Nanomedicine and Nanoscale Delivery

Pulmonary surfactant-based pirfenidone-loaded nanovesicles for inhalation therapy of idiopathic pulmonary fibrosis

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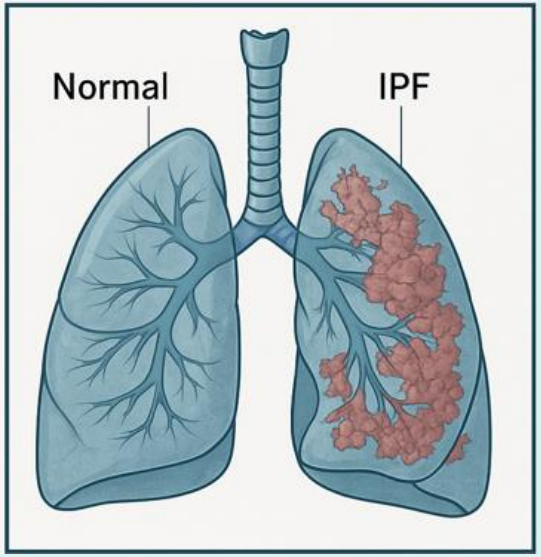
NEXT-GENERATION DELIVERY INNOVATIONS

KU MEDICINE

◈ Idiopathic pulmonary fibrosis (IPF)



Irreversible fibrosis of the alveolar walls accompanied by chronic inflammation

Symptoms and Diagnosis

01	02	03	04	05
Cough	Sputum	Dyspnea	Weightloss	Clubbing

1. *Honeycombing on chest HRCT is a hallmark finding of IPF*
2. *Usual interstitial pneumonia (UIP) pattern confirmed by bronchoscopic biopsy histology*
3. *Pulmonary function tests assess lung impairment based on disease progression*

◈ Treatment of Idiopathic pulmonary fibrosis (IPF)

1

Drug treatment

Pirfenidone

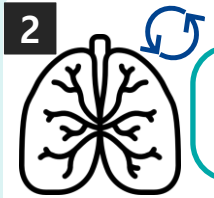
Transforming Growth Factor-beta (TGF-β) inhibitor

Nintedanib

Tyrosine kinase (TKI) inhibitor

No cure exists;
current drugs slow progression
but cause systemic side effects

2

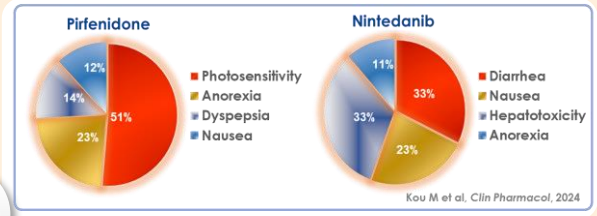


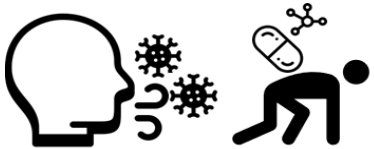
Surgical treatment

lung transplantation

Only curative option
with high mortality
and impaired quality of life

Limitations of current treatments

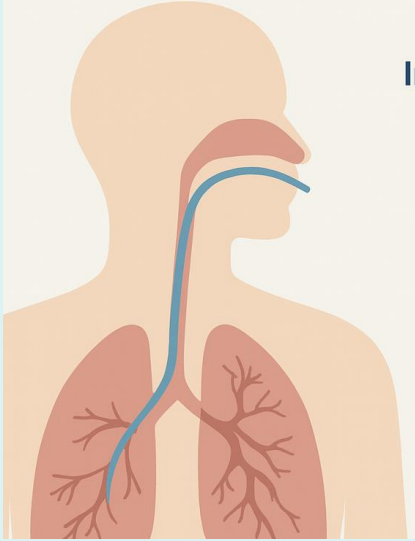




Infection, Adverse effects of immunosuppressive agents

Inhalation-based drug delivery strategies for pulmonary diseases

Lung-targeted delivery to enhance of drug therapeutic efficacy



Advantages of Inhalation Delivery

- Direct delivery to the lesion from the respiratory system
- High delivery efficiency
- Low systemic toxicity
- Low therapeutic doses
- More stable dosage forms

