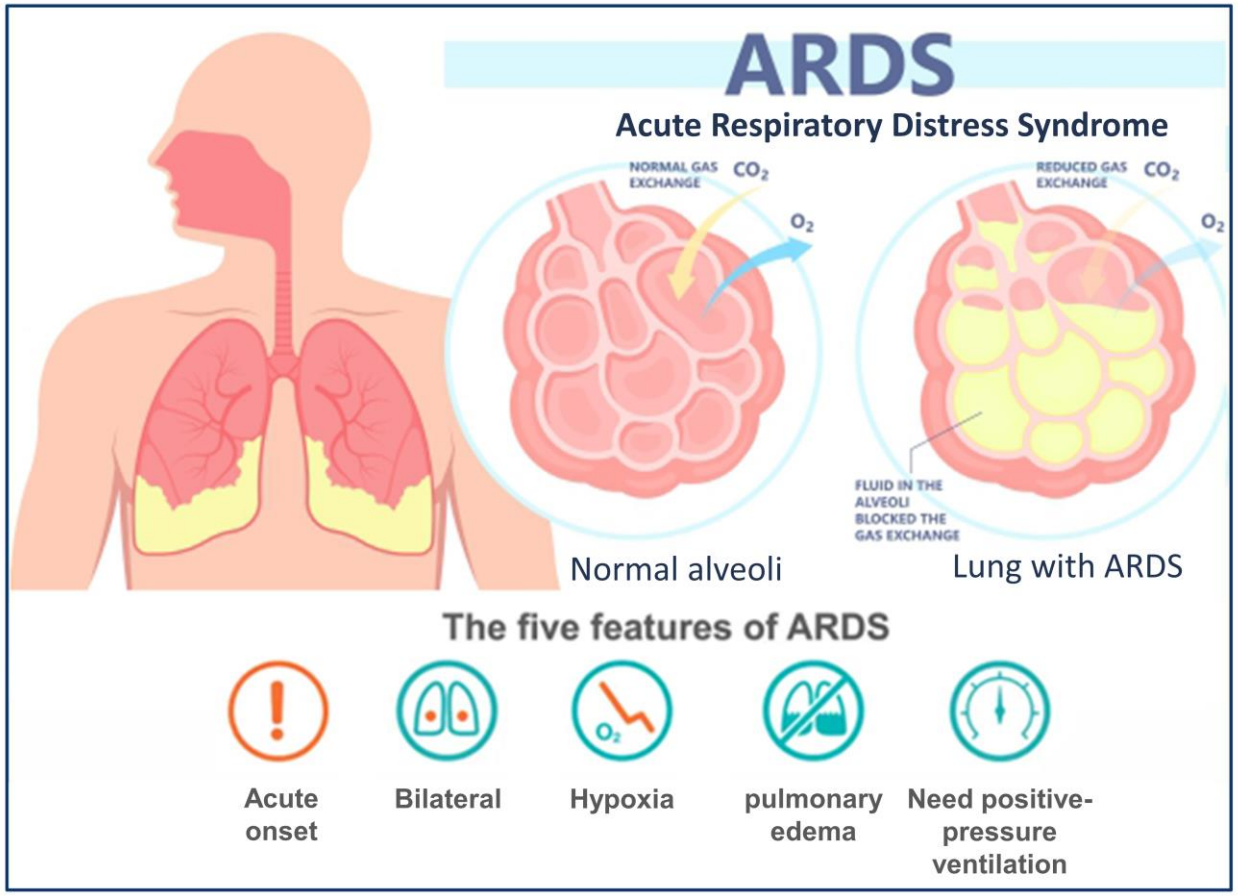
Background
Acute lung injury (ALI)

Research project
An inhalable biomimetic nanoplatform for ALI treatment

Conclusions & Acknowledgements

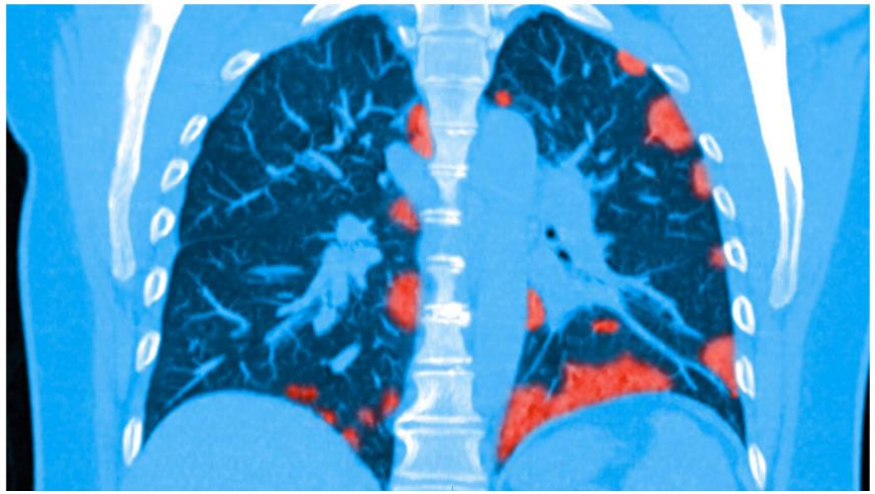
1. Research background

What is Acute Lung Injury (ALI or ARDS)?



Some patients who survive COVID-19 may suffer lasting lung damage

The similar respiratory disease SARS left lasting lung injury in some patients



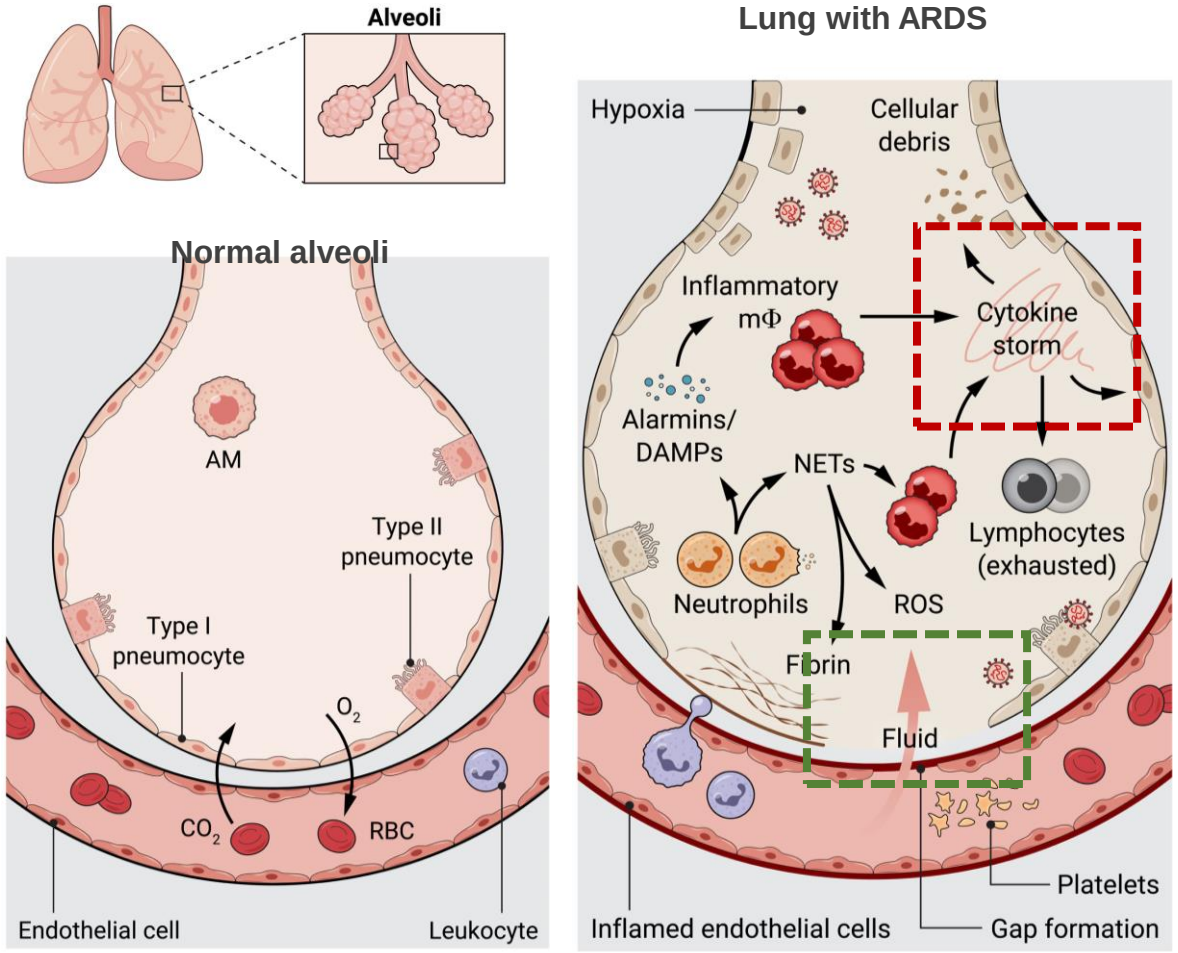
> ***Estimated mortality rate for patients with severe COVID-19-related ARDS is 80%***

STEVEN NEEDELL/SCIENCE SOURCE,2020

ALI/ARDS is a type of respiratory failure caused by
the rapid onset of the spread of inflammation in the lungs.

