

The Development of an Inhalable Platelet-Based Therapy for Lung Injury

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Drug Delivery to the Lungs
Edinburgh

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What is Acute Lung Injury?

Definition = acute, inflammatory lung injury
Results from insults to the lung

Direct

Pneumonia
Chest injury
Inhalation of smoke/toxic gases

Indirect

Sepsis
Blood transfusion
Burns/severe trauma

Characterised by

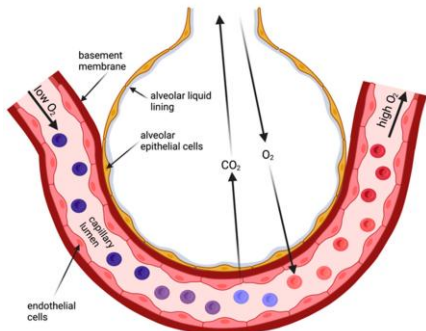
- Loss of alveolar-capillary barrier integrity
- Pulmonary oedema
 - Impaired gas exchange

*Current treatments: **do not**
restore alveolar-capillary barrier
prevent oedema formation
reverse inflammation-driven lung damage*

Current treatments (supportive care only)

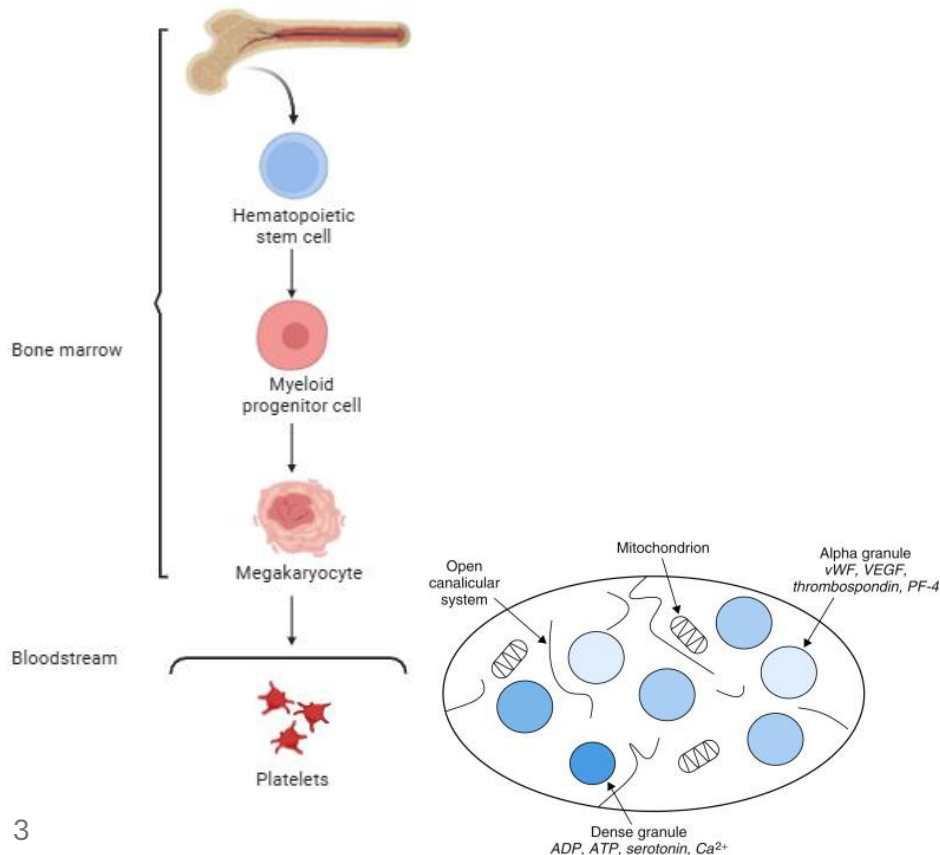
- Ventilation
- Steroids
- Treating underlying pathology

*Novel therapies targeting **mechanistic drivers** of acute lung injury are urgently needed*



What are platelets?

