COPD model

-SMC's CRO services-

SMC Laboratories, Inc.

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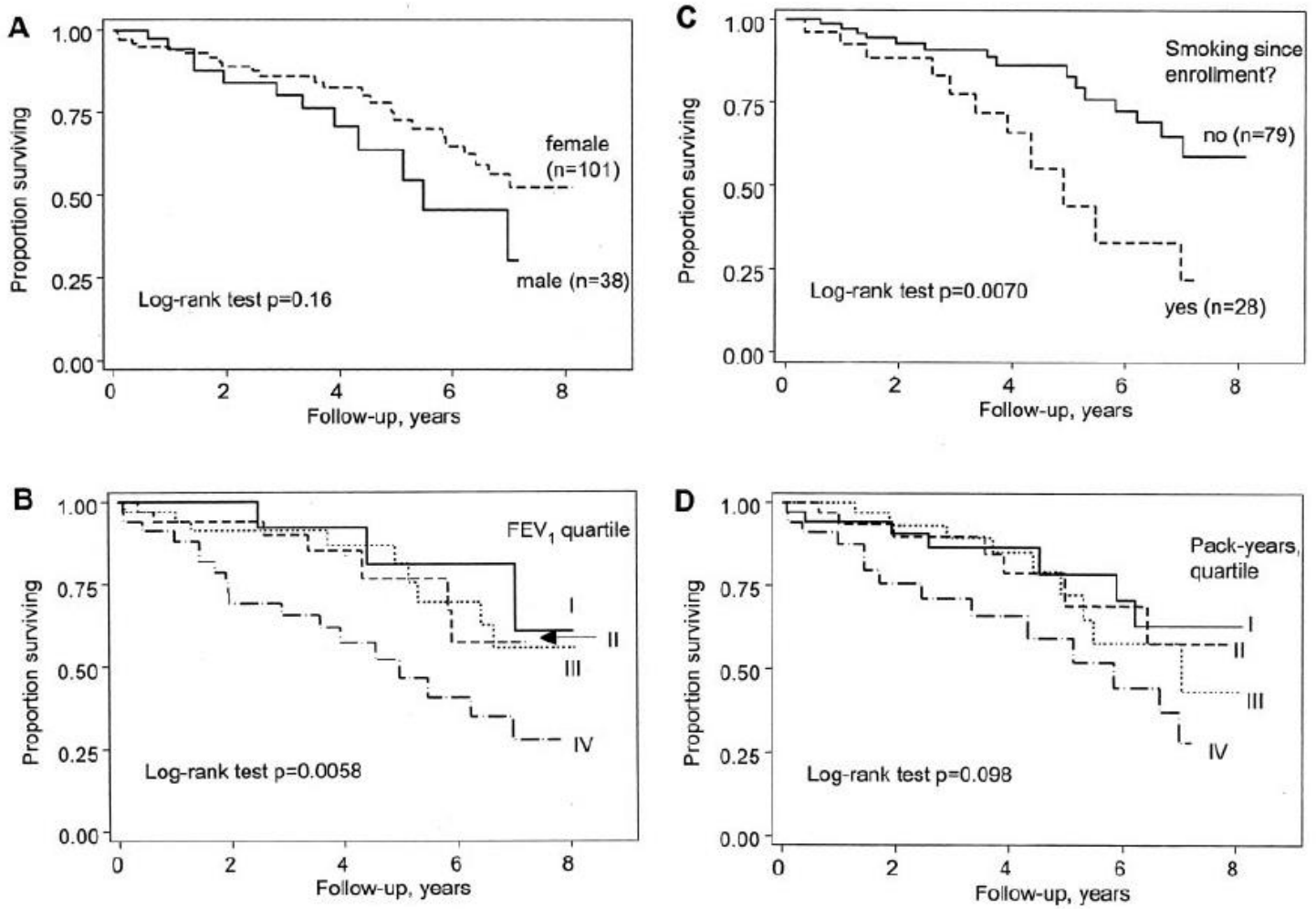
Ver. 2021.1