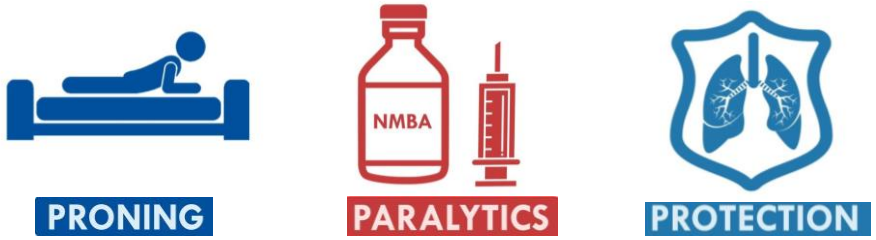
1. Research background

Hurdles for ALI/ARDS Treatment



SCIENCE IMMUNOLOGY, 2021, 2, 75.

Therapy options in ARDS treatment



No specific pharmacotherapies have been identified.

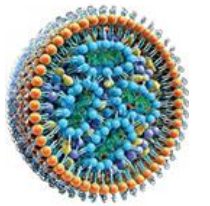
Insights from clinical studies

- **The heterogeneity of ARDS**
  Targeting one pathway may be suboptimal
- **The unique pulmonary physiological barrier**
  Low drug delivery efficiency to the lungs

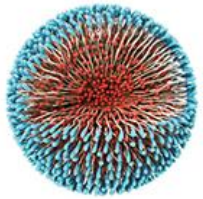
1. Research background

Inhalable Nanoparticle (NP)-Based Therapeutics

Inhalation delivery

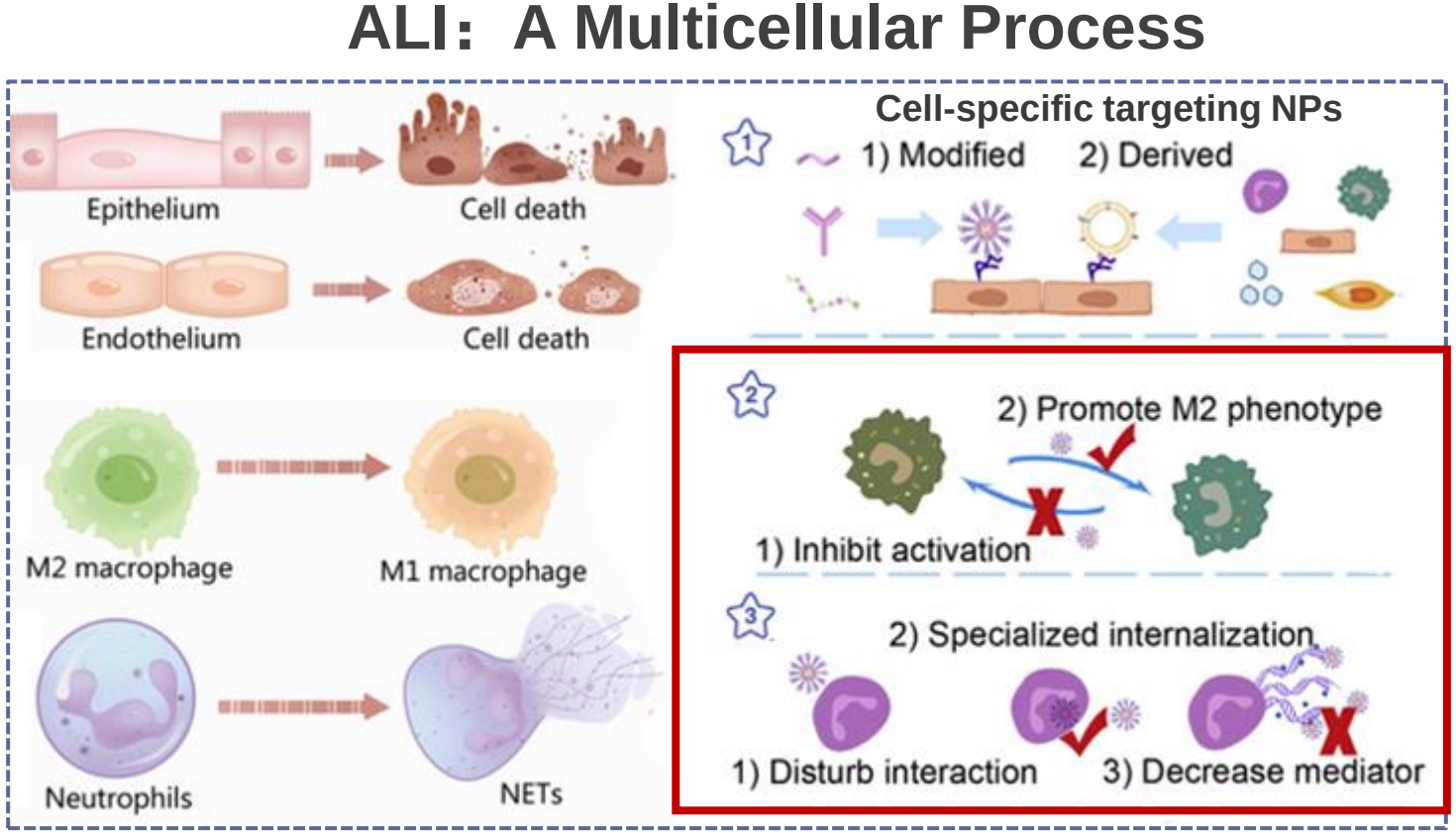


Nucleic acid lipid NPs



Polymeric NPs

Liposomes

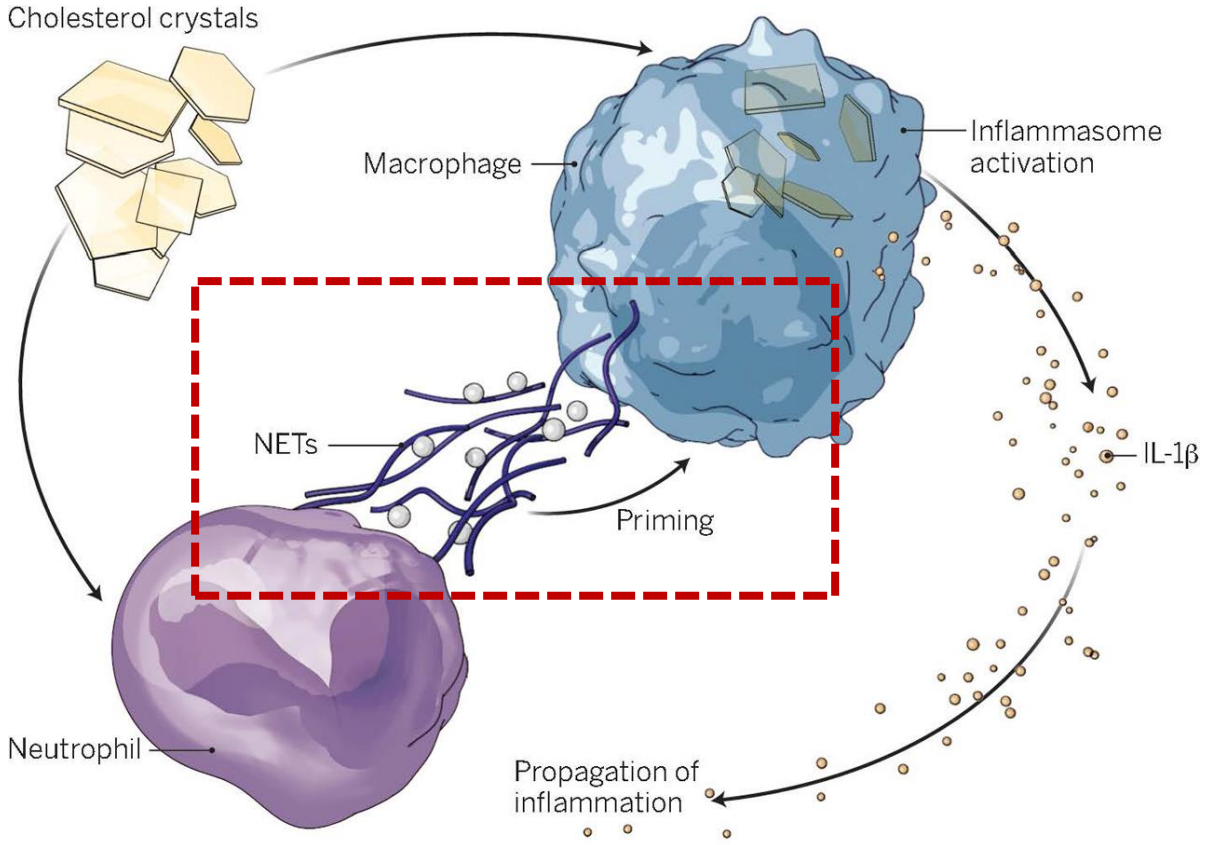


Limitation: 1. Single-targeted strategies 2. Insufficient for restoring pulmonary functions

