Pulmonary Macrophage Transplantation Therapy

Rare Pediatric Respiratory Disease: Science Shapes Precision Care Conference
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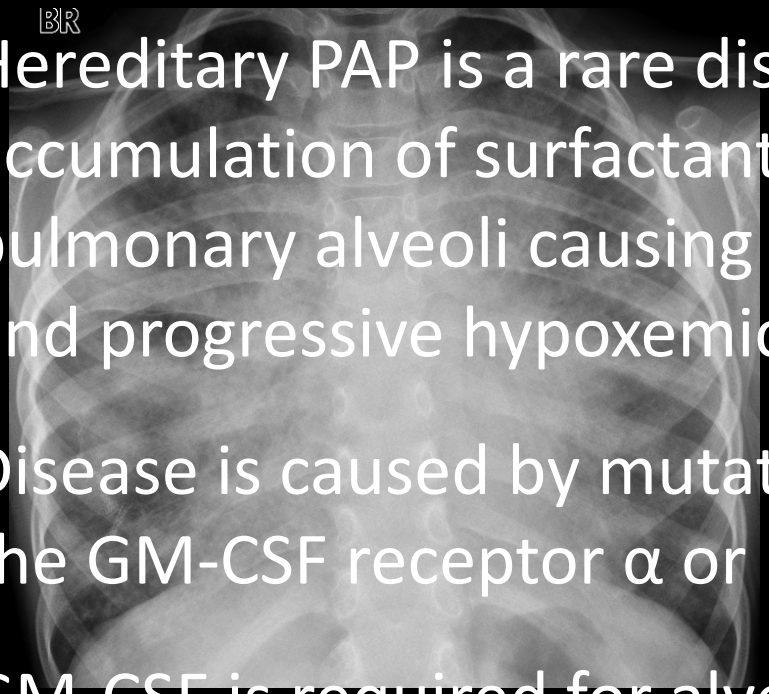
Bruce Trapnell, M.D.
Director, Translational Pulmonary Science Center
Professor of Medicine and Pediatrics
University of Cincinnati Medical Center

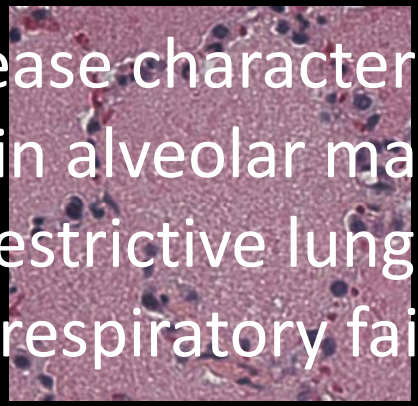
Cincinnati Children's
UNIVERSITY OF Cincinnati
TPSC
RARE LUNG DISEASES CONSORTIUM

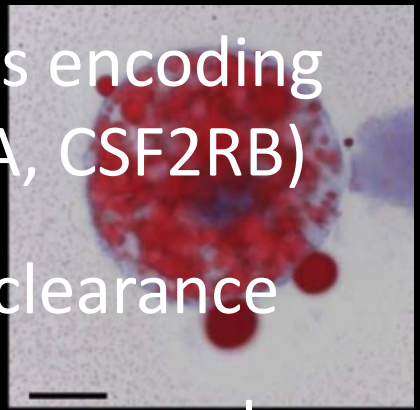
Outline

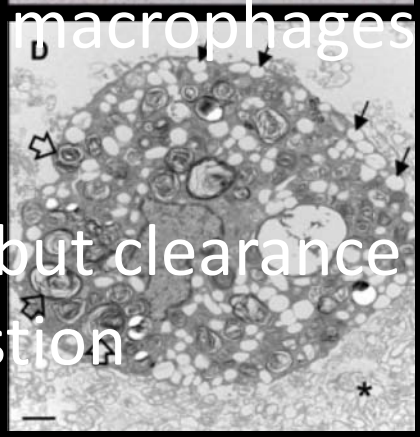
- Background
  - Hereditary pulmonary alveolar proteinosis (hPAP)
  - Validated model – *Csf2rb*-/- mice (KO)
- Pulmonary macrophage transplantation (PMT) therapy
  - Overview of approach
  - Therapeutic efficacy
  - Cell localization, engraftment, differentiation
  - Safety
  - WT versus gene-corrected macrophages
  - Nonclinical data status
  - Clinical trial plan

Hereditary pulmonary alveolar proteinosis (hPAP)









Hereditary PAP is a rare disease characterized by accumulation of surfactant in alveolar macrophages and pulmonary alveoli causing restrictive lung impairment, and progressive hypoxemic respiratory failure

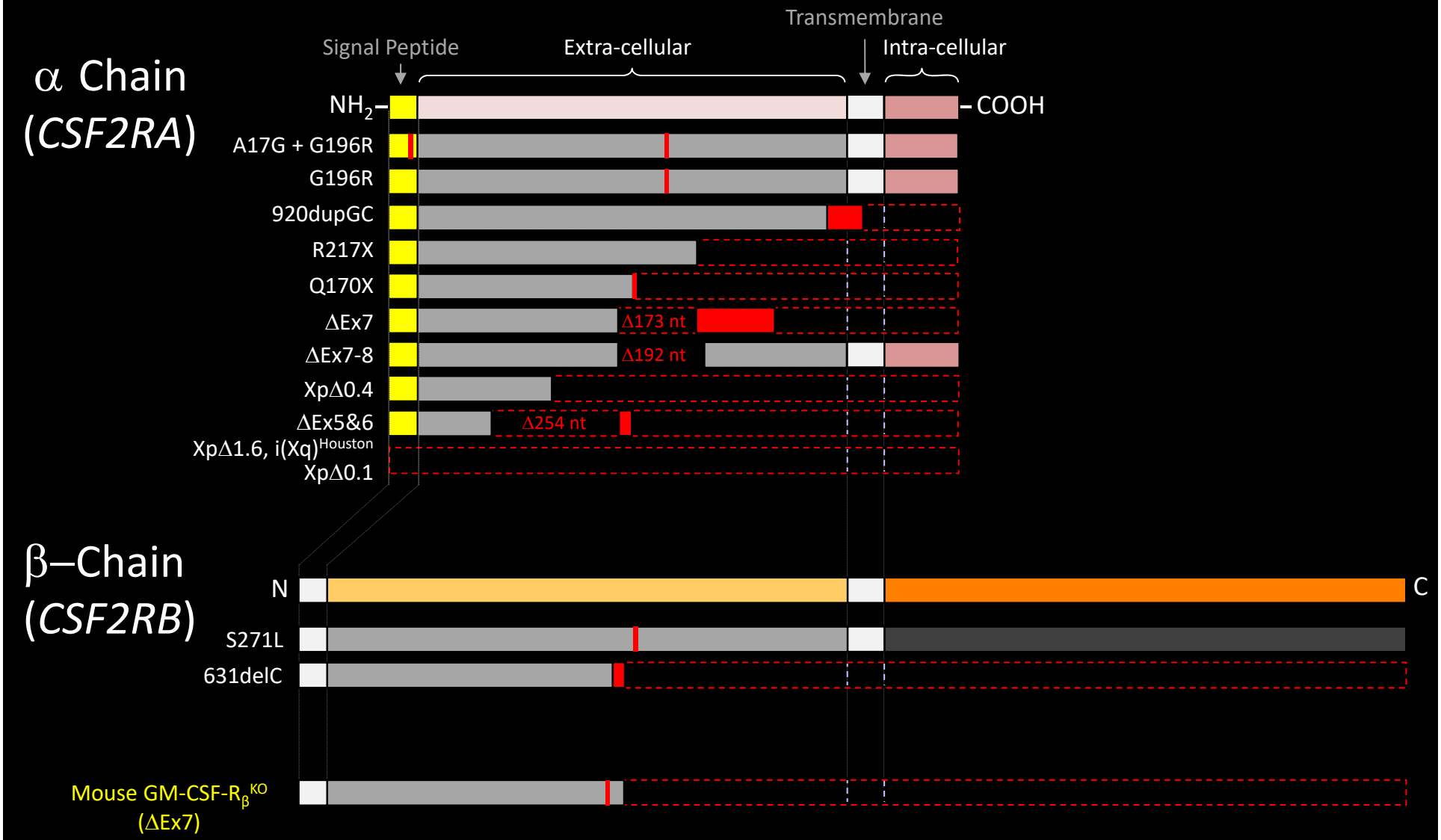
Disease is caused by mutations in the genes encoding the GM-CSF receptor α or β chains (CSF2RA, CSF2RB)

GM-CSF is required for alveolar surfactant clearance

GM-CSF regulates cholesterol clearance by macrophages constitutively and in reversible fashion