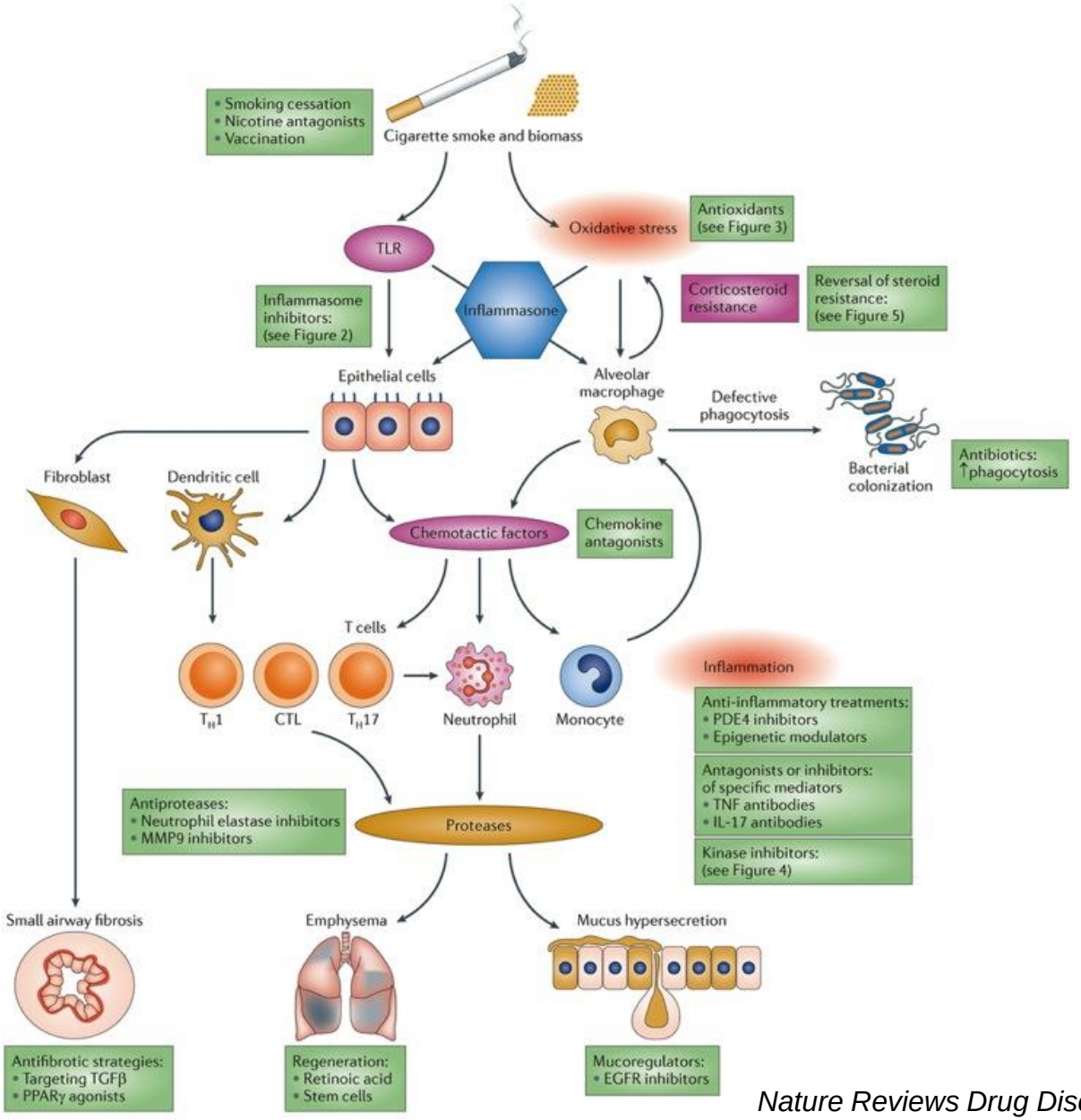
COPD as a life-limiting illness



- COPD is recognized as a major cause of death in developed countries.
- COPD is characterized by chronic, slowly progressive airway obstruction and destruction.
- FEV1 is reported to be the best single correlate of mortality.
- FEV1 is also used to define the staging of disease severity in recent COPD guidelines.