Key points: Deliver sufficient drug to the lung;
Control overwhelming inflammation; Repair lung function

2. Research Project

Attempt to modulate multiple immune cells

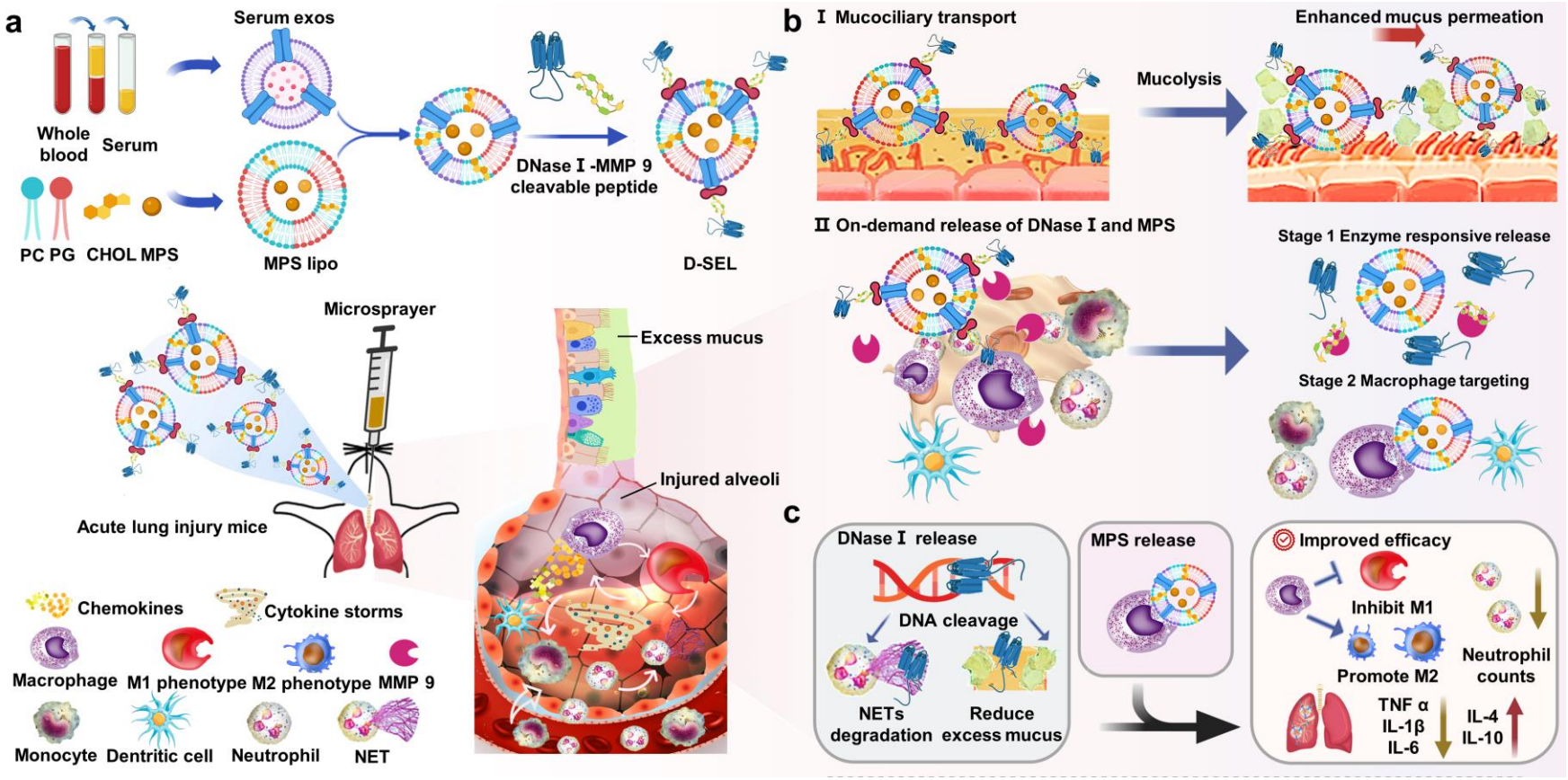


SCIENCE,2015,349.

Interactions of lung macrophages and recruited neutrophils with lung microenvironment are strongly implicated in the progress of lung inflammation.

2. Research Project

An inhalable biomimetic nanoplatform (D-SEL)

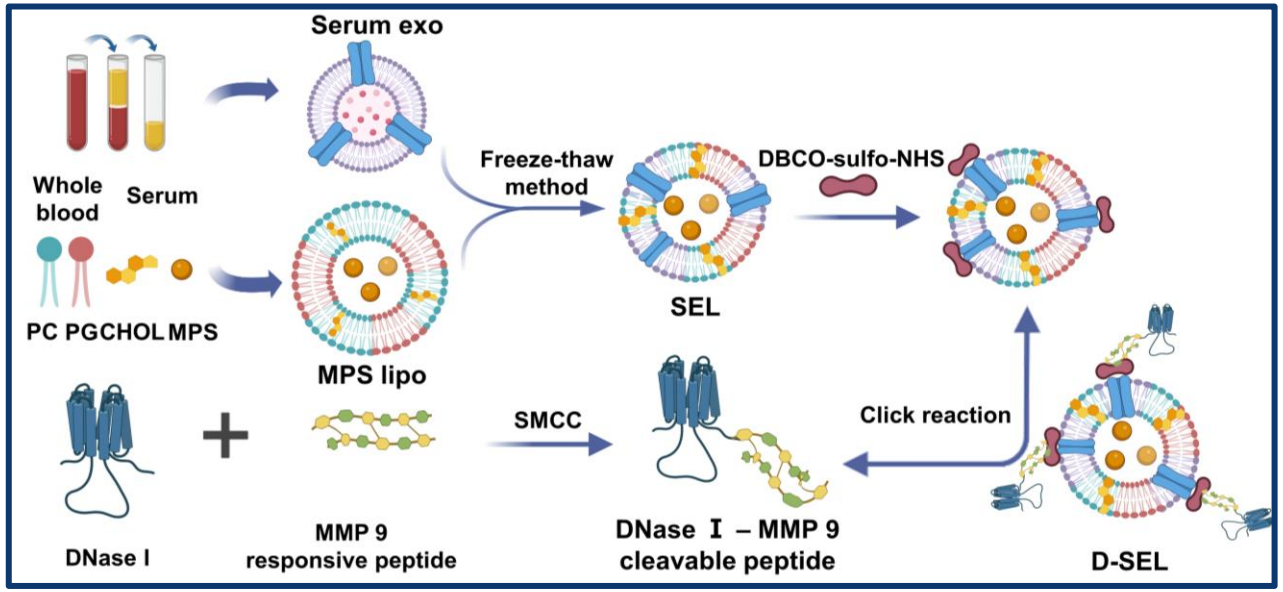


Inhalation of D-SEL can directly degrading dysregulated neutrophil extracellular traps (NETs) and efficiently modulating lung macrophages polarization into M2 phenotype.