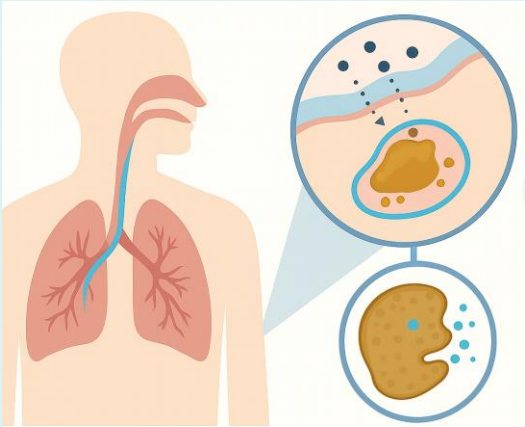
Antifibrotic drugs

Research of inhalation therapy in lung disease

Classification	Drugs	Indication	Ref.
Liposome	Ciprofloxacin	Tuberculosis	Pharmaceutics. 2016
	Rifampicin	Tuberculosis	AAPS PharmSciTech. 2015
	Nitrocamptothecin	Lung cancer	Clin Cancer Res. 2000
	Budesonide	Pneumonia	International Journal of Pharmaceutics, 2011
	Ketotifen fumarate	Asthma	Int J Pharm. 2001
Nanoparticle	Mometasone furoate	Asthma	Journal of Research in Pharmacy, 2021
	Isoniazid, rifampicin, pyrazinamide	Tuberculosis	Frontiers in Bioengineering and Biotechnology. 2022
	Rifampicin, isoniazid, pyrazinamide	Tuberculosis	European Journal of Pharmaceutics and Biopharmaceutics, 2020, International Journal of Pharmaceutics, 2021
Microparticle	Ciprofloxacin	Tuberculosis	Drug Delivery and Translational Research, 2017
	Doxorubicin	Lung cancer	International Journal of Pharmaceutics, 2013
	Rifampicin	Tuberculosis	Int J Pharm. 2019
	Tobramycin	Tuberculosis	Frontiers in Pharmacology, 2025

◈ Inhalation-based drug delivery strategies for pulmonary diseases

Limitations of inhaled drug delivery



Alveolar macrophage/Mucociliary clearance limits efficacy

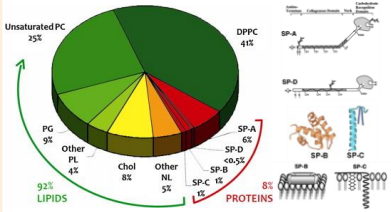
Limitation of inhalation therapy research in lung disease

Classification	Drugs	Indication	Presence of limitations	Ref.
Lipid nanomedicine	Bergapten	ALI	AM clearance limits drug efficacy	Sci Adv. 2025
HYA–DEX nanoparticles	Dexamethasone	Pneumonia	AM clearance limits drug efficacy	Front Pharmacol. 2025
Lipid nanomedicine	Bergapten	ALI	AM clearance limits drug efficacy	Bioact Mater. 2024
Charged liposomes	Roflumilast	ALI	Mucociliary clearance limits efficacy	Eur J Pharm Biopharm. 2023
Arginine- liposomes	Curcumin	ALI	AM clearance limits drug efficacy	Eur J Pharm Biopharm. 2023
Mesoporous silica NP	Dexamethasone	Pneumonia	AM clearance limits drug efficacy	Pharmaceutics. 2023
Albumin nanoparticles	Roflumilast	COPD	Mucociliary clearance limits efficacy	Pharmaceutics. 2022
Dex-liposome	Dexamethasone	IPF	AM clearance limits drug efficacy	Front Immunol. 2021
Liposomal aerosol	Amikacin	Cystic Fibrosis, Tuberculosis	AM clearance limits drug efficacy	Int J Pharm. 2016
liposomes	Tobramycin, Colistin	Pneumonia	Mucociliary clearance limits efficacy	Clin Microbiol Rev. 2015

◈ Pulmonary surfactant-based inhalable pirfenidone for IPF

Pulmonary surfactant (PS)