CHEST 2004;126:1443–1451

Therapeutic targets in COPD



Nature Reviews Drug Discovery 2013;12:543–559

SMC's advantages in pharmacology study in COPD model

■ SMC's pharmacology study service offers

-**Porcine Pancreatic Elastase (PPE)**-induced emphysema model which can be used for evaluation of anti-COPD therapeutic candidates

-Sampling scheme allowing multiple analyses in a single mouse (histology, gene expression, biochemistry and BALF analysis*)

-**Expert histology** based on the knowledge of fibrotic/inflammatory diseases

-In-life evaluation of emphysematous lesions by **CT scan** as in clinical studies

*Histology and BALF analysis are incompatible in the COPD model.

■ Performance

- **Over 20 test substances have been evaluated in lung disease filed**
- **Both small-molecule compounds and antibodies were experienced**

Current animal model for COPD

Model	Pathology	Positive of Model	Negative of Model
Cigarette Induced COPD	Dilated alveolar ducts, abnormal parenchyma and increased numbers of goblet cells. Pulmonary function tests show decrease in effectiveness.	The most similar to the human disease in terms of that produces emphysema.	It is not debilitating in animals. Lesion do not progress beyond a certain point to mimic the human disease.
Apoptosis Induced COPD	Induction of air space enlargement. Matrix breakdown.	Induces enlarged airspaces in short period of time.	Pathophysiological mechanisms are not permanent.
Elastase Induced COPD	Increased numbers of neutrophils, elevated elastase	Rapid and easy onset, easy to measure functional changes and possibly relevant to the repair and remodeling issues in COPD.	Mechanism of disease induction is secondary to the initiators of clinical COPD.
Starvation-Induced COPD	Decreased lung volume, changes in lung structure and function	Limited variability and short term impact on disease development.	Compassionate care of animals. The pathology may be due to decreased repair mechanisms.
LPS Induced COPD	Produces enlarged airways in chronic scenarios. Matrix metalloproteinase production.	Short-term model with parenchymal changes.	Inflammatory differential is not the same as pollutant induced insult which may reflect different mechanisms of pathophysiology.

Tracey L. Bonfield (2012). In Vivo Models of Lung Disease, Lung Diseases - Selected State of the Art Reviews, Dr. Elvisegran Malcolm Irusen (Ed.), ISBN: 978-953-51-0180-2, InTech, Available from: http://www.intechopen.com/books/lung-diseases-selected-state-of-the-art-reviews/in-vivo-models-of-lungdisease

Similarity of human and experimental emphysema

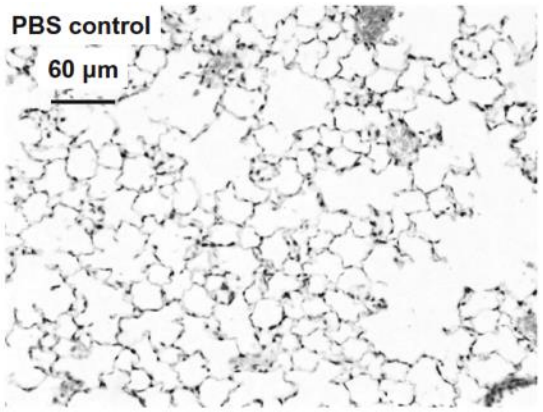
Features	Human emphysema	Elastase-induced emphysema	Smoke-induced emphysema
Cachexia	Yes	Yes	Yes
Time of development	Long	Brief	Long
Progression of disease after stimuli cessation	Yes	No	No, regression of lesions
Endurance reduction	Yes	Yes	Yes
Epithelial and endothelial cell apoptosis	Yes	Yes	Yes
Extracellular matrix degradation	Yes	Yes	Yes
Type of lesion	Centrilobular/Panacinar/Irregular	Panacinar	Centrilobular
Presence of oxidative stress	Yes	Yes	Yes
Respiratory muscle weakness	Yes	Yes	Yes
severity	Mild/Moderate/Severe	Depends on the enzyme dose	Mild
Presence of systemic alterations	Yes	Yes	Yes