2. Research Project

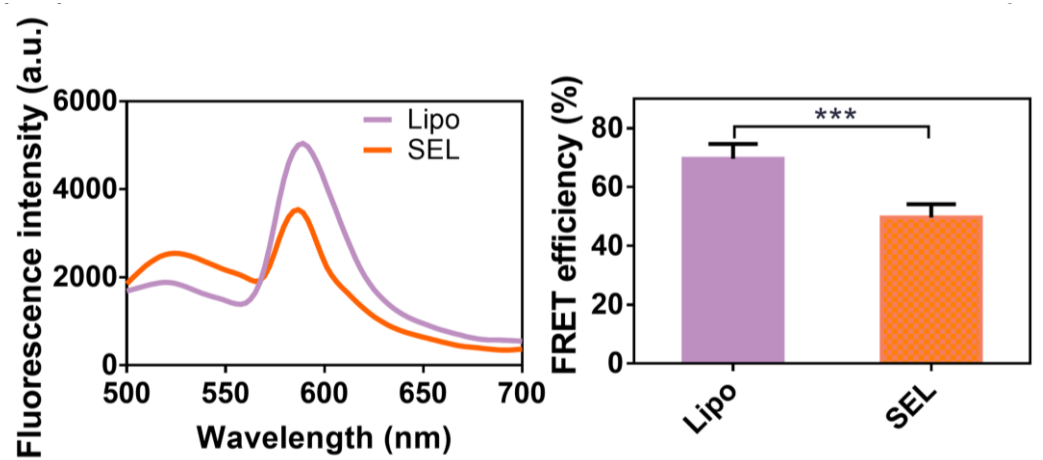
Results

An inhalable biomimetic sequential drug-releasing nanoplatform (D-SEL) for the combinatorial treatment of ALI

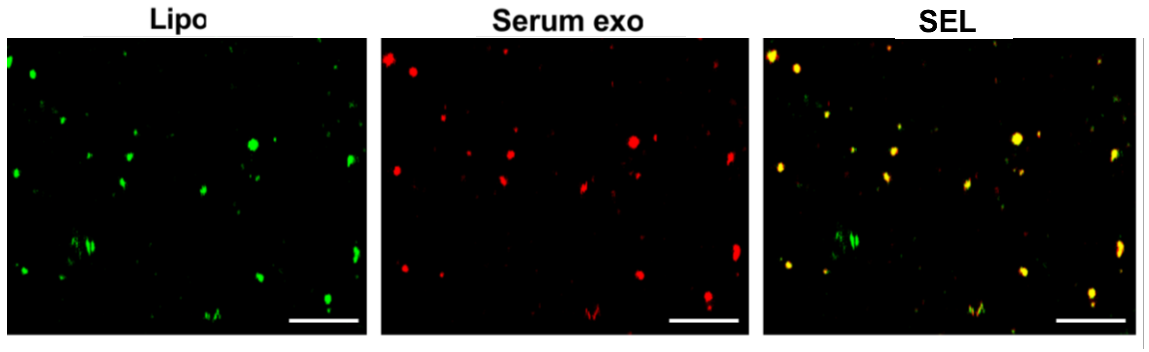


Model drug:
methylprednisolone sodium succinate(MPS) and DNase Ⅰ.

(A) FRET ratio



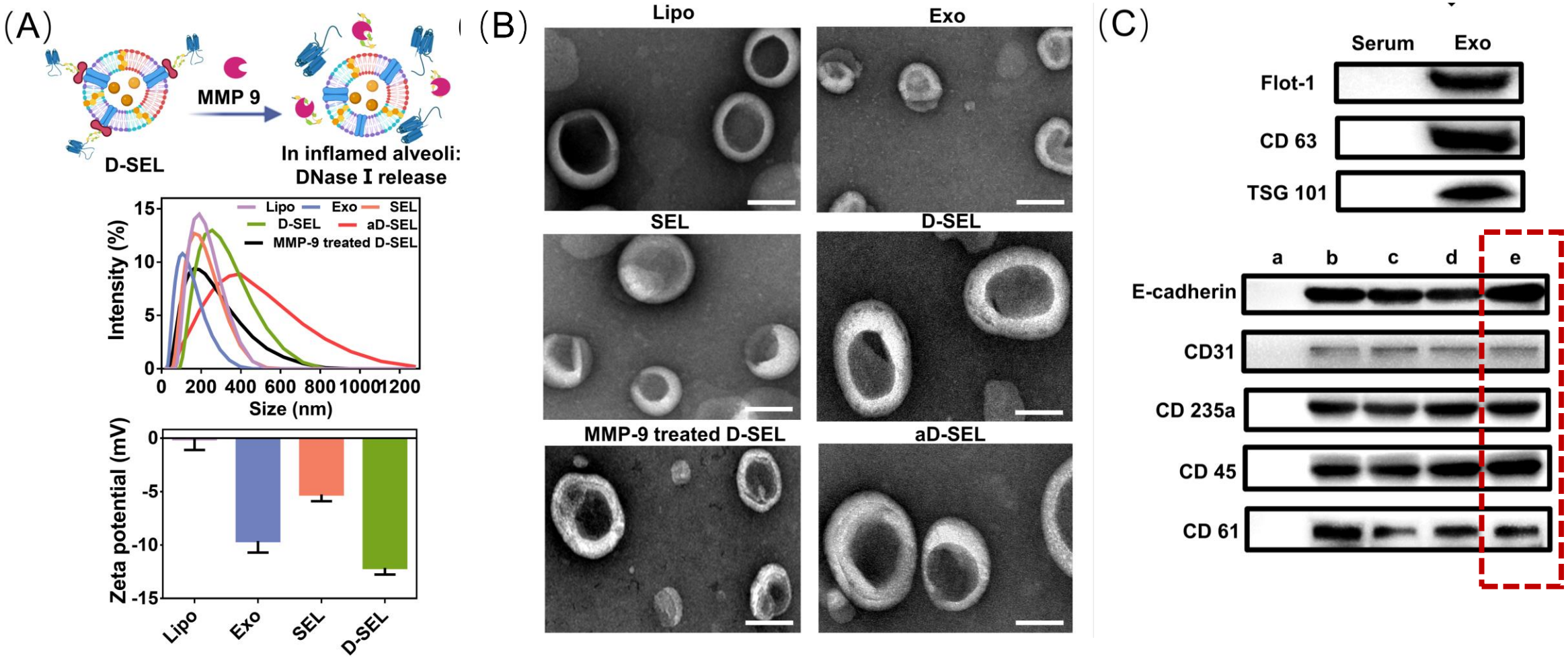
(B) Representative CLSM images



Construction of D-SEL.

2. Research Project

Results

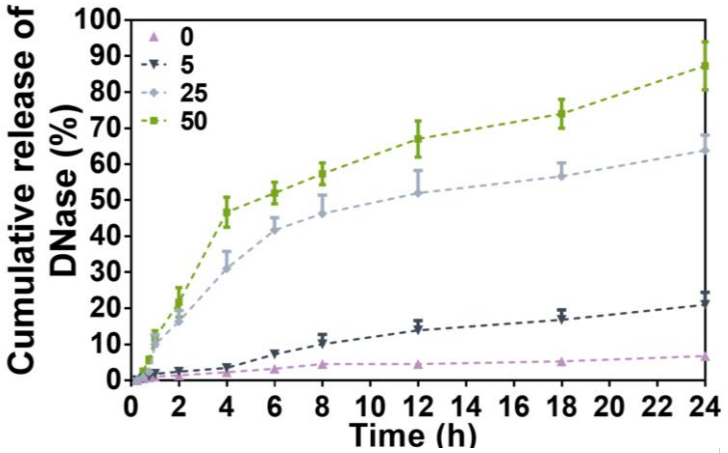


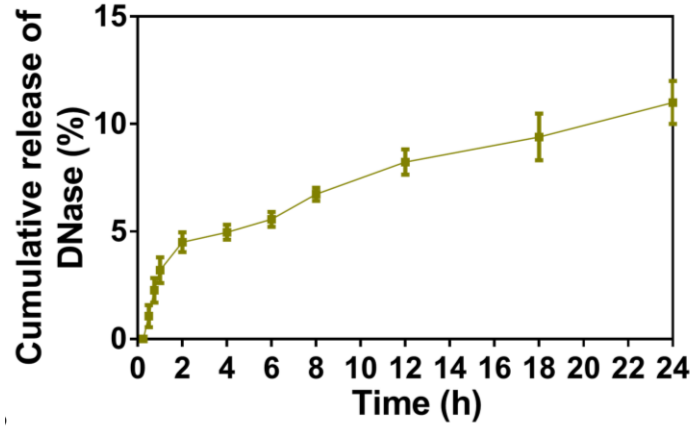
Physicochemical and protein characterization of D-SEL.