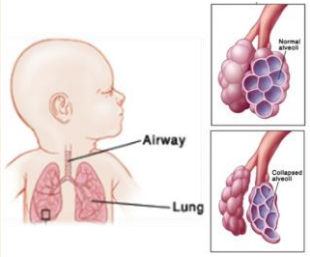
Structure of PS



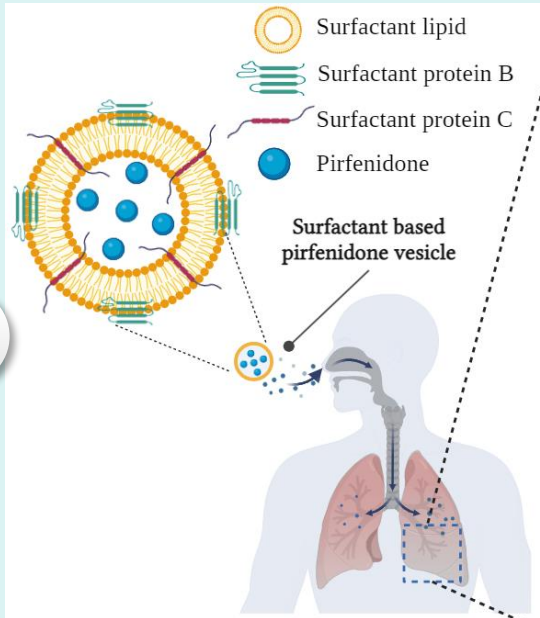
Surfactant protein A&D
-Hydrophilic
-pagocytosis induction against pathogens
-Pulmonary surfactant secretion control

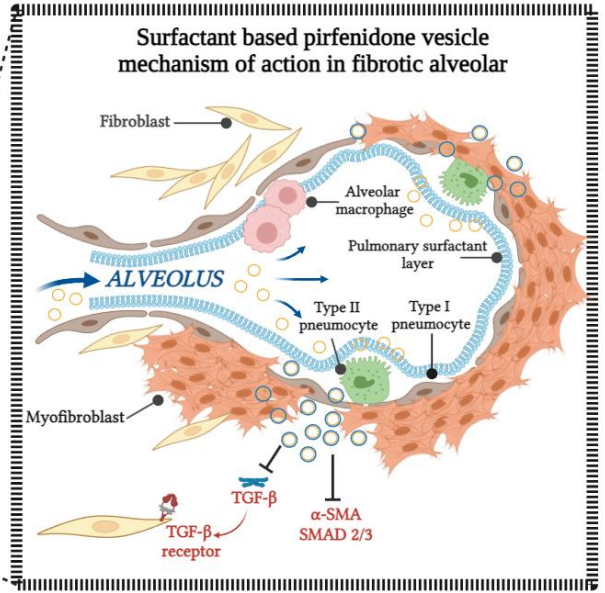
Surfactant protein B&C
-Hydrophobic
-Mediates binding to surfactant membrane proteins

Clinical application of PS



"Clinically approved liposomal formulation" for the treatment of Neonatal Respiratory Distress Syndrome (RDS)





◈ Preparation and characterization of PFD-PSNVs

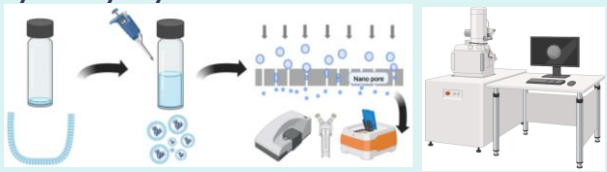
Pulmonary surfactant (PS)-based PFD-loaded nanovesicles ;PFD-PSNVs

Pulmonary surfactant for PFD-PSNVs preparation

Curosurf® is the pulmonary surfactant used in this study, clinically approved and derived from porcine lungs

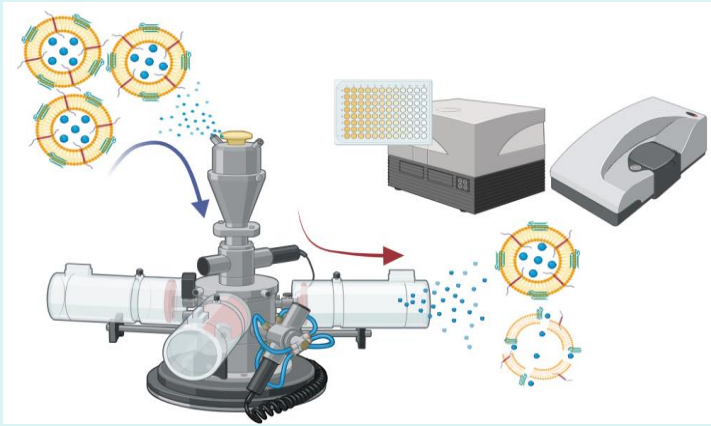
Preparation and characterization of PFD-PSNVs