- Anucleate cells
- Size: 2-4um
- Circulate in the blood
- $1.50-4.50 \times 10^5$ platelets/ml of blood



Role of platelets in the lungs

- Interact with endothelial cells to help seal small gaps in the capillary wall
- Interact with epithelial cells to support alveolar fluid clearance and barrier function
- Secrete protective factors to strengthen tight junctions
- Anti-inflammatory = dampen down the severity of inflammation
- Angiogenesis = forming new blood vessels
- Contribute to alveolar cell proliferation

In Acute Lung Injury

- Can provide **barrier support**
- Can **limit oedema** formation

A platelet-based therapy

How platelet-rich plasma is produced:

Regenerative therapy

- Platelet rich plasma (PRP)

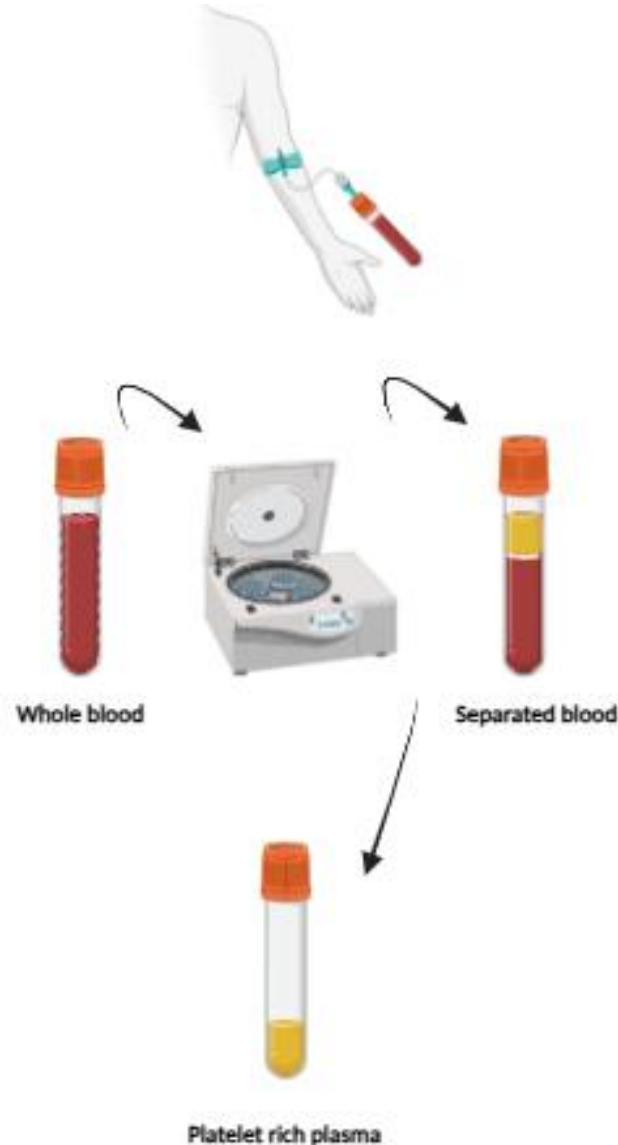
- A **concentrate of platelets** derived from patients' whole blood

- Known as a form of regenerative medicine that harnesses and amplifies the platelets and their **natural growth factors**

- Natural growth factors contribute to **cell proliferation, tissue proliferation, tissue remodeling, tissue repair**

- Examples of clinical applications of PRP currently:

1. Surgery (open wounds) – to speed up the wound healing process
2. Sports injuries – to stimulate tissue repair



Experimental overview

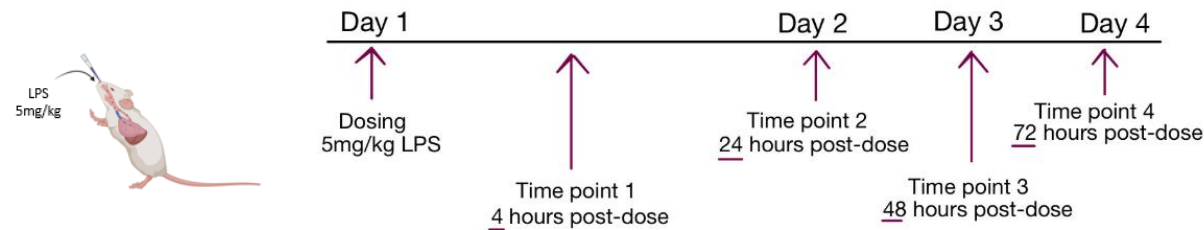
Investigating the feasibility of inhaling platelet formulations via nebulisation