2. Research Project

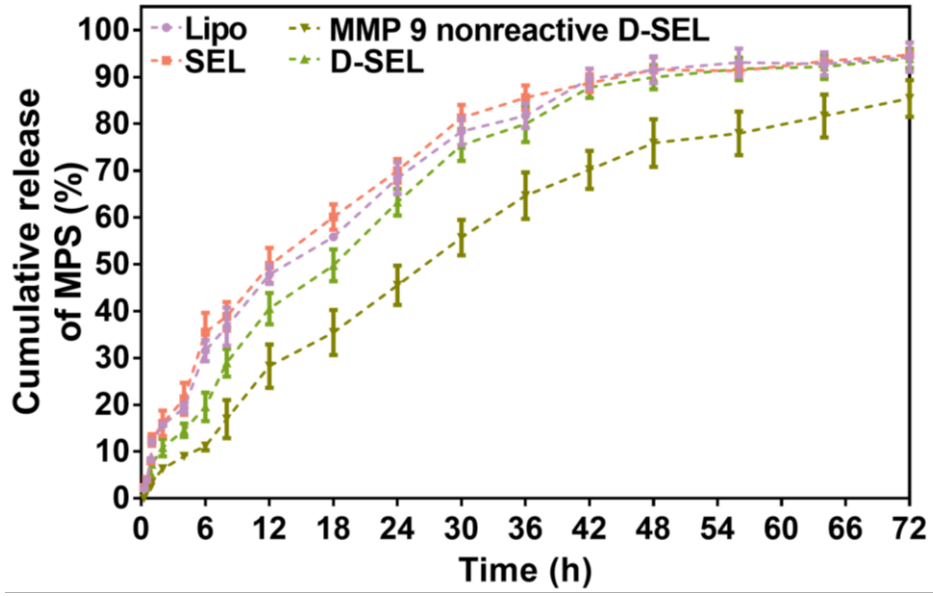
Results

(A) DNase release profile in medium





(B) MPS release profile in medium



For comparison, the MMP-9 nonreactive MPS/D-SEL was established.

- DNase Ⅰ was released faster than that of MPS from the MPS/D-SEL within the same period of time.

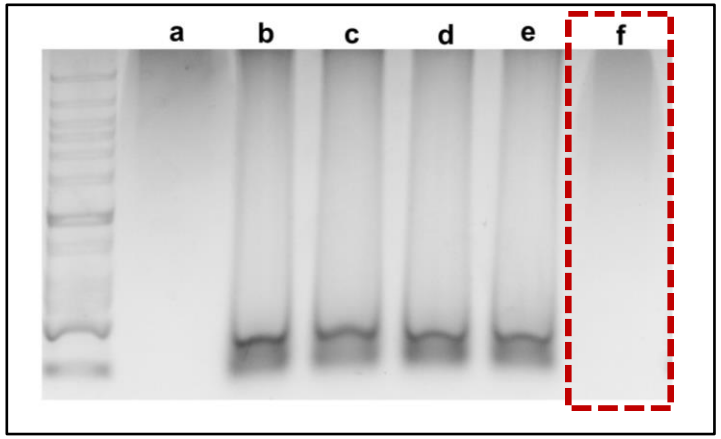
The sequential release of DNase I and MPS from the MPS/D-SEL exhibited a high MMP-9-responsiveness.