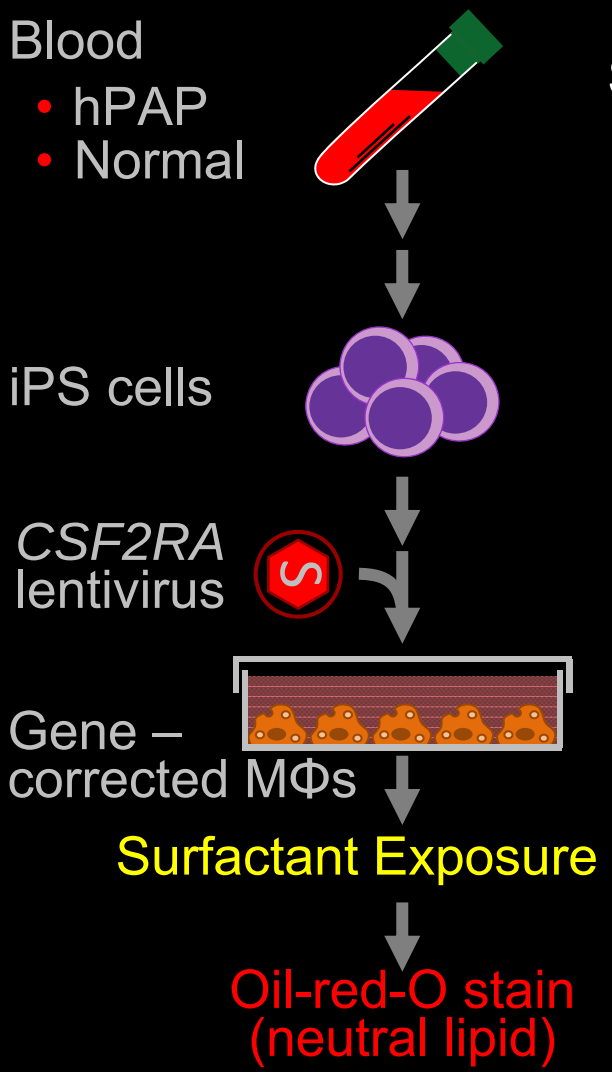
Surfactant catabolism is not impaired PAP, but clearance is reduced secondary to cholesterol congestion

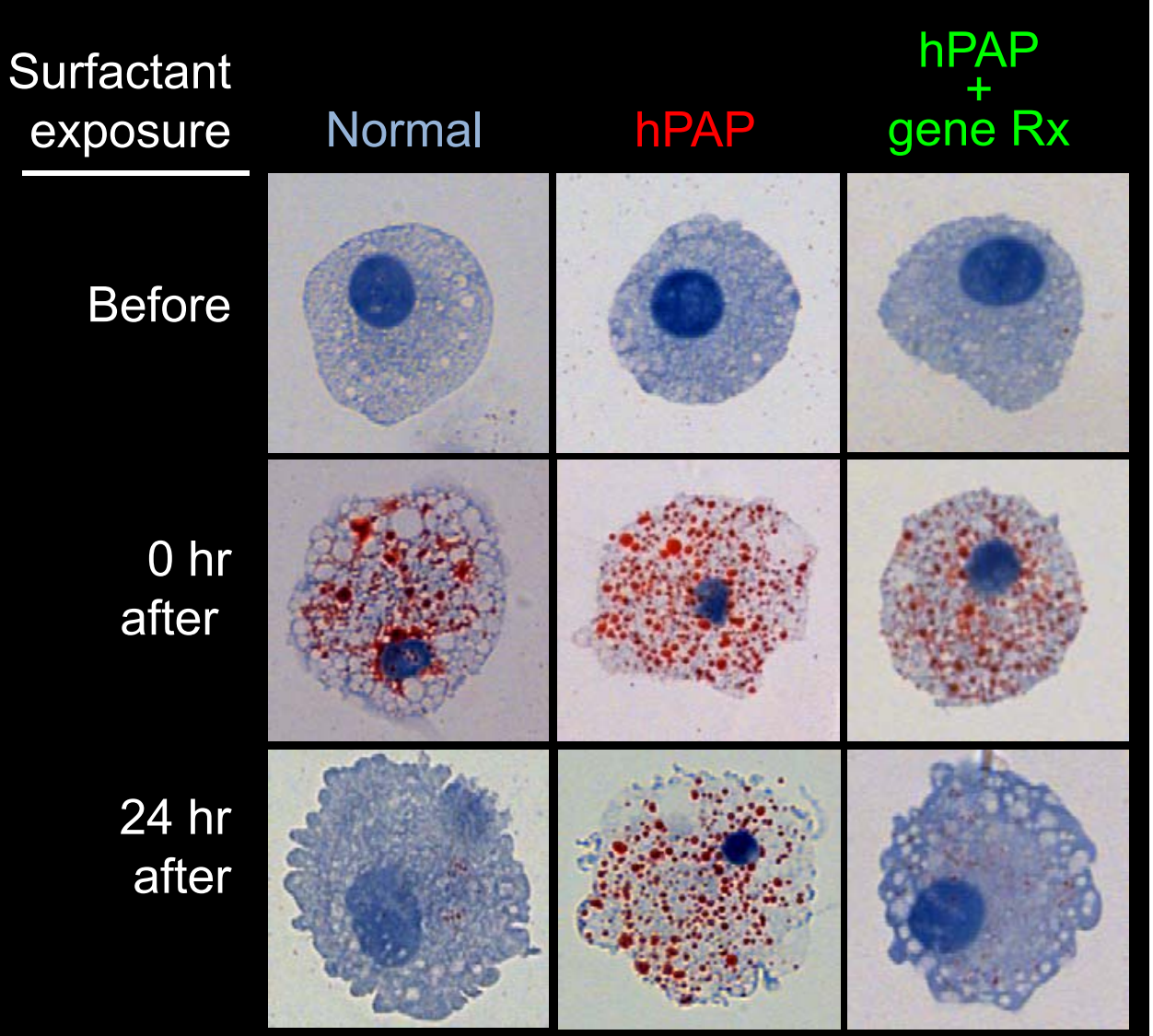
CSF2RA/B mutations known to cause hPAP



Adapted from: Suzuki… *AJRCCM*, 2010

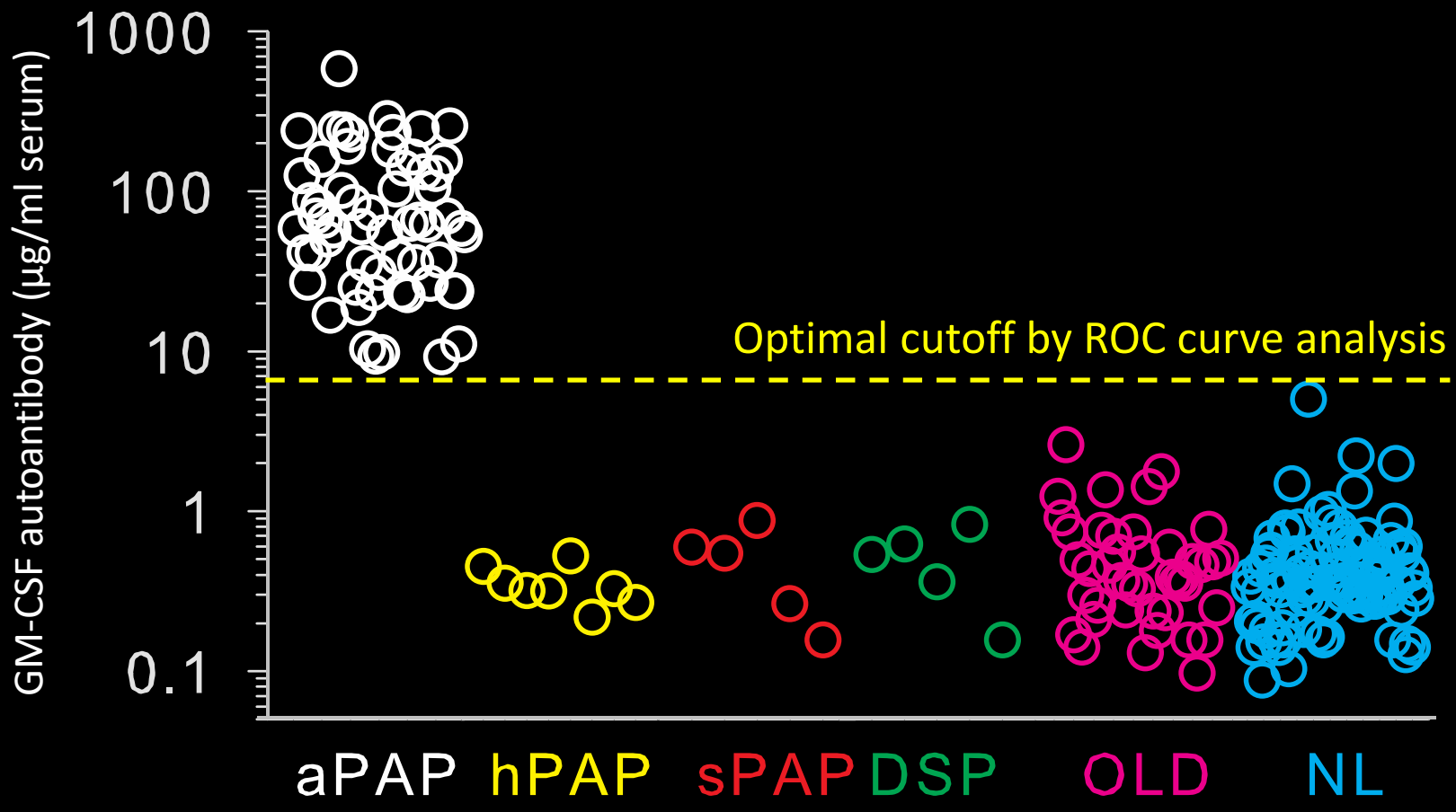
hPAP Pathology Reproduced in iPS Cell-Derived Macrophages