1. Characterised an *in vivo* model of acute lung injury
2. Introduced platelets in this model of acute lung injury – helped reduce the levels of lung injury
3. Exploring how to deliver this therapy to humans

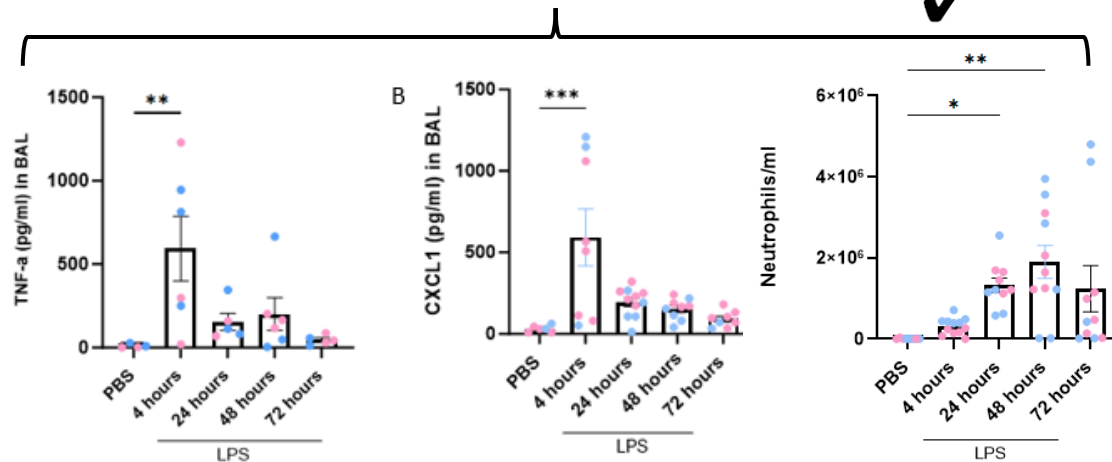
Validated an *in vivo* model of acute lung injury using the American Thoracic Society criteria

Kulkarni, H.S. *et al.* (2022) 'Update on the features and measurements of experimental acute lung injury in animals: An official American Thoracic Society Workshop Report', *American Journal of Respiratory Cell and Molecular Biology*, 66(2). doi:10.1165/rcmb.2021-0531st.

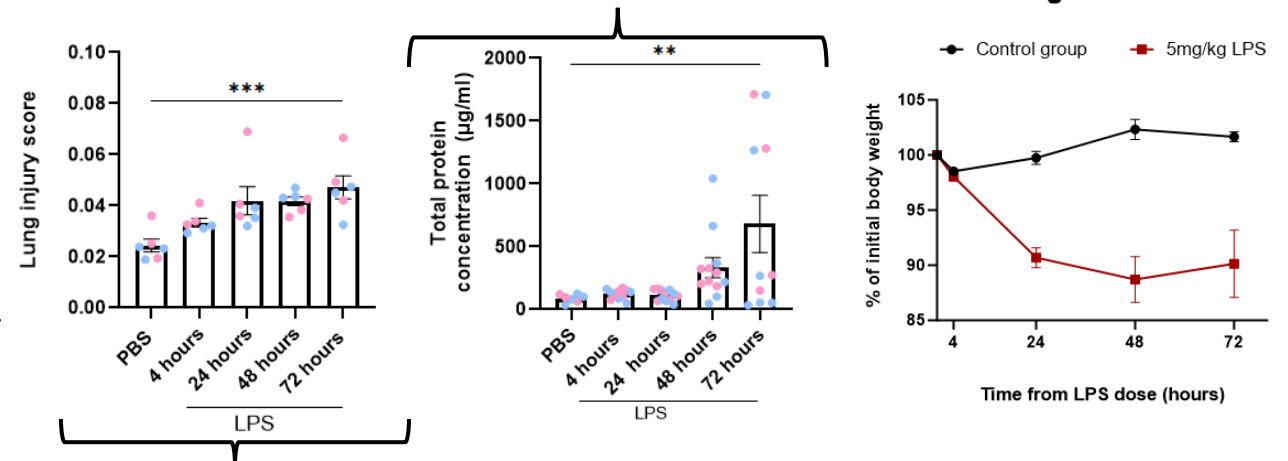
1. Presence of an inflammatory response 2. Histological evidence of tissue injury 3. Alteration of the alveolar-capillary barrier 4. Physiological dysfunction