2. Research Project

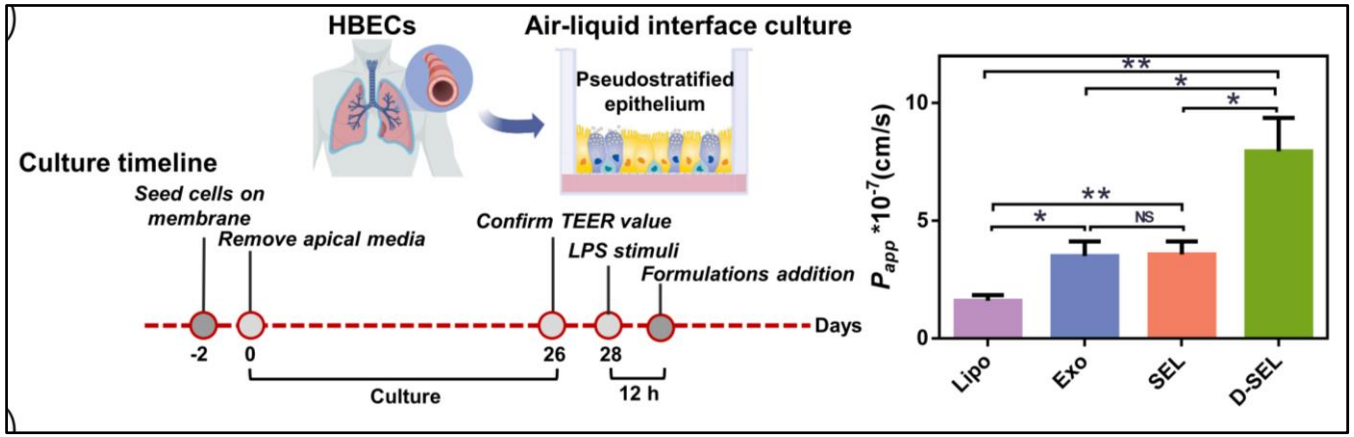
Results

(A) DNA digestion assay

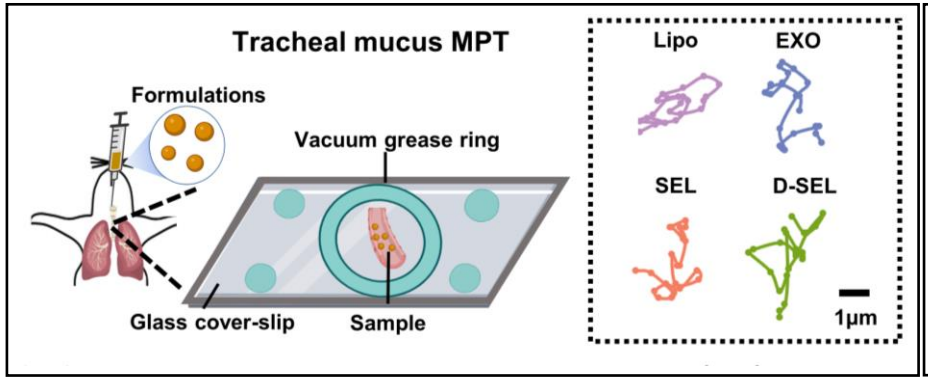
Artificial mucus

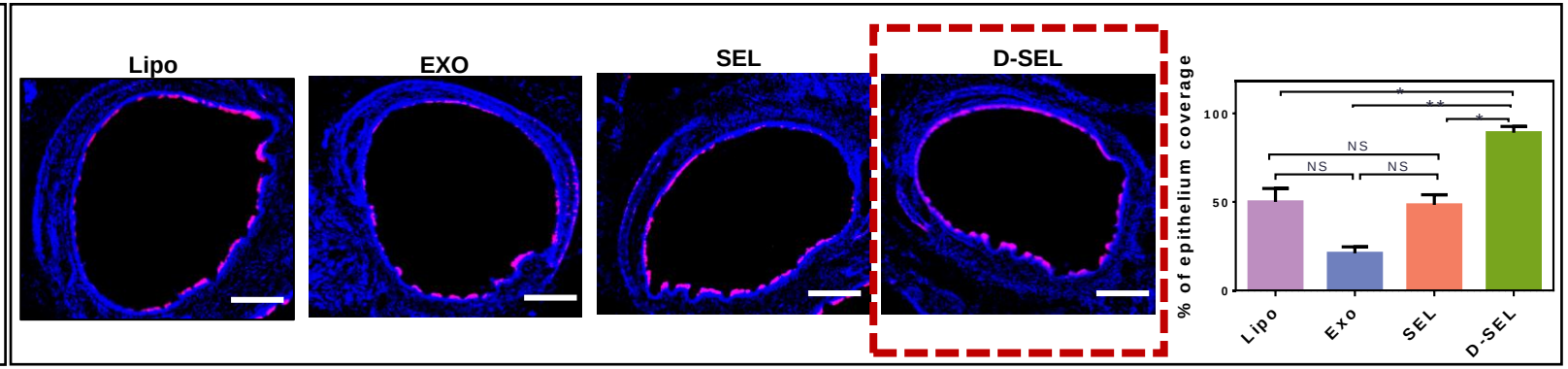


(B) Transwell multi-plate assay



(C) Particle distribution in airways following intratracheal administration



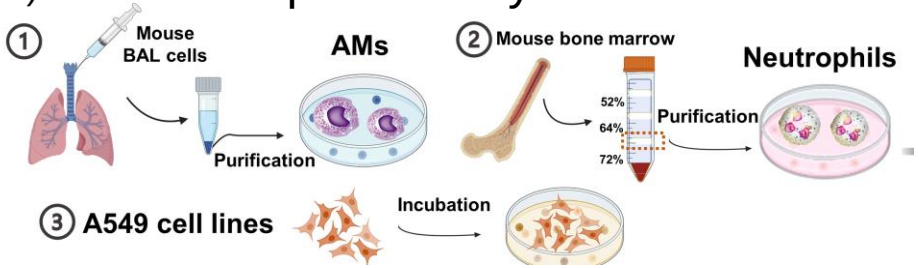


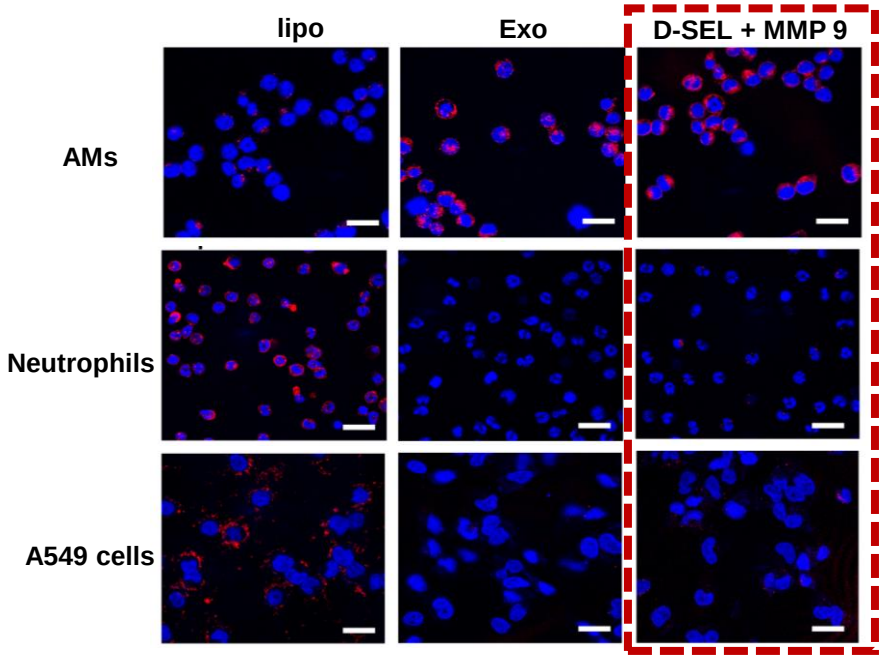
DNase Ⅰ grafting enhanced particle permeation through mucus *in vitro* and *in vivo*.

2. Research Project

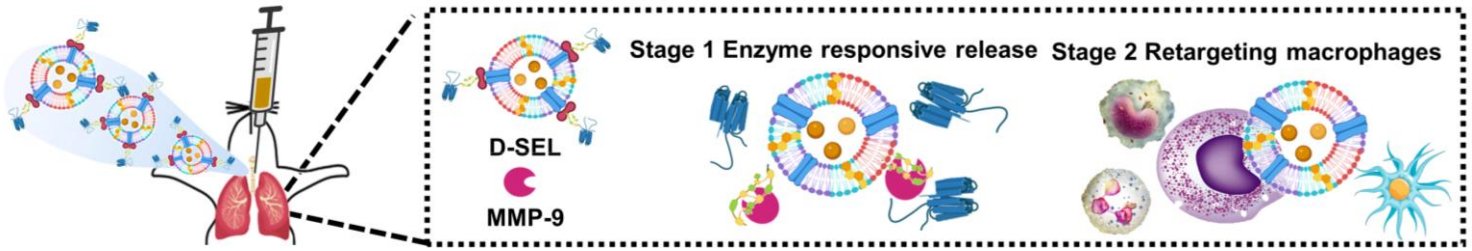
Results

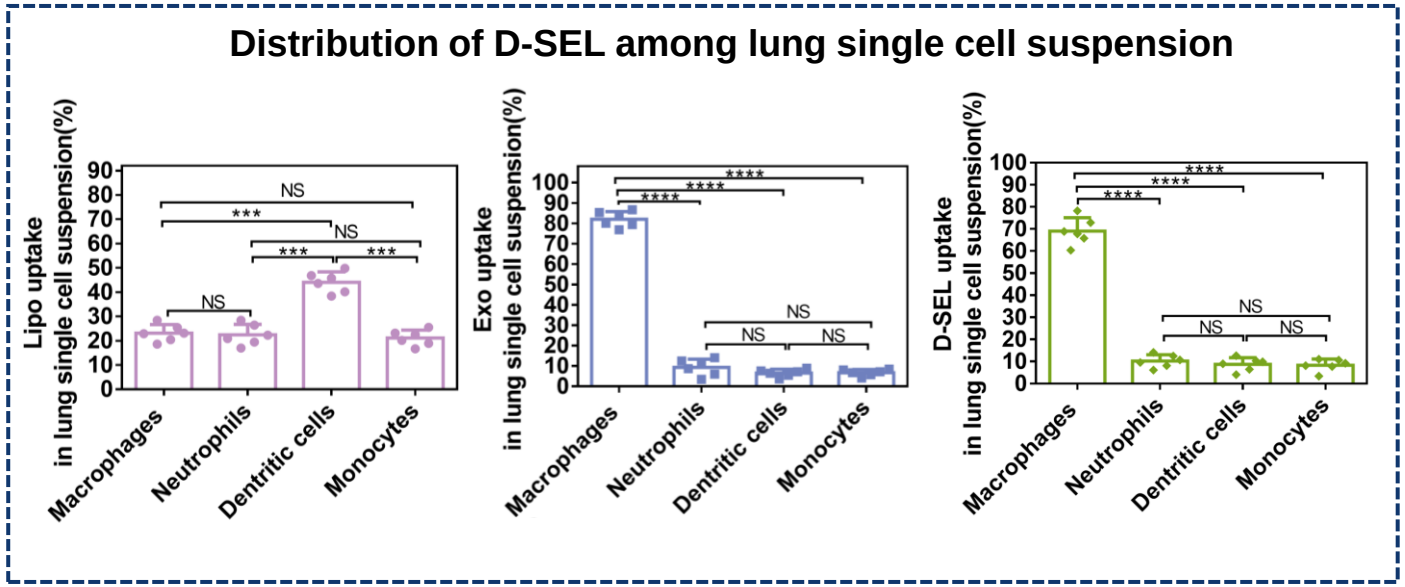
(A) A cellular uptake study *in vitro*





(B) A cell targeting study *in vivo*



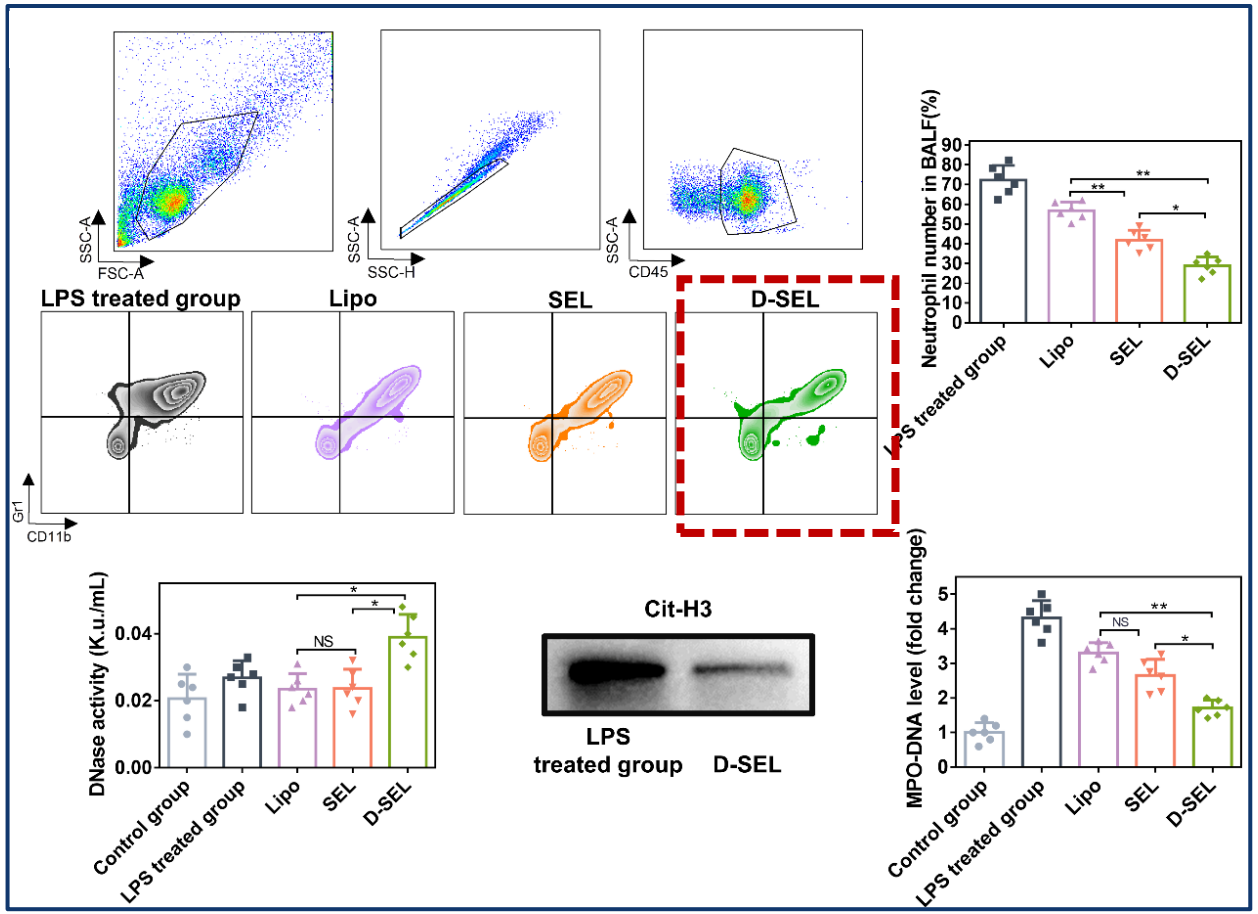


The D-SEL would detach their DNase Ⅰ arms and accurately retarget the macrophages.