PFD-PSNVs were prepared in four ratios via film-drying and hydration, followed by extrusion for size uniformity, with size and surface charge measured by DLS and morphology analyzed by cryo-TEM.



Nebulization stability of PFD-PSNVs

The particle stability before and after nebulization was evaluated using a small animal nebulizer device, and drug loading and particle size were measured pre- and post-nebulization.



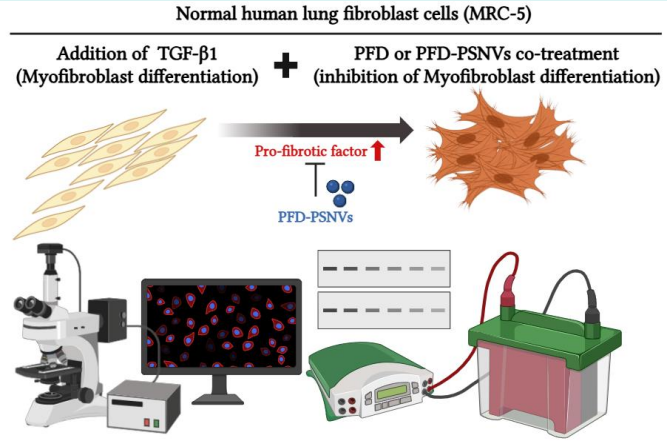
Animal alosols: InExpose system (SCIREQ), Aeroneb Lab Nebulizer unit
Dynamic light scattering (DLS) device: Nano-ZS90, Malvern

KU MEDICINE

◈ Anti-fibrotic effects and biodistribution of PFD-PSNVs *in vitro* and *in vivo*

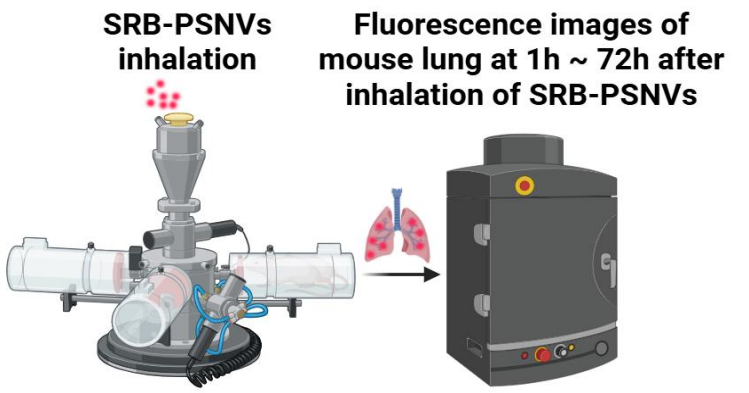
Anti-fibrotic effects of PFD-PSNVs in vitro

The *in vitro* anti-fibrotic effect of PFD-PSNVs was assessed in normal human lung fibroblast cells (MRC-5) stimulated with TGF-β (10 ng/mL), by comparing the expression of a-SMA, ERK, and SMAD between treated and untreated groups using IF staining and Western blotting.



Biodistribution of SRB-PSNVs after inhalation in vivo

To assess time-dependent lung distribution and clearance, mice were exposed to inhalation of SRB-labeled NVs or PSNVs, and their lungs were harvested at 1, 6, 24, 48, and 72 hours post-inhalation to analyze retention and clearance over time.