1. Presence of an inflammatory response ✓

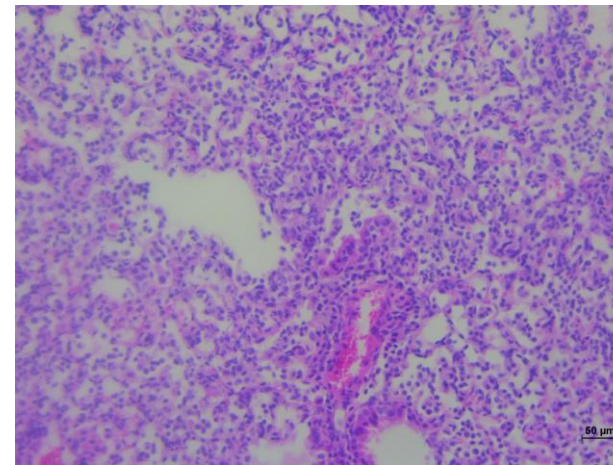
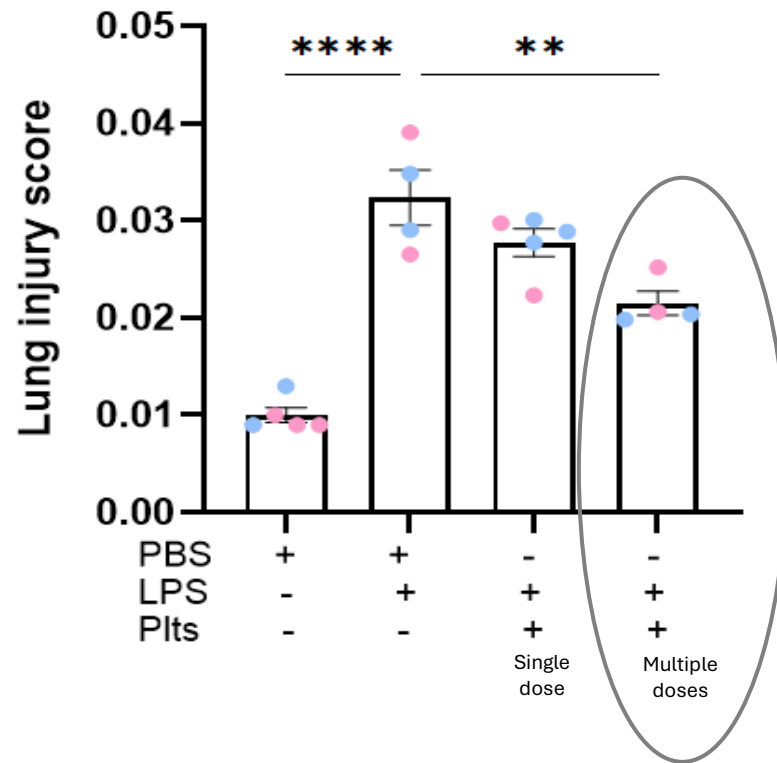
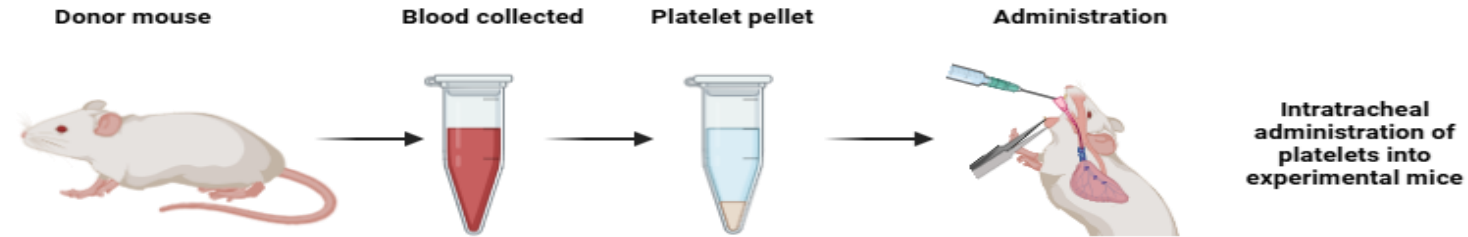