Suzuki… *AJRCCM.* 189: 183-193; 2014

Serum GM-CSF Autoantibody ELISA Test

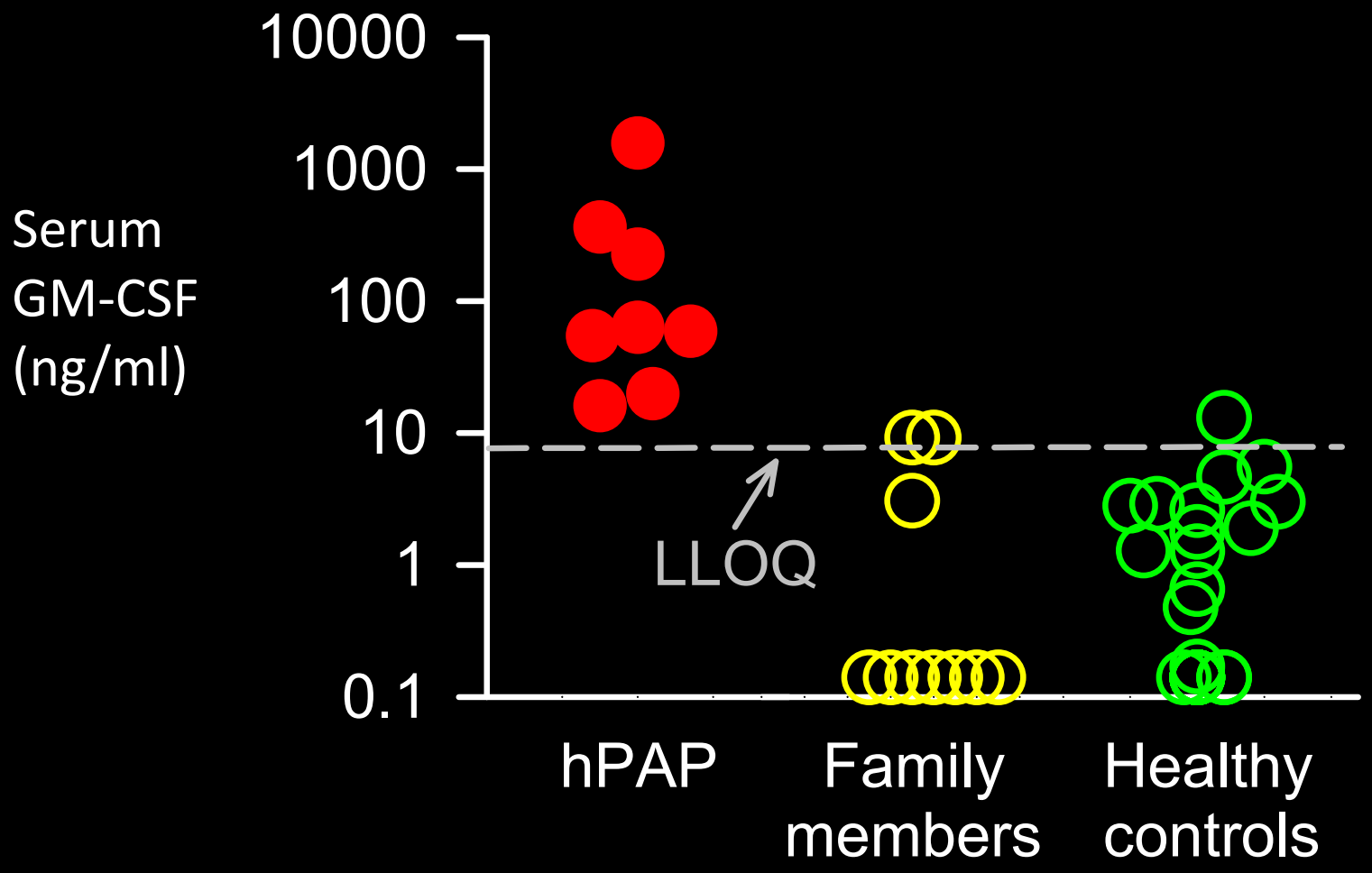


Sensitivity & specificity = 100% based on ROC analysis

Adapted from Uchida et al. J, Immunologic Methods. 402: 57-70; 2014

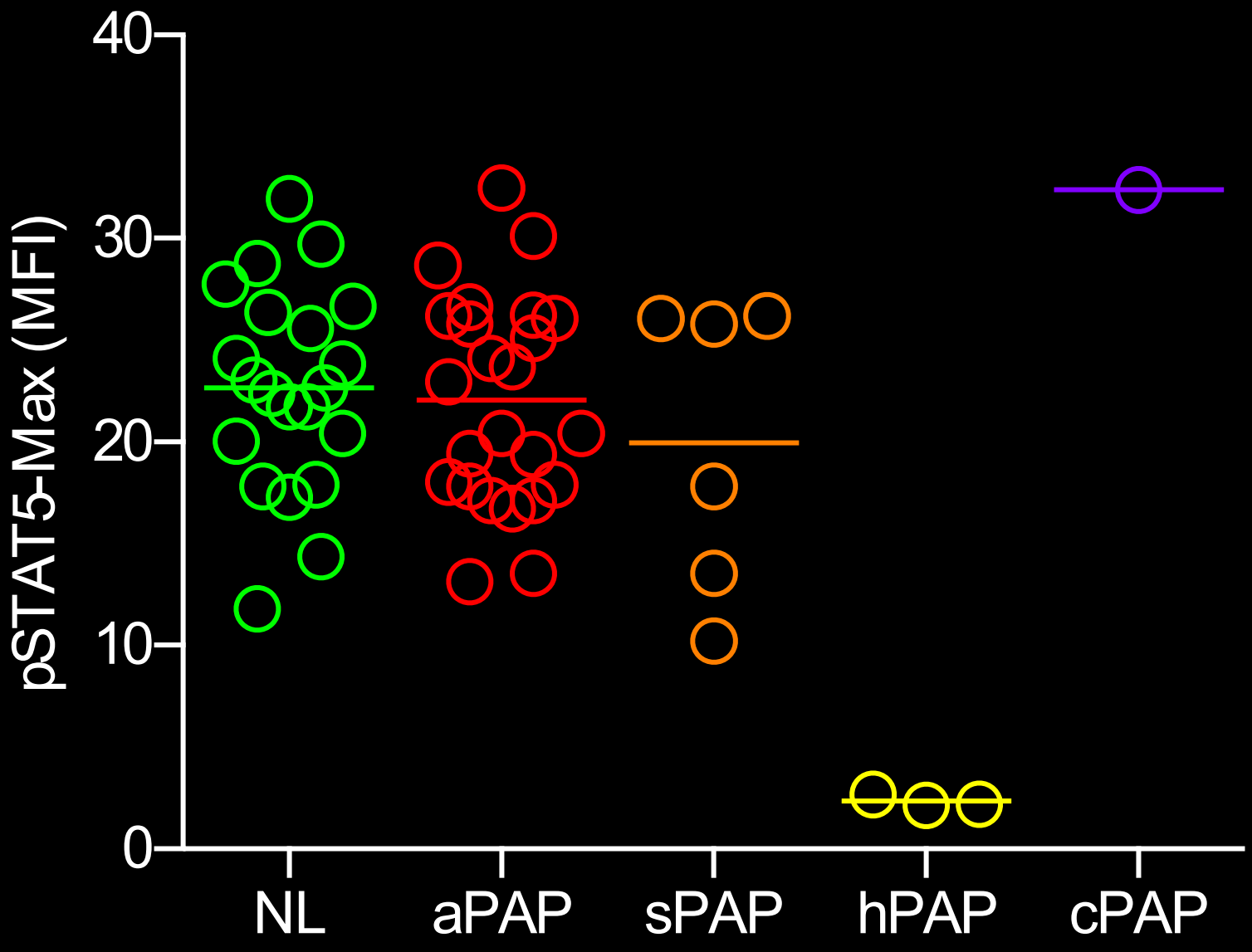
Serum GM-CSF Concentration

- Routine ELISA performed using serum
- Used to screen for GM-CSF receptor dysfunction