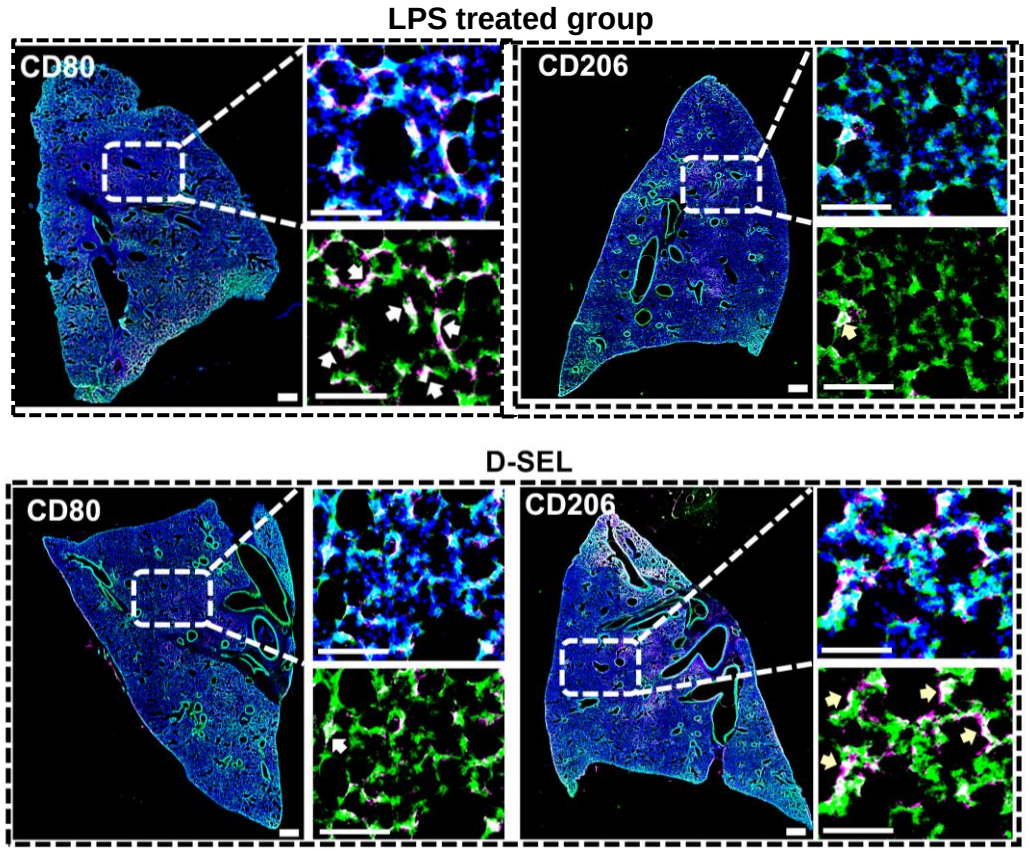
2. Research Project

Results

(A) Favorable NET degradation by released DNase Ⅰ arms



(B) Promoted expression of M2 Macrophages



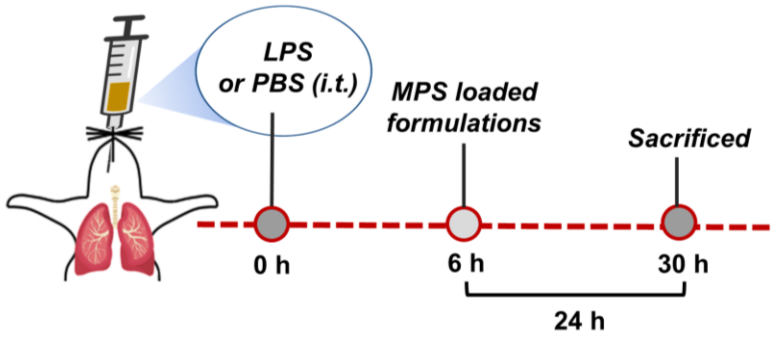
Inhalation of MPS/D-SEL could efficiency disturb the coordinated interaction between neutrophils and lung macrophages.

2. Research Project

Results

ALI mice

- Severe lung injury
- Cytokine release syndrome (CRS)