3. Alteration of the alveolar-capillary barrier ✓

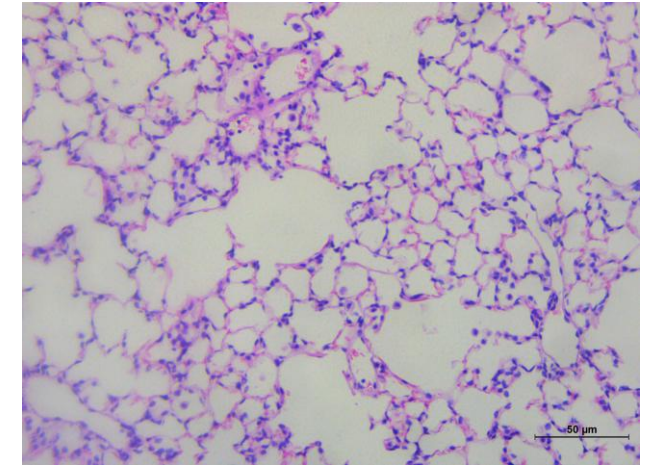


2. Histological evidence of tissue injury ✓

Platelet administration reduces LPS-induced lung injury

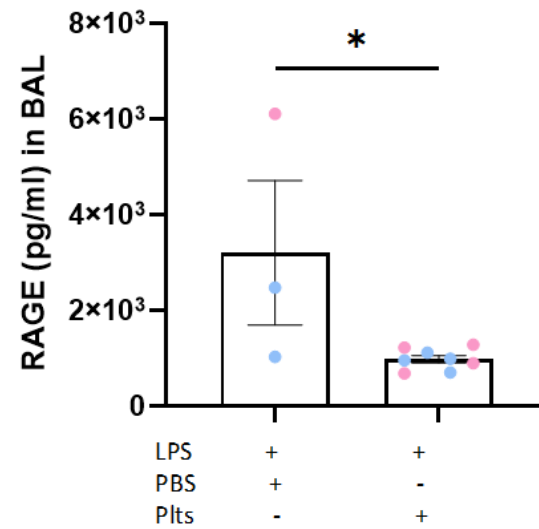
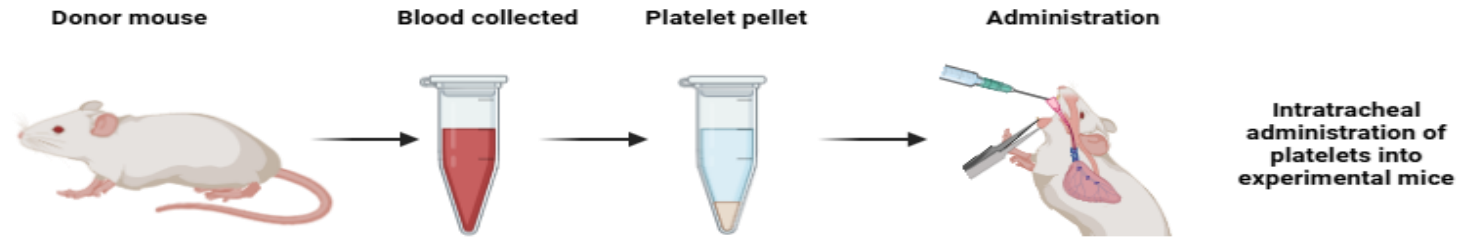