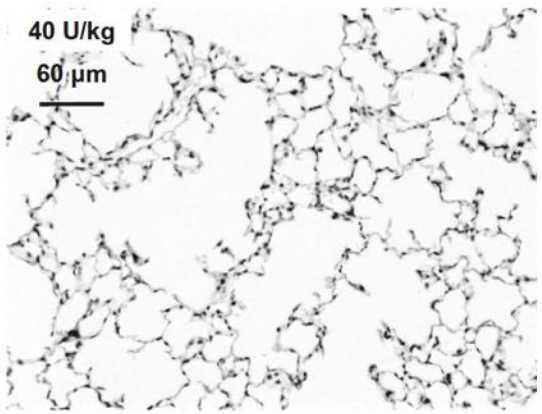
- Histological and morphological characteristic features are compatible with those of panacinar emphysema
- Lesion severity can be modulated by enzyme dose
- Induced morphological and functional changes are detectable in the long term

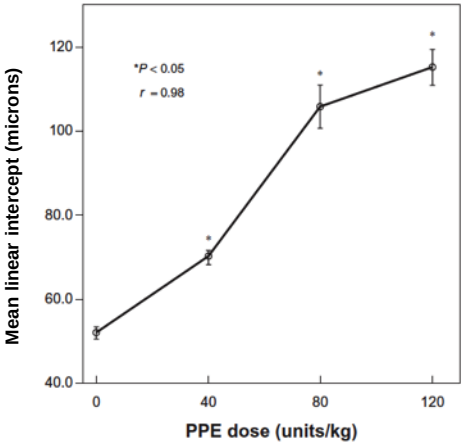
⇨ ***Elastase emphysema has become a useful tool to validate variety of new drugs and interventions***

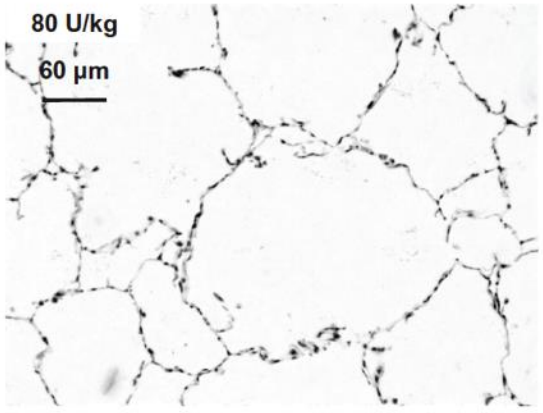
An Acad Bras Cienc 2011;83:4

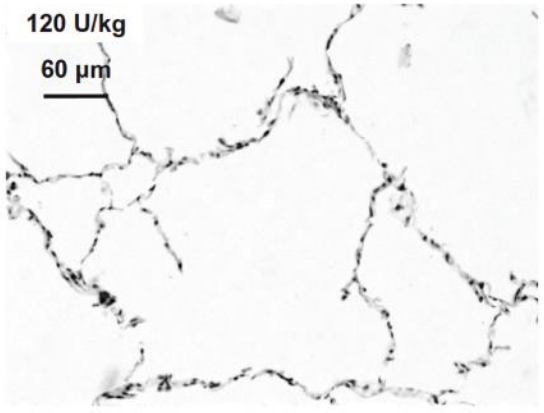
Dose dependency of PPE-induced emphysema model