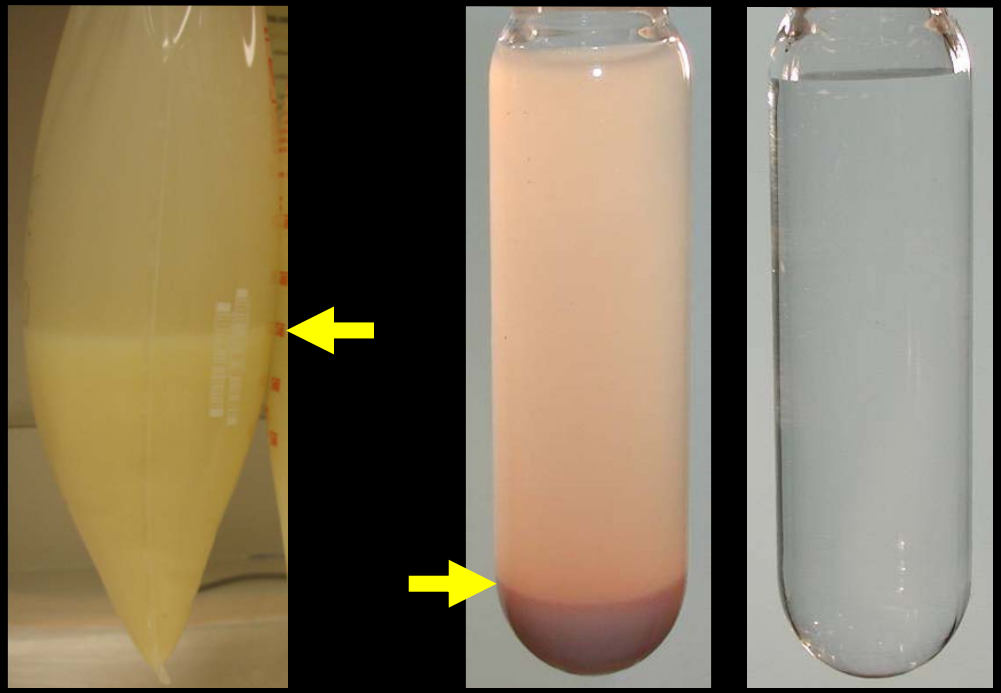


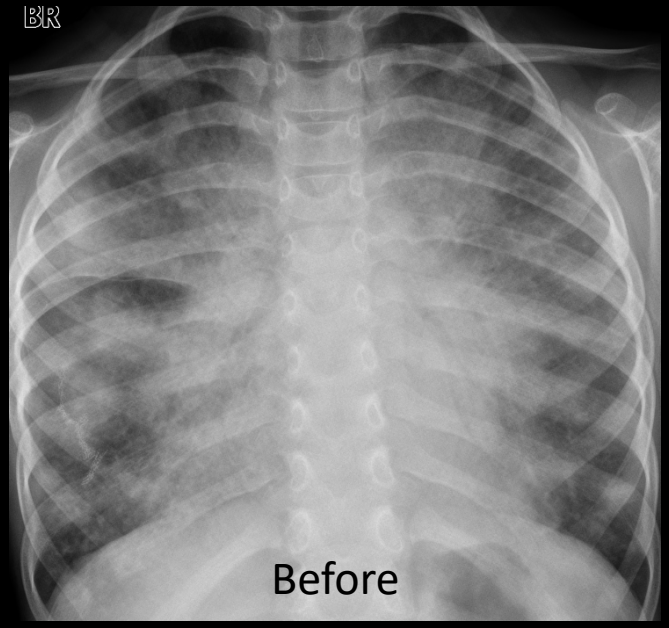
Suzuki, et al *AJRCCM.* 182: 1292-1304; 2010.

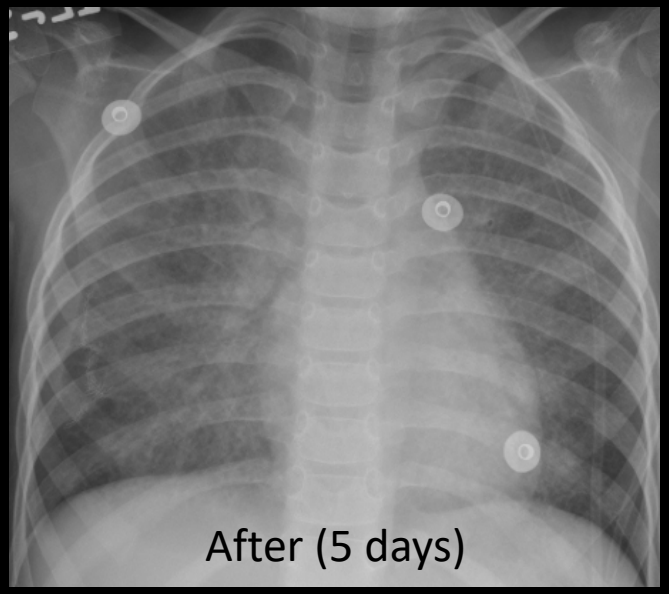
GM-CSF Signaling pSTAT5-Max Identifies Hereditary PAP