LPS + PBS

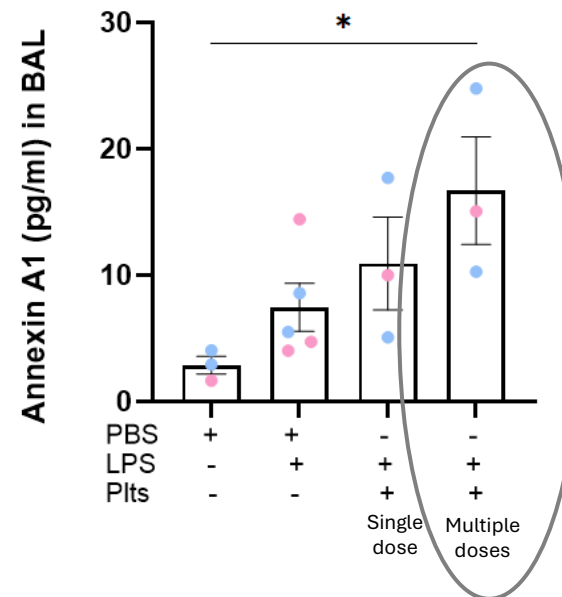


LPS + Platelets

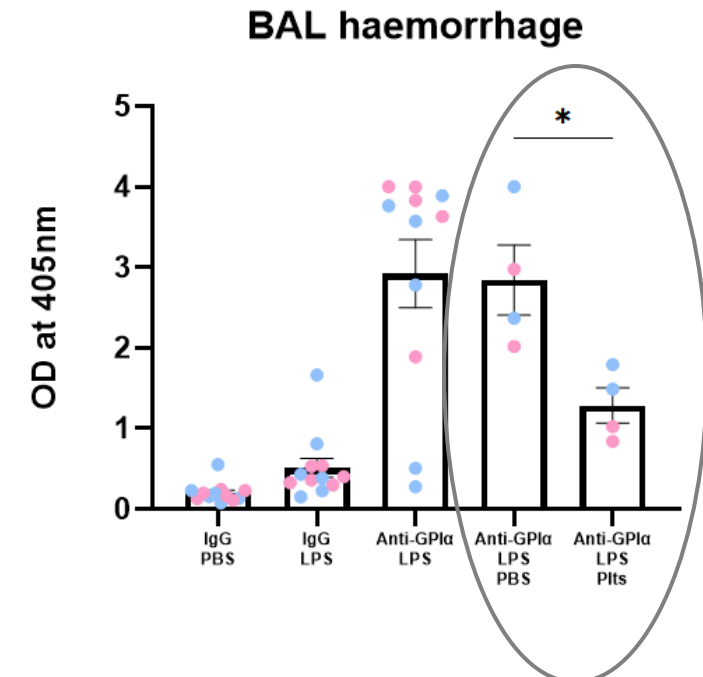
Platelet administration reduces LPS-induced lung injury