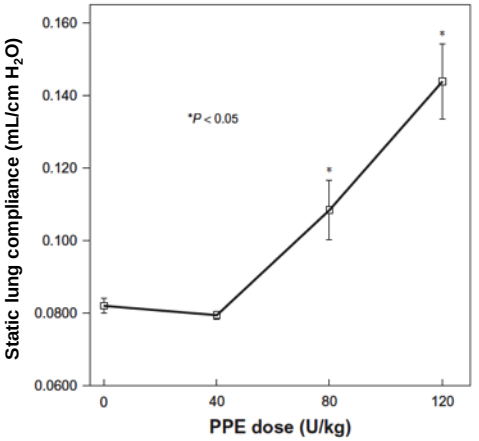












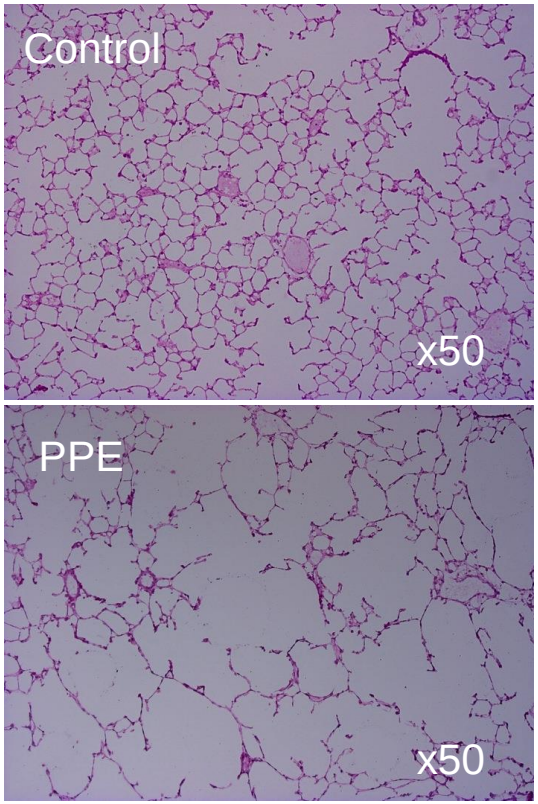
- Intratracheal instillation of increasing doses of PPE yields a scale of progression from mild to severe emphysema.

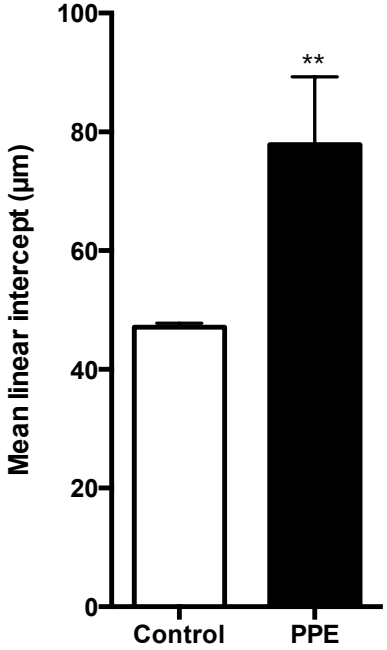
⇨ ***Elastase emphysema model can be adjust to replicate the severer to mild emphysema by the instillation doses***