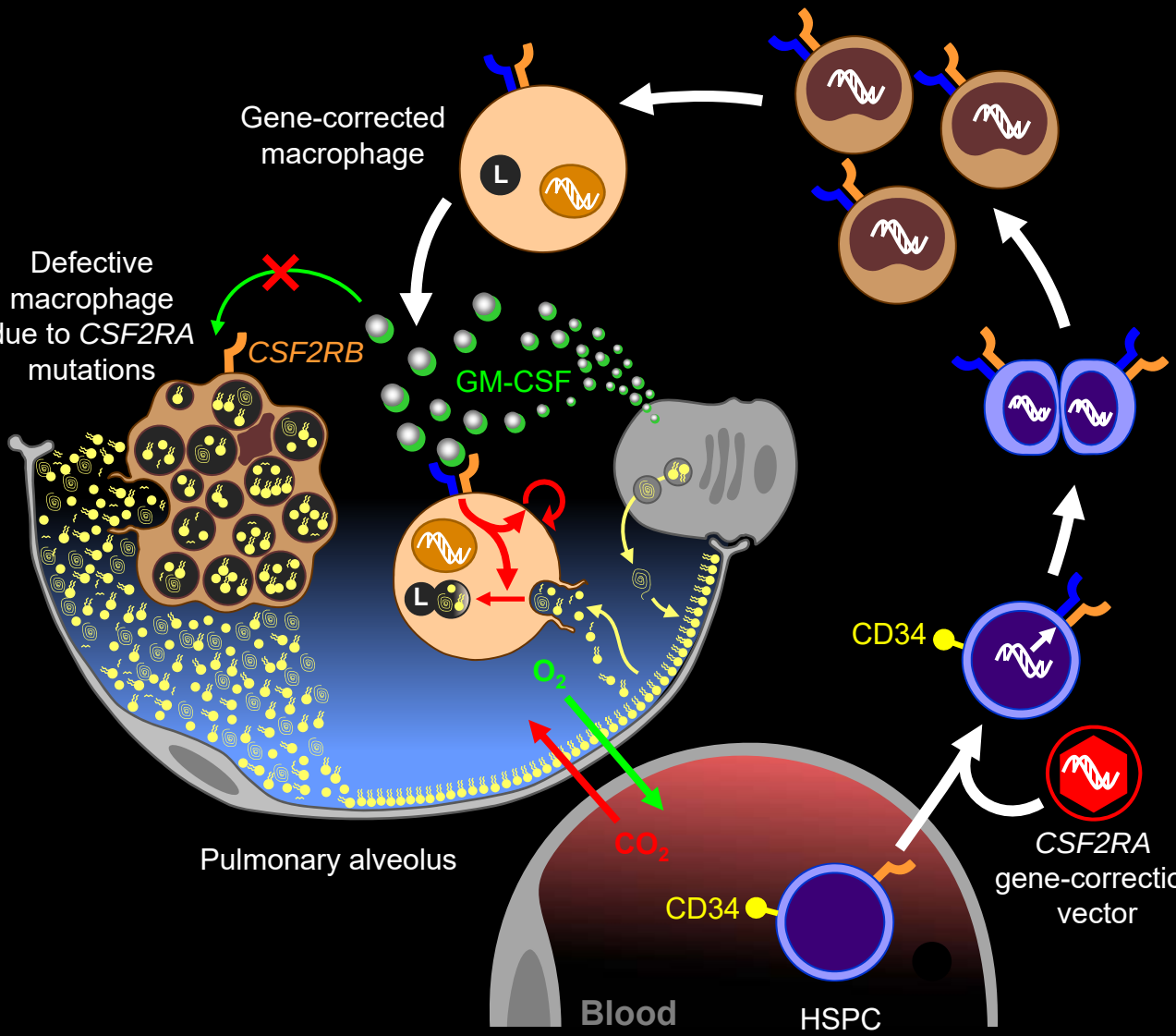
Current Therapy: Whole lung lavage



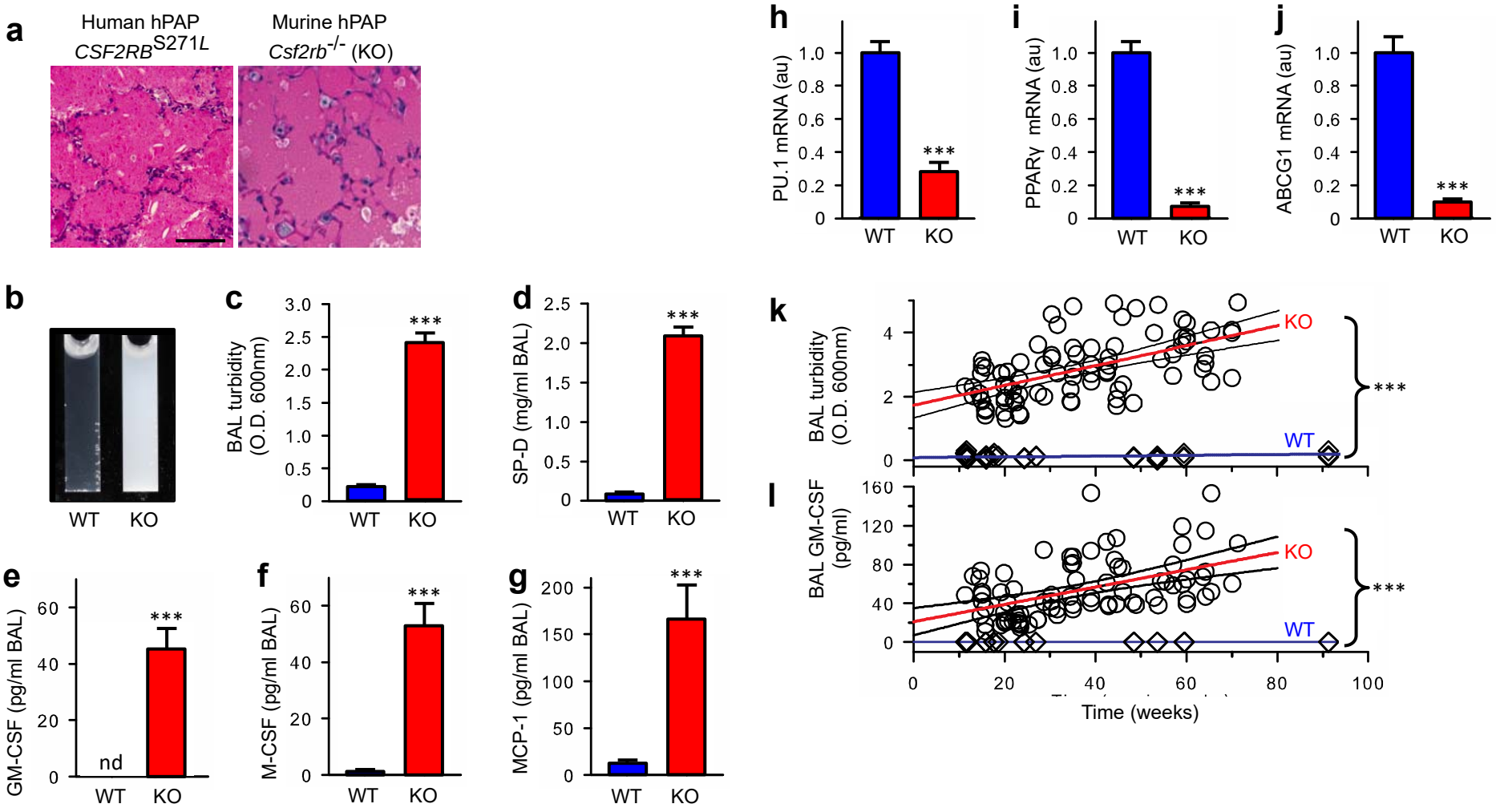




PMT therapy of hereditary PAP

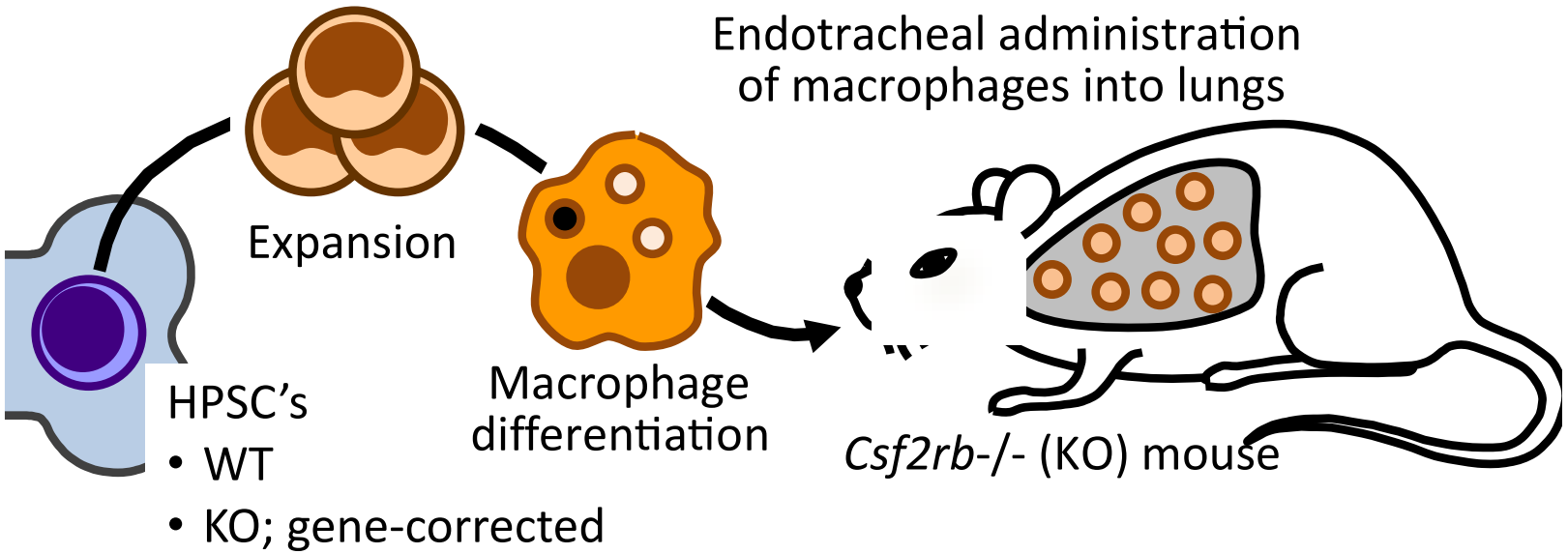


Csf2rb-/- (KO) mice recapitulate human hPAP



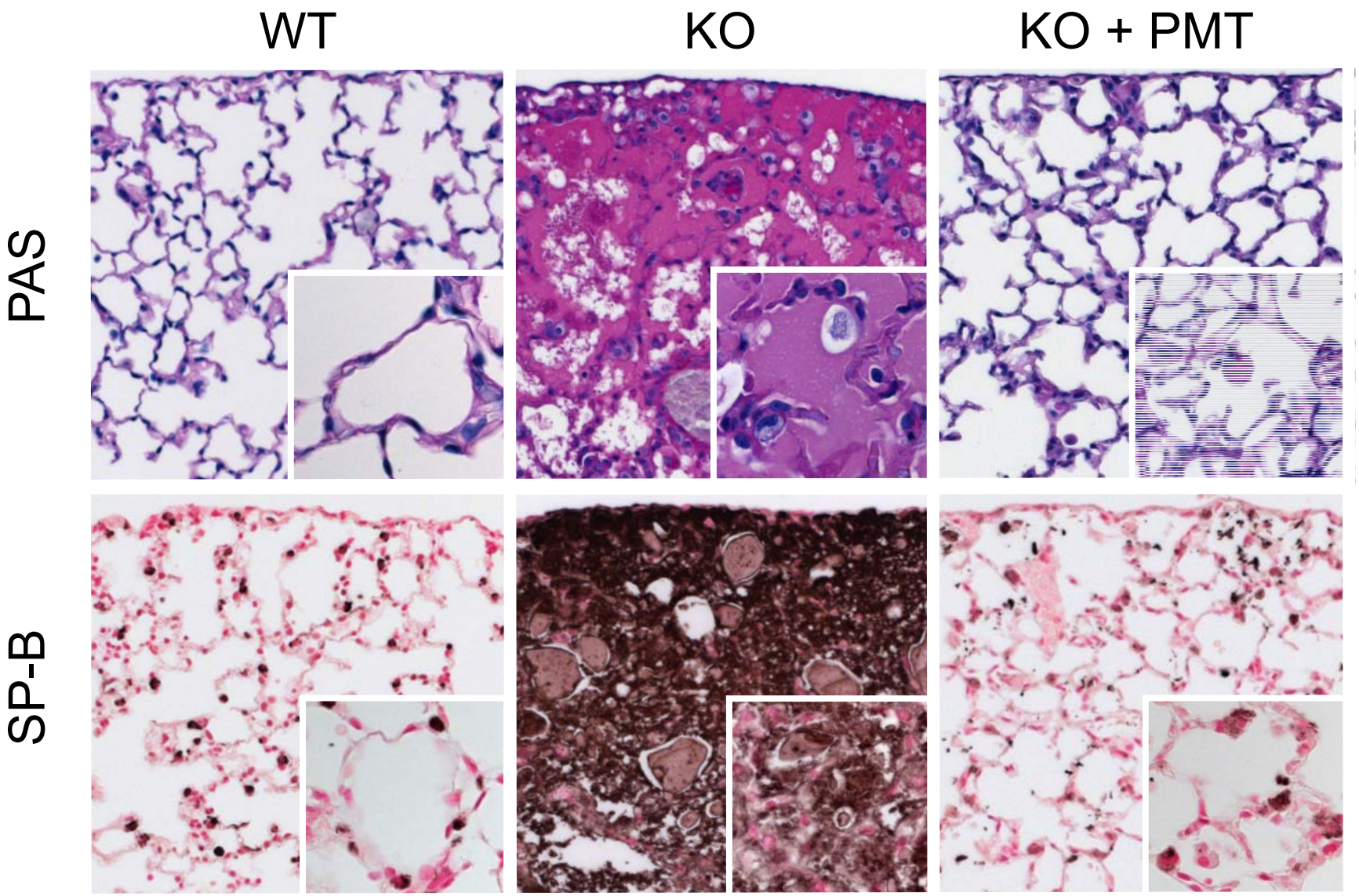
Suzuki… *Nature*, 2014.

Preclinical evaluation of PMT therapy of hPAP