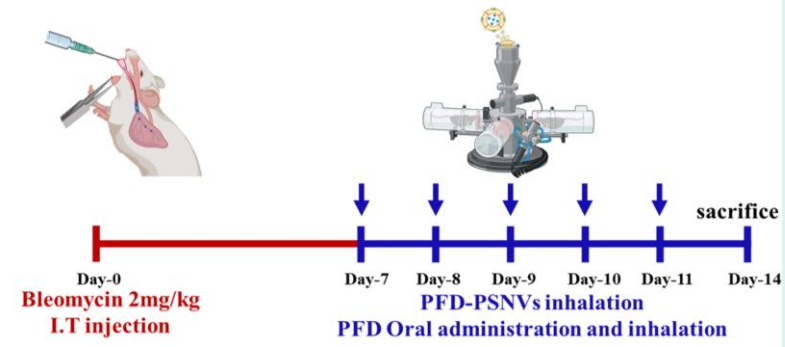
The fluorescence of the lungs was measured using an IVIS Lumina instrument (PerkinElmer, Waltham, MA, USA)

◈ Anti-fibrotic effects and biosafety of PFD-PSNVs *in vivo*

Anti-fibrotic effects of PFD-PSNVs in vivo

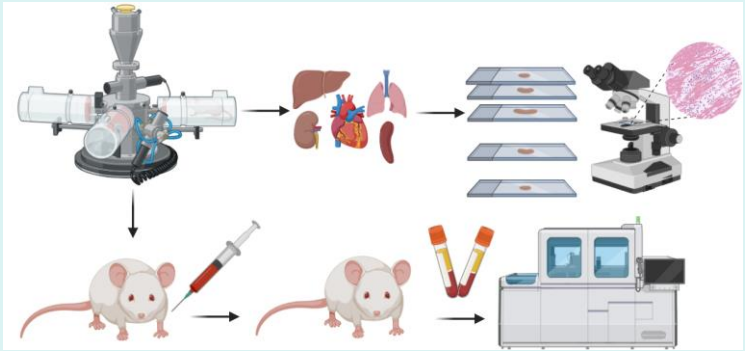
The in vivo anti-fibrotic effect of PFD-PSNVs was assessed in IPF mice induced by intratracheal bleomycin (2 mg/kg, n = 3), using H&E, MT, and a-SMA IHC staining to evaluate fibrosis progression and treatment efficacy.

PFD-PSNVs were administered via inhalation once daily for 5 consecutive days, starting on day 7 after bleomycin-induced inflammation, when fibrosis progression begins.



Biosafety of PFD-PSNVs in vivo

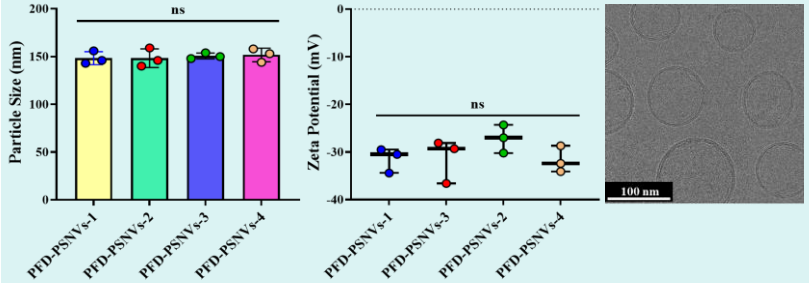
To assess the toxicity of PFD-O (PFD oral administration), PFD-I (inhalation), PSNVs-I, and PFD-PSNVs-I, mice received treatments five times over one week. Serum and major organ were collected three days later to measure CREA, BUN, LDH, ALT, and AST levels. Major organs were examined via H&E staining.



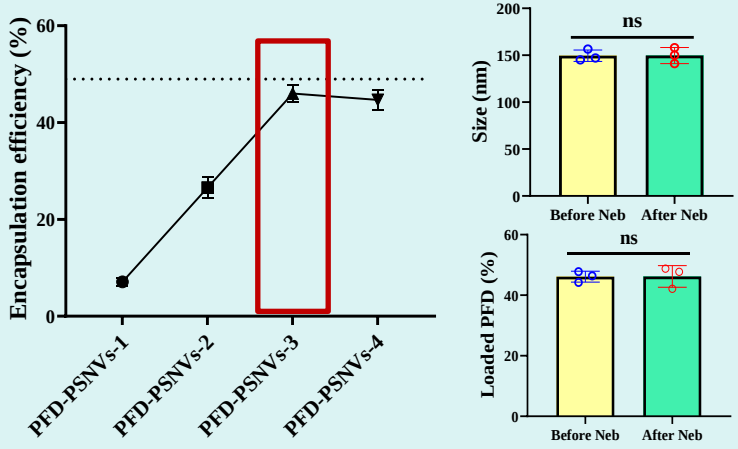
◈ Characterization of synthetic PFD-PSNVs

Size and zeta potential of synthetic PFD-PSNVs by PS:PFD ratio.