International Journal of COPD, 2012;7:235-243

Primary endpoint: Mean linear intercept

- Representative microphotographs HE stained lung sections



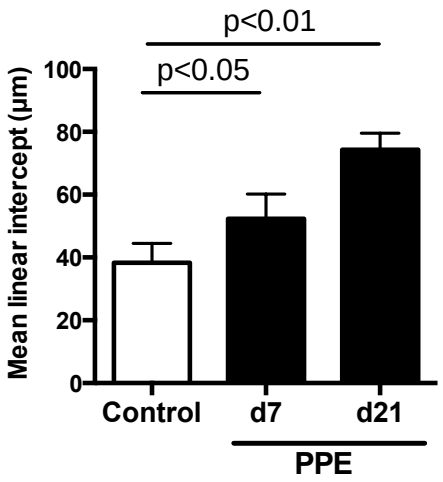


Mean linear intercept is

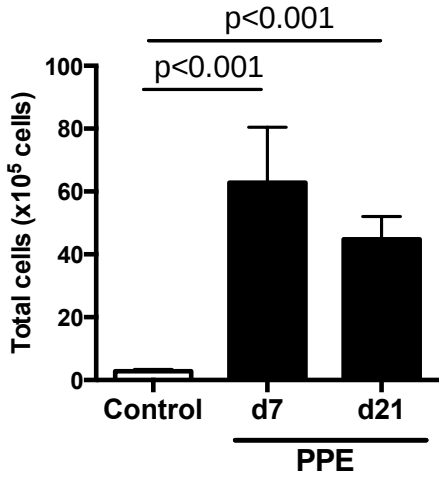
- simple method of estimating severity of pulmonary emphysema using HE-stained section
- widely used in to estimate air space size for sensitivity and efficiency of measurement