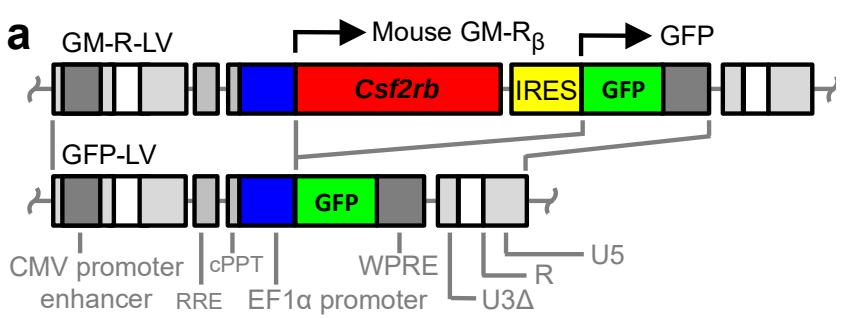
Suzuki… *Nature*, 2014.

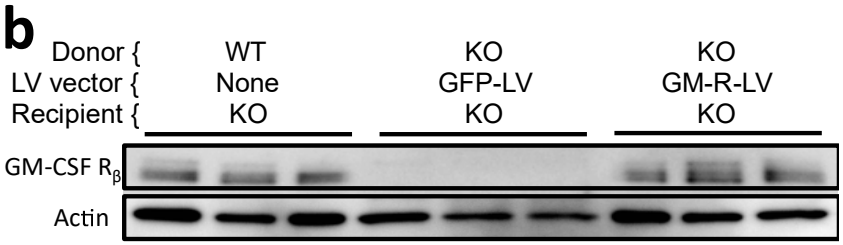
Lung histology 1 year after PMT

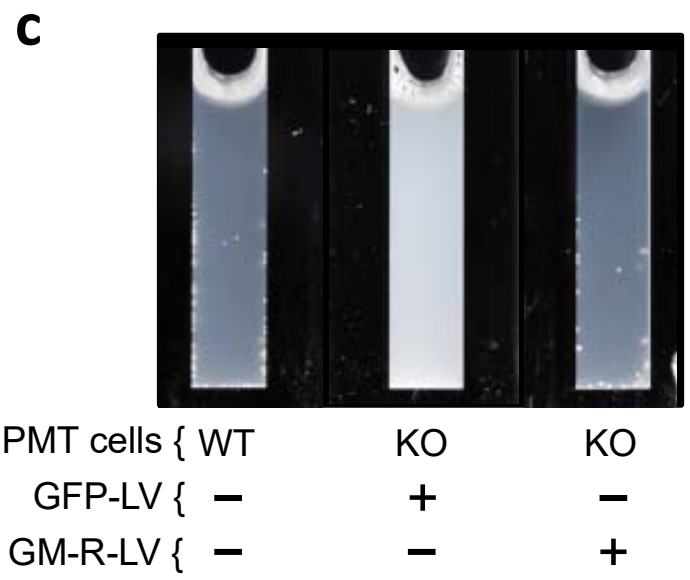


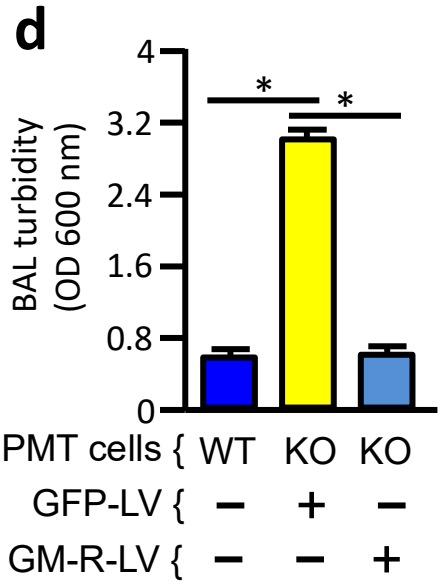
Suzuki. *Nature*, 2014.

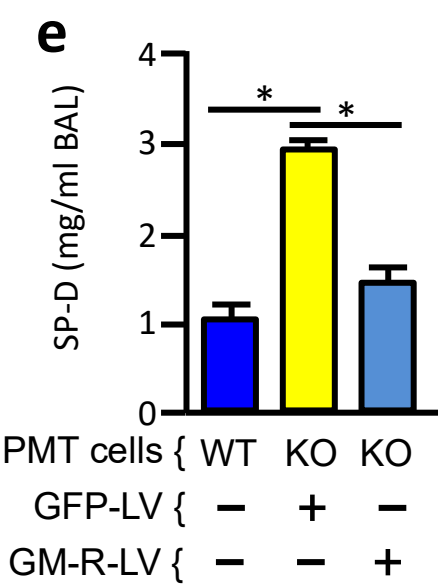
PMT using WT or gene-corrected KO macrophages have similar therapeutic efficacy