Rage = marker of epithelial damage



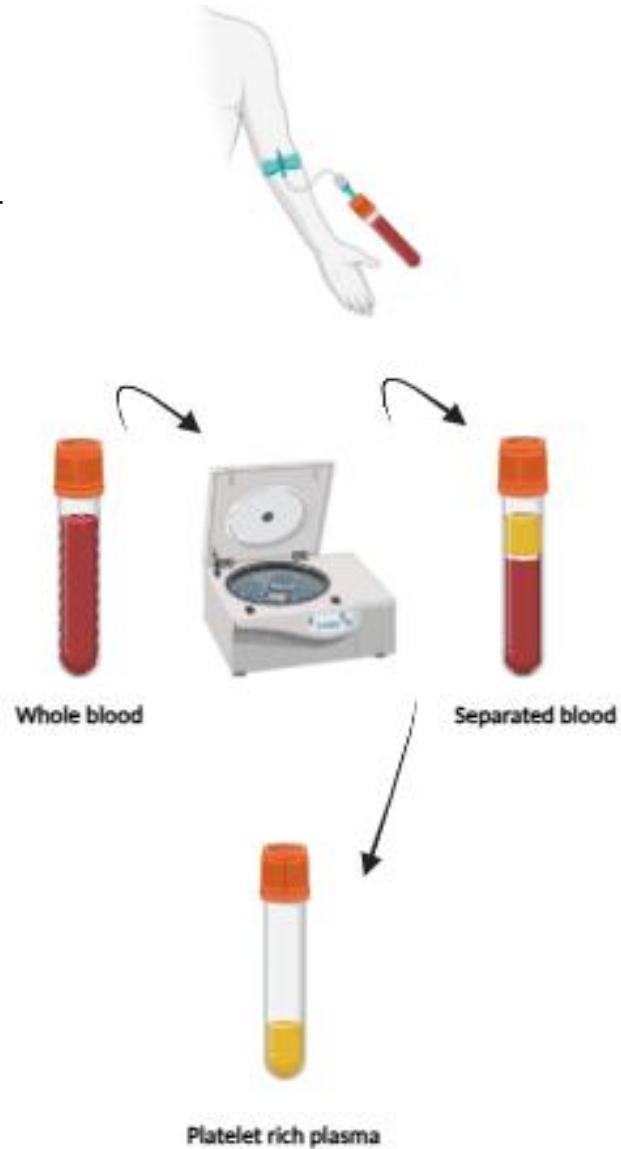
Annexin A1 = specialised pro-resolving mediator



BAL haemorrhage = blood in lungs

Effect of nebulisation on platelet function

Formulation:



Nebulisation

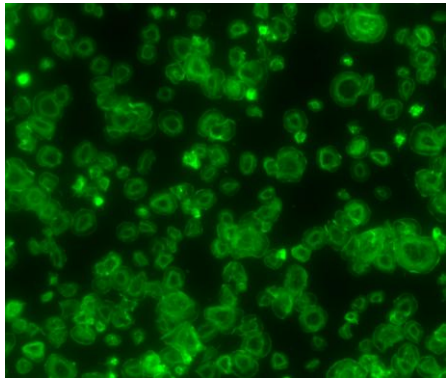


Aerogen Pro mesh nebuliser

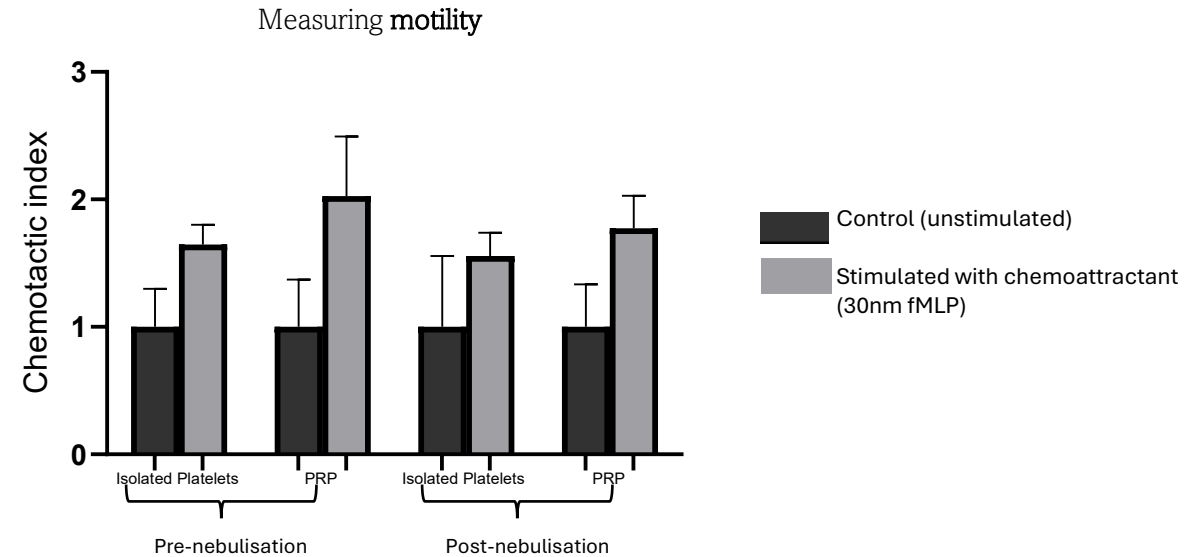
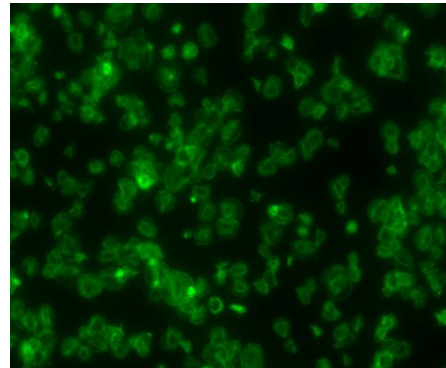
Effect of nebulisation on platelet function