	Curosurf (R) : Pirfenidone mass ratio (μg/ml)	Curosurf (R) : Pirfenidone concentration ratio (mM)	Pirfenidone encapsulation efficiency (%)
PFD-PSNVs-1	1000 : 500	1.25 : 2.7	7.1 ± 2
PFD-PSNVs-2	1000 : 100	1.25 : 540	26.5 ± 1
PFD-PSNVs-3	1000 : 75	1.25 : 404	46.0 ± 1
PFD-PSNVs-4	1000 : 50	1.25 : 230	44.6 ± 2



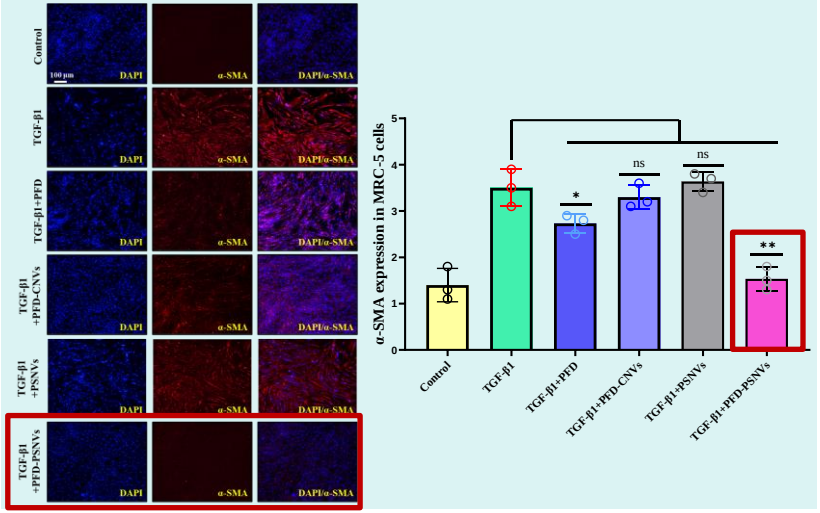
Encapsulation and size were assessed by PS:PFD ratio and before/after nebulization.



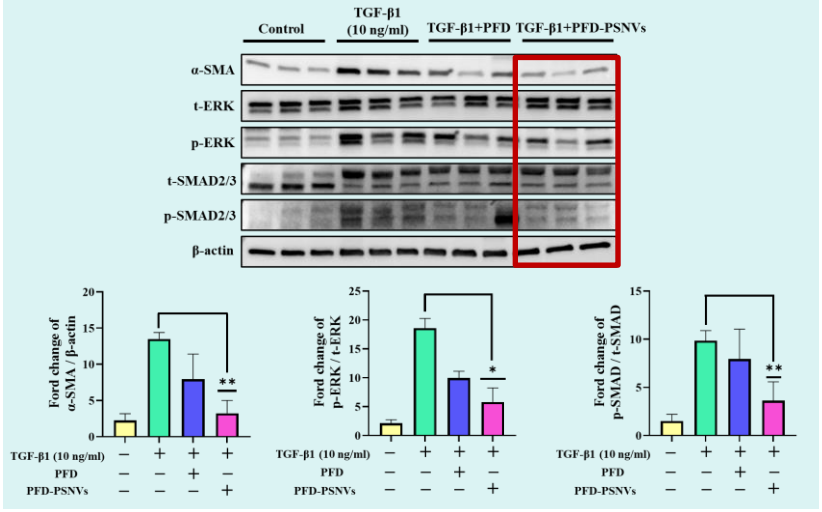
The third PFD-PSNVs ratio showed highest loading and was used for all studies. Size and loading remained stable after nebulization

◈ Anti-fibrotic effects of PFD-PSNVs *in vitro*

Immunofluorescence (IF) staining of α-SMA expression in MRC-5 cells with PFD-PSNVs treatment.