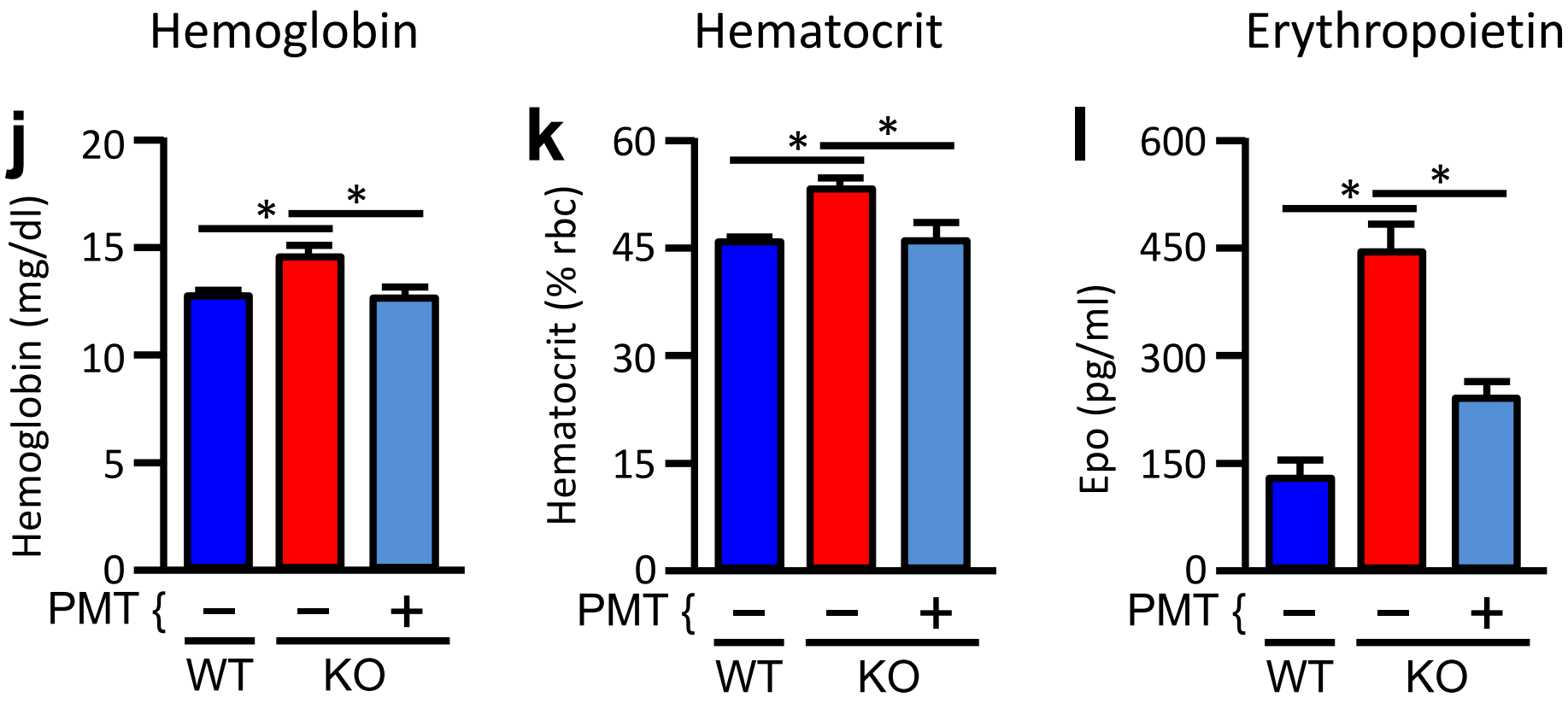






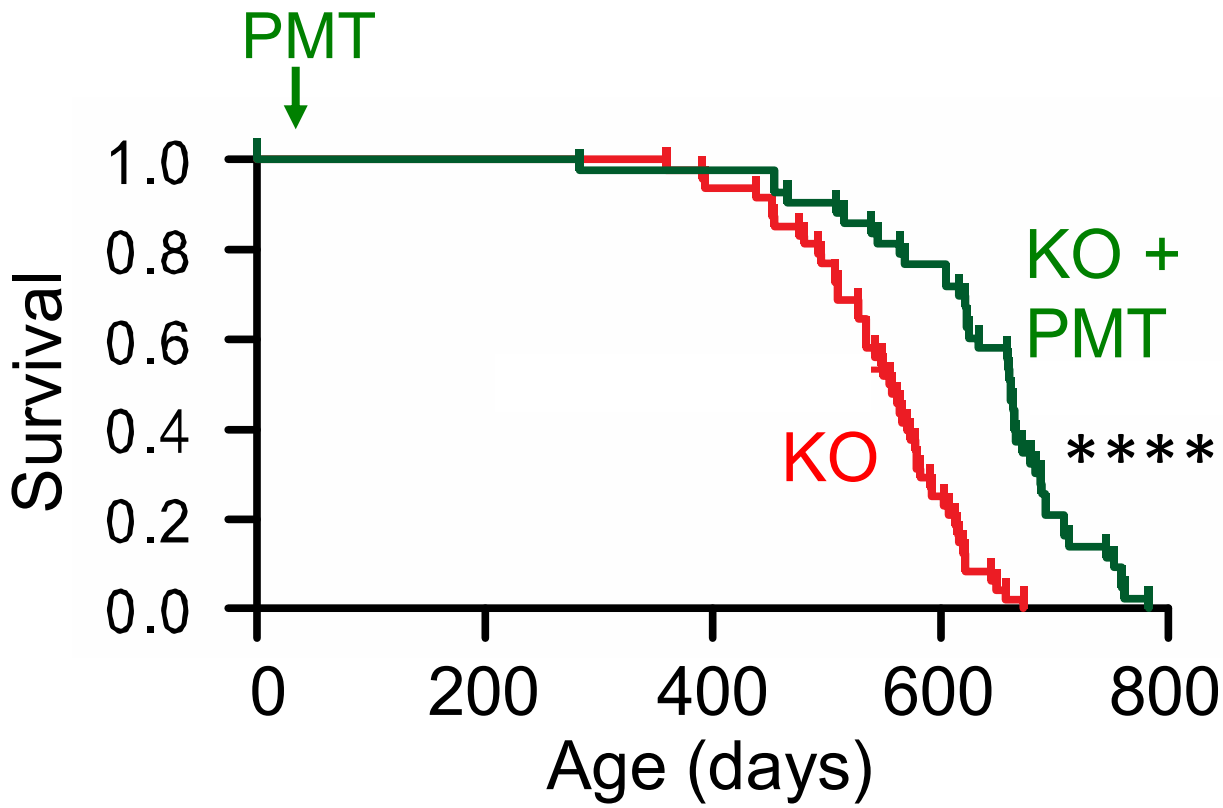
Suzuki… *Nature*, 2014.

PMT corrects secondary polycythemia



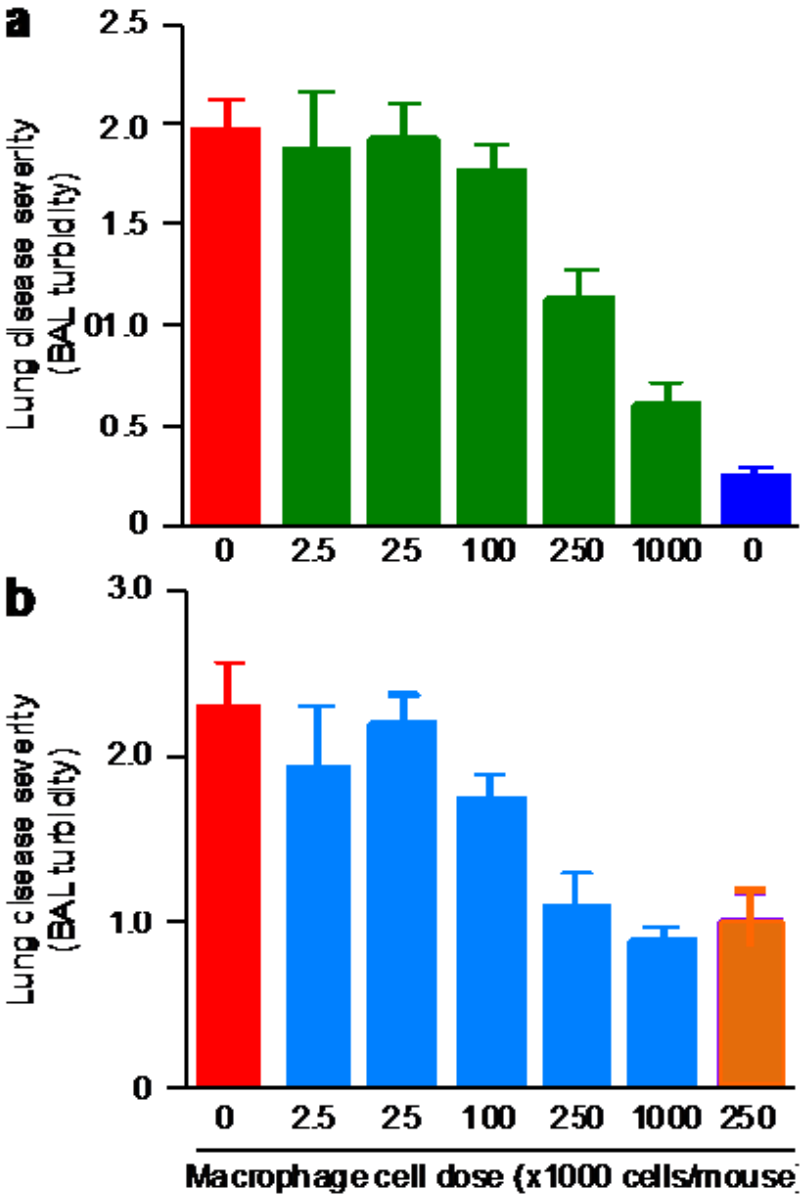
Suzuki… *Nature*, 2014.