COPD model: Disease progression

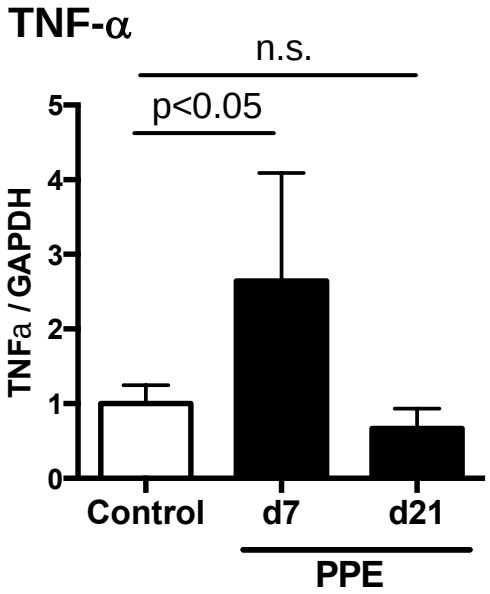
- Mean linear intercept

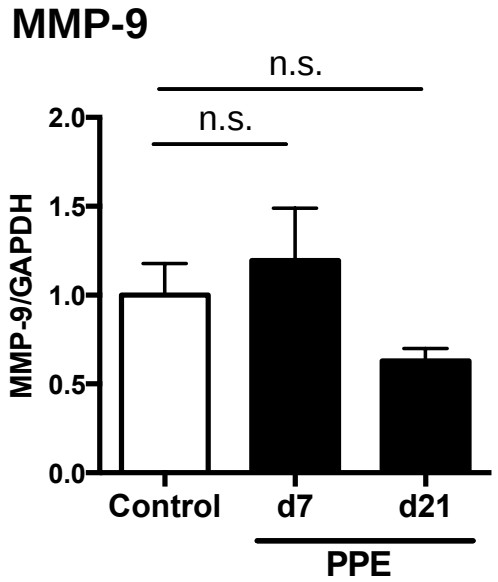


- BALF total cells



- Gene expression

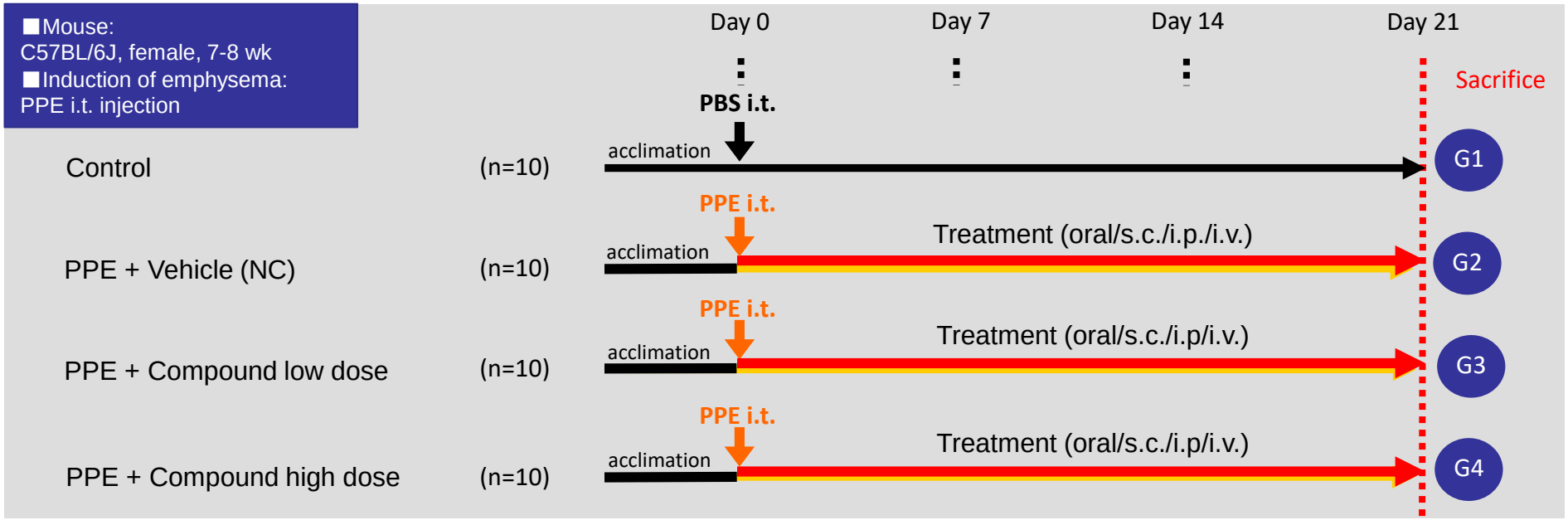




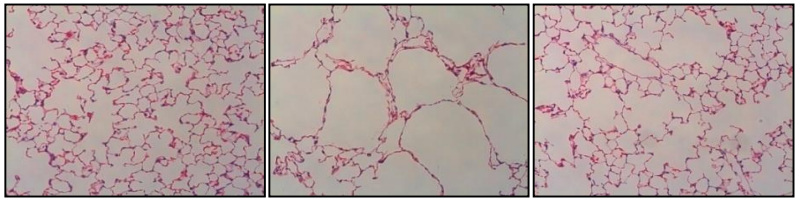
(Mean ± SD, n=4)

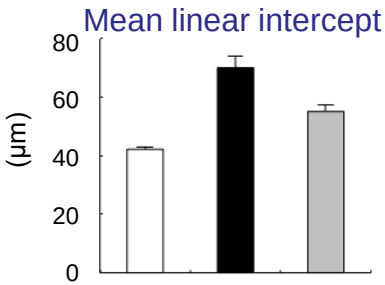
Study plan for assessing effects of compounds in PPE-induced emphysema model in mice

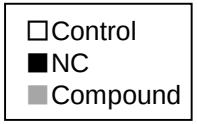
■Mouse:
C57BL/6J, female, 7-8 wk
■Induction of emphysema:
PPE i.t. injection

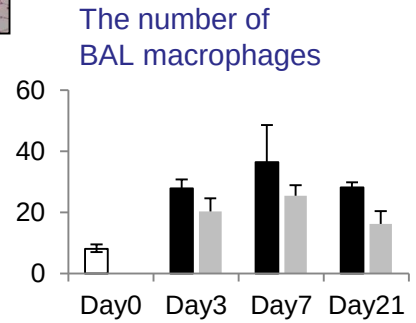


Study design
■Arm: 4
Control, Vehicle, Test substance x 2 doses
■The number of mice/group before dosing: n=10
■Baseline: day 0 (just prior to PPE inhalation)
■Randomization: Body weight at day 0
■Treatment period: 3 weeks
■Endpoints (day 21):
Mean linear intercept (HE)
<Analytical items>
BAL: cell number, ELISA
Gene expression in the lung
Immunohistochemical staining
CT (option)
General condition (BW, lung volume)









BALF: bronchoalveolar lavage fluid, oral: oral administration, s.c.:subcutaneous injection, i.t.: intratracheal injection, i.p.: intraperitoneal injection, i.v.:intravenous injection
NC: Negative Control