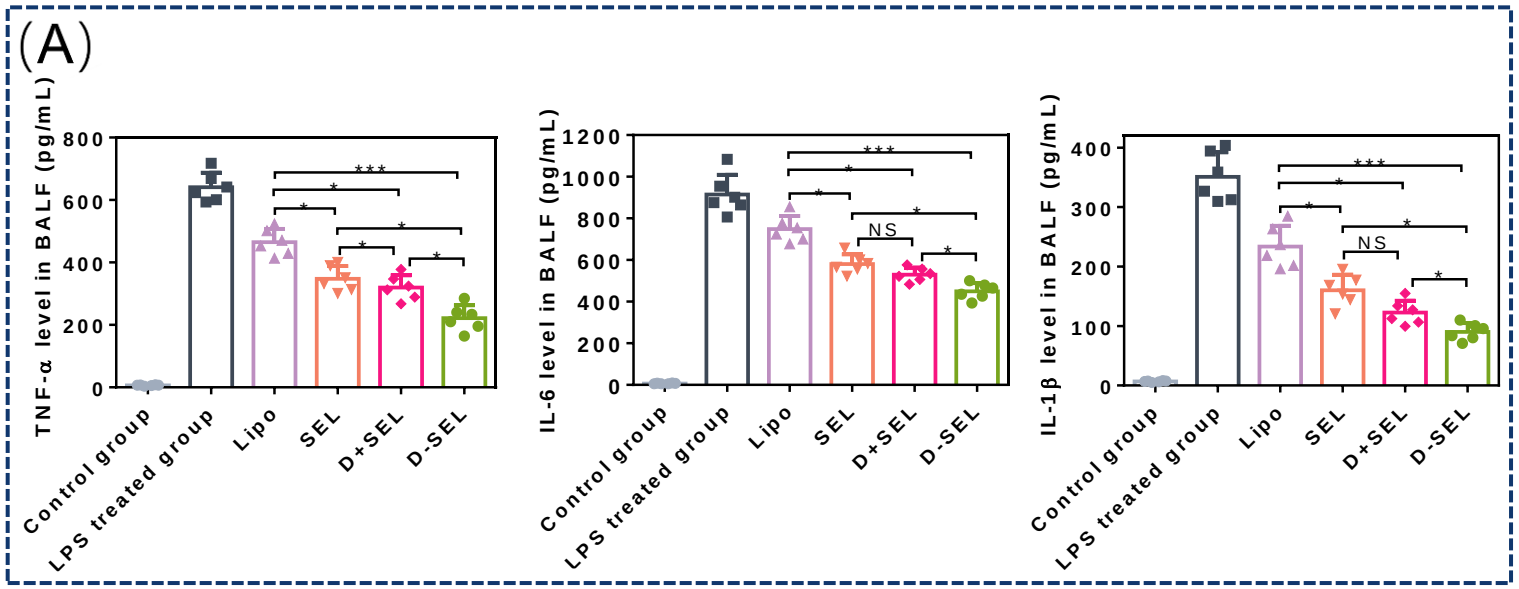


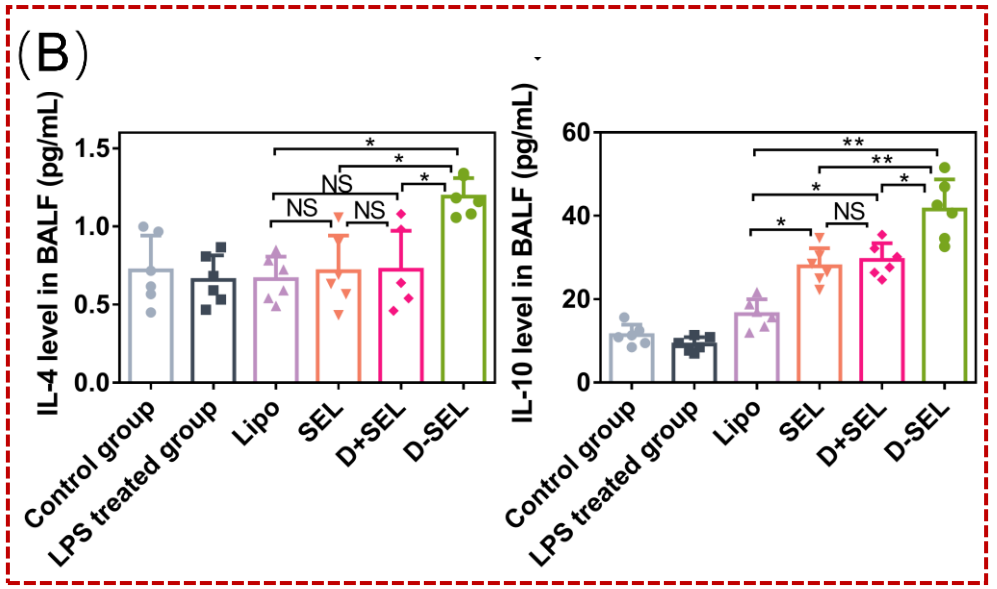
Harvest BALF

- Inflammatory cytokines
- mucin secretion

Harvest lung tissue

- Lung histology
- Mucus staining
- Wet/Dry lung tissue weight ratio

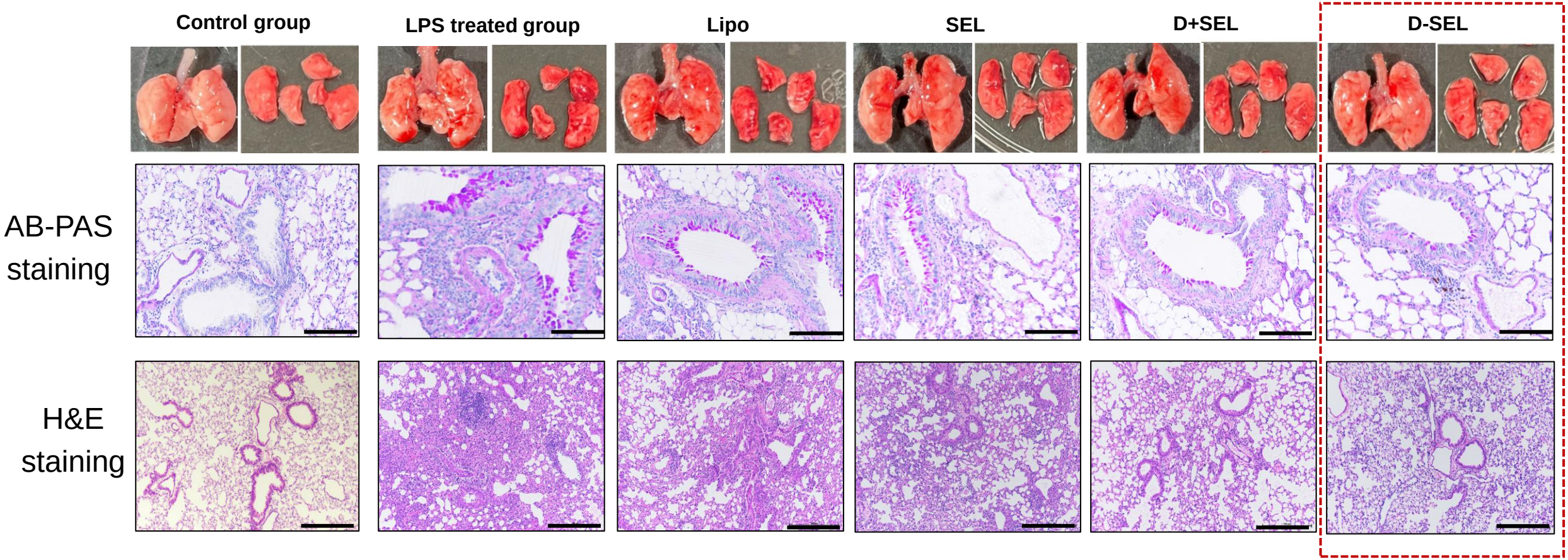




Inhalation of MPS/D-SEL remarkably decrease proinflammatory cytokines but higher expression levels of anti-inflammatory cytokines.

2. Research Project

Results



Inhalation of MPS/D-SEL remarkably alleviate lung pathological disorders in LPS induced mice.

3. Conclusions

- The fabrication of dual drug–loaded nanoplatform was facile and efficient;
- Excellent mucus penetration;
- On-demand targeting towards multiple inflammatory cells ;
- Offering new solutions to achieve precise modulation of the lung immune responses in ALI treatments.

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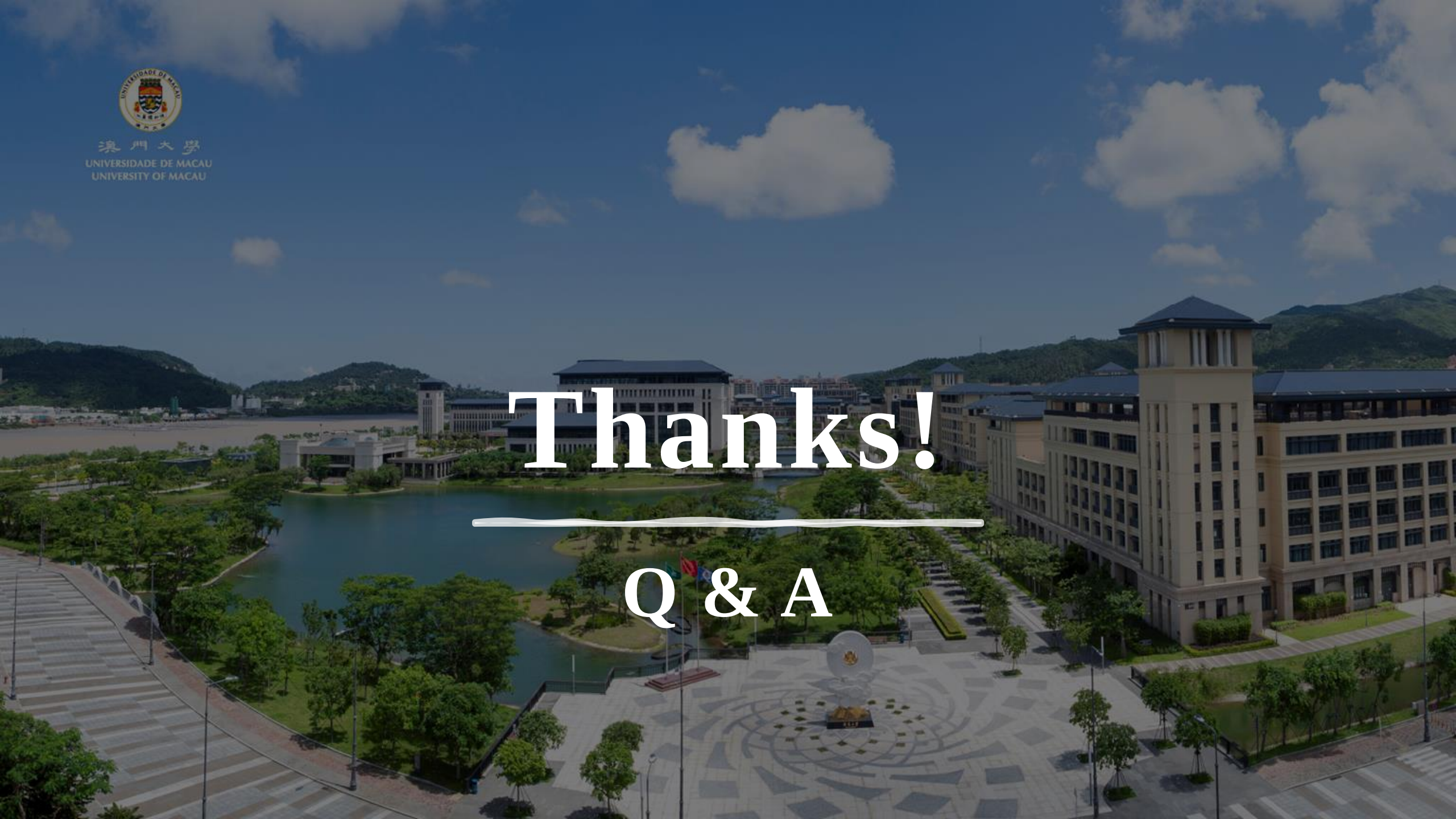

Thanks!

Q & A