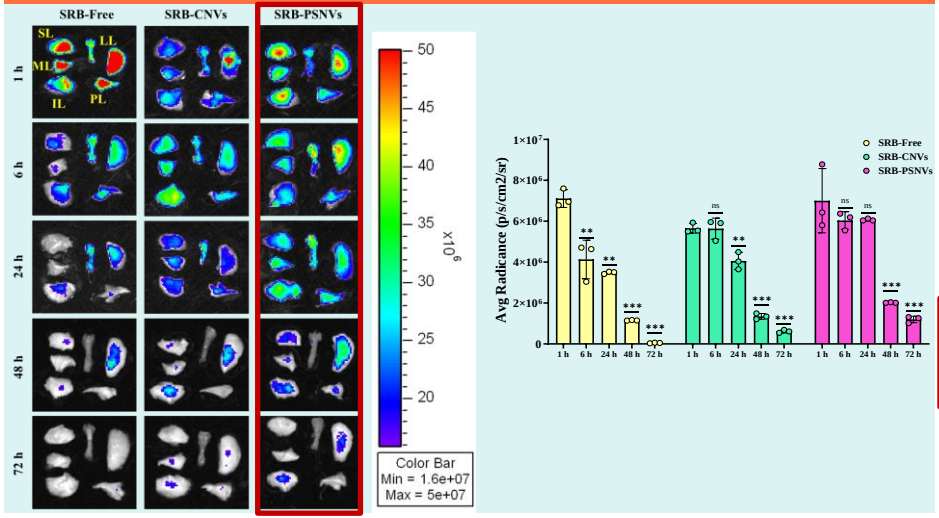
Western blot analysis of ERK signaling protein in MRC-5 cells treated with PFD-PSNVs



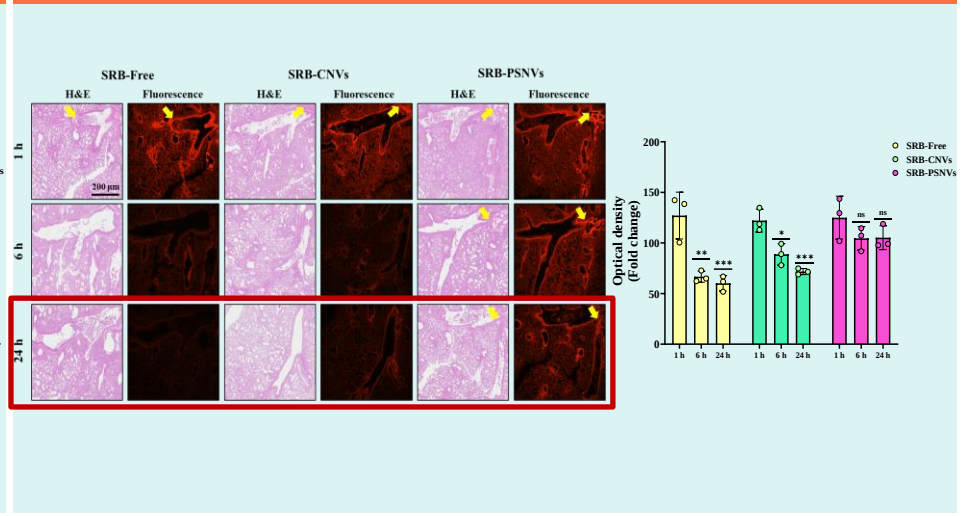
PFD-PSNVs significantly reduced α-SMA expression in TGF-β-activated fibroblasts and also suppressed ERK and SMAD pro-fibrotic protein levels.