Platelets remain intact

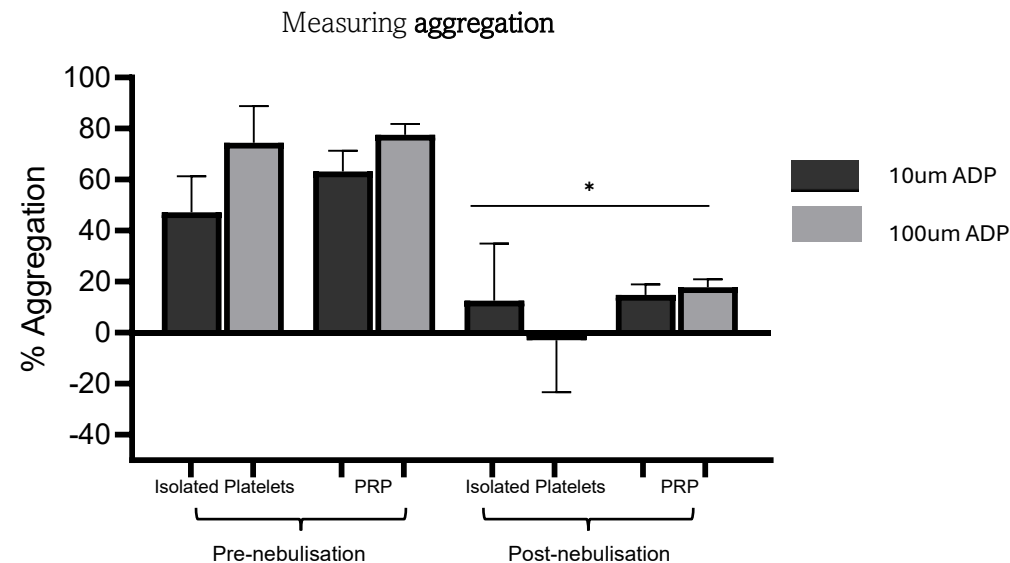
Pre-nebulised isolated platelets



Post-nebulised isolated platelets



Reparative and chemotactic activity maintained



Nebulisation reduces aggregation – a safety advantage

Summary

1. Characterised an *in vivo* model of acute lung injury

2. Introduced platelets in this model of acute lung injury – reduced the levels of lung injury

- Platelets provide **barrier support**
 - **Limit oedema** formation
- **Decrease** levels of **inflammation**

Focus on **replacement therapy** (PRP) rather than depletion therapy (anti-inflammatory agents that block key pro-inflammatory mediator pathways).

Could be developed as a novel therapy targeting mechanistic drivers of acute lung injury

3. How the nebulisation process affects 2 main platelet functions

- **Chemotactic** function remains **intact**
- Platelet **aggregation** is **reduced**

Future work involves optimising formulation and delivery conditions to maximise function and ensure pulmonary safety

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