◈ Investigation of lung retention properties after PSNVs inhalation

Fluorescence images of mouse lung after inhalation of SRB free, SRB-CNVs and SRB-PSNVs



Microscope lens image of H&E staining and SRB fluorescence after inhalation of SRB free dyes, SRB-ANVs and SRB-PSNVs



SRB-loaded PSNVs showed slower clearance compared to SRB-only and SRB-CNVs (non-PS protein liposome) groups, indicating enhanced pulmonary retention and sustained PFD release potential

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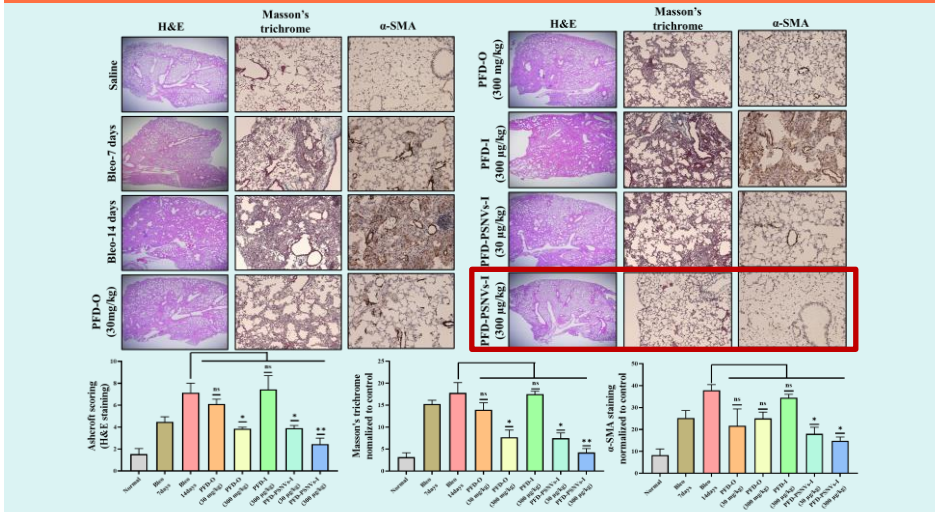
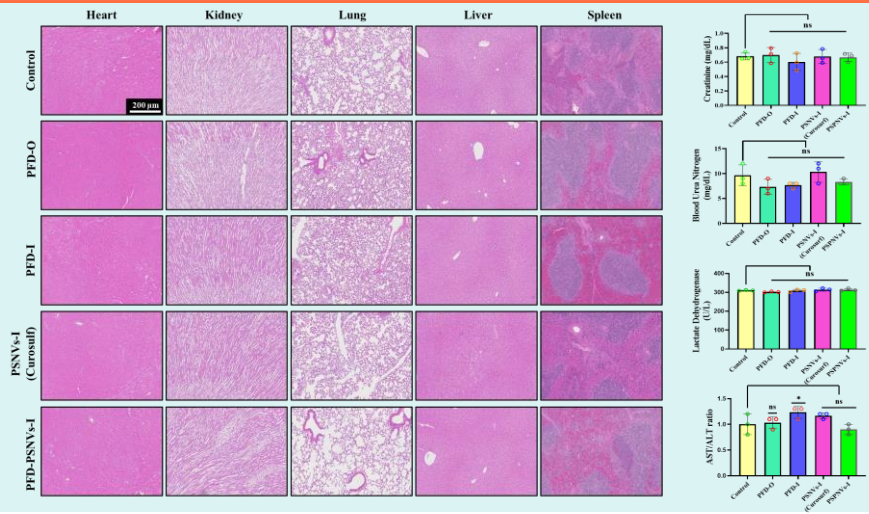
◈ Anti-fibrotic effects and biosafety of PFD-PSNVs *in vivo*

Anti-fibrotic effects of PFD-PSNVs on BLM induced IPF mice



Biosafety of inhalation treatments of PFD-PSNVs in mice



Inhaled PFD-PSNVs significantly reduced fibrosis progression in IPF mice compared to other groups, including oral PFD, with confirmed safety from histological and blood analyses

- This study developed PFD-PSNVs as an inhalable system to efficiently deliver pirfenidone (PFD) to the lungs for IPF treatment.
- The nanovesicles, containing exogenous pulmonary surfactant (PS), were optimized to ~150 nm for effective cellular uptake in the lung.
- PFD-PSNVs showed prolonged lung retention up to 24 hours, surpassing that of clinically approved inhalable liposomes.
- Inhaled PFD-PSNVs inhibited IPF progression more effectively than oral PFD, mainly through EMT and TGF-β1/SMAD signaling pathways.
- These results highlight a promising strategy using inhalable, low-dose, PS-based formulations of FDA-approved drugs like PFD for safe and effective IPF therapy.

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Show more

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06 Acknowledgement

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Q & A