PMT improves survival



Suzuki… *Nature*, 2014.

Effect of cell dose on therapeutic efficacy of PMT



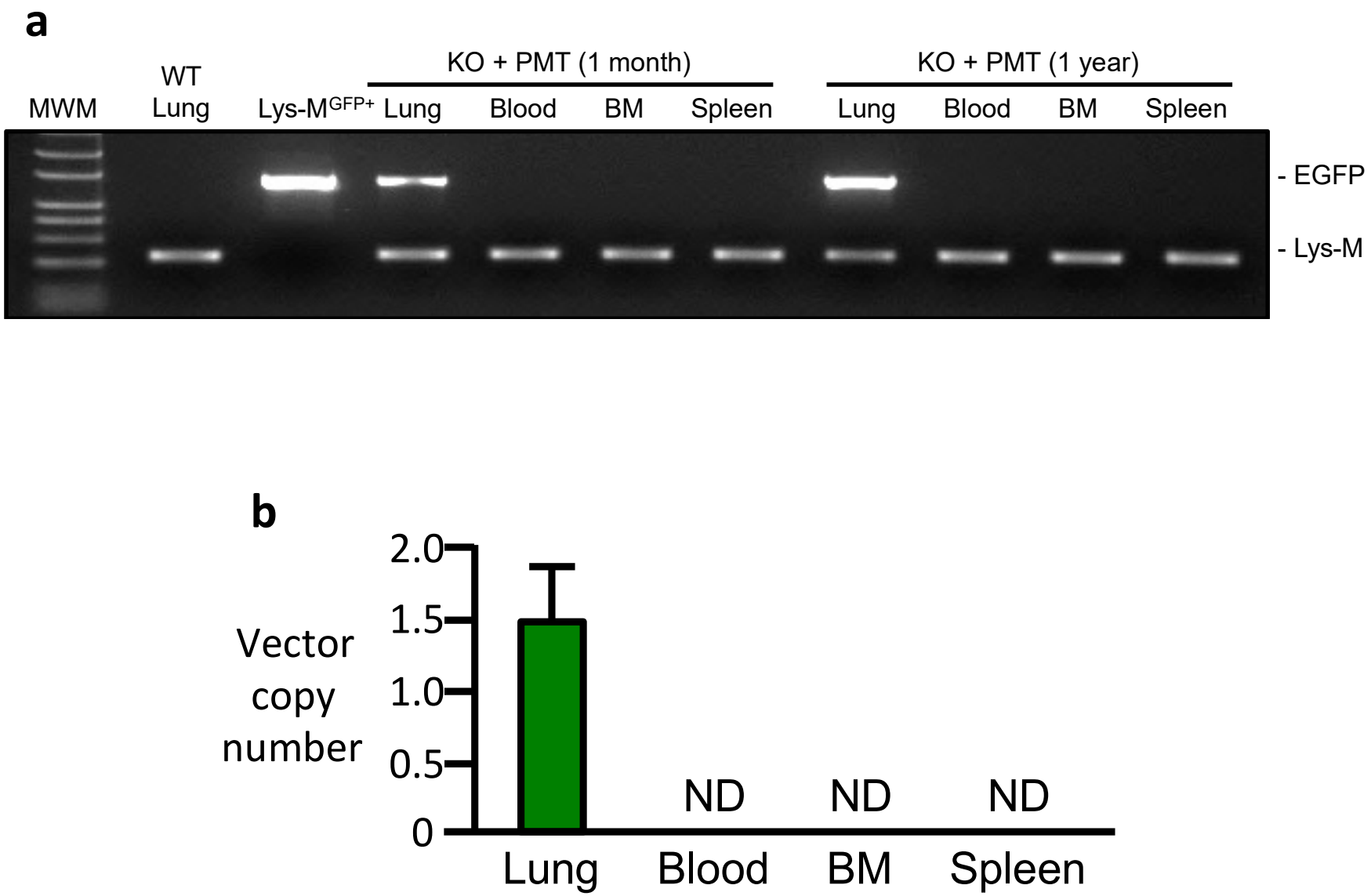
Mouse	PMT donor source
Csf2rb-/-	No PMT
Csf2rb-/-	Csf2b+/+
Csf2rb+/+	No PMT
Csf2rb-/-	Csf2b-/- *Csf2rb*-LV transduced
Csf2rb-/-	Csf2b+/+

Efficacy results summary (Pre-clinical)

- Effector cell - AMs, mature BMDMs, and progenitors have Rx efficacy
- Cell doses ≥ 5 x10e5 => similar efficacy
- 10e5 cells – Rx effective at two months
- Cell dose/time to Rx effect = constant
- Strong cell survival advantage drives Rx
- Preclinical studies with clinical vector in patient cells completed/successful

Trapnell, Pre-Pre-IND information package

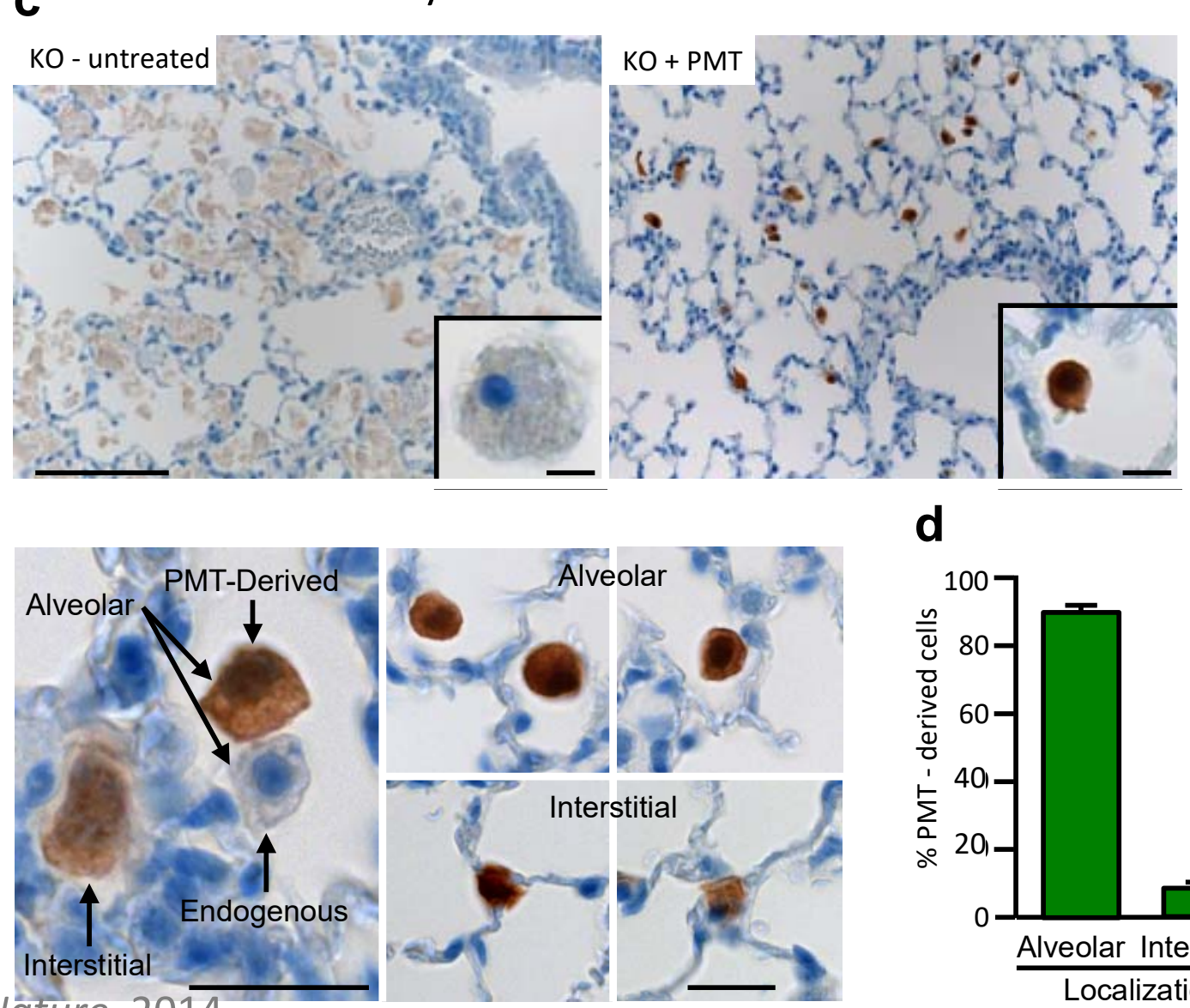
Transplanted macrophages remain in the lungs



Suzuki… *Nature*, 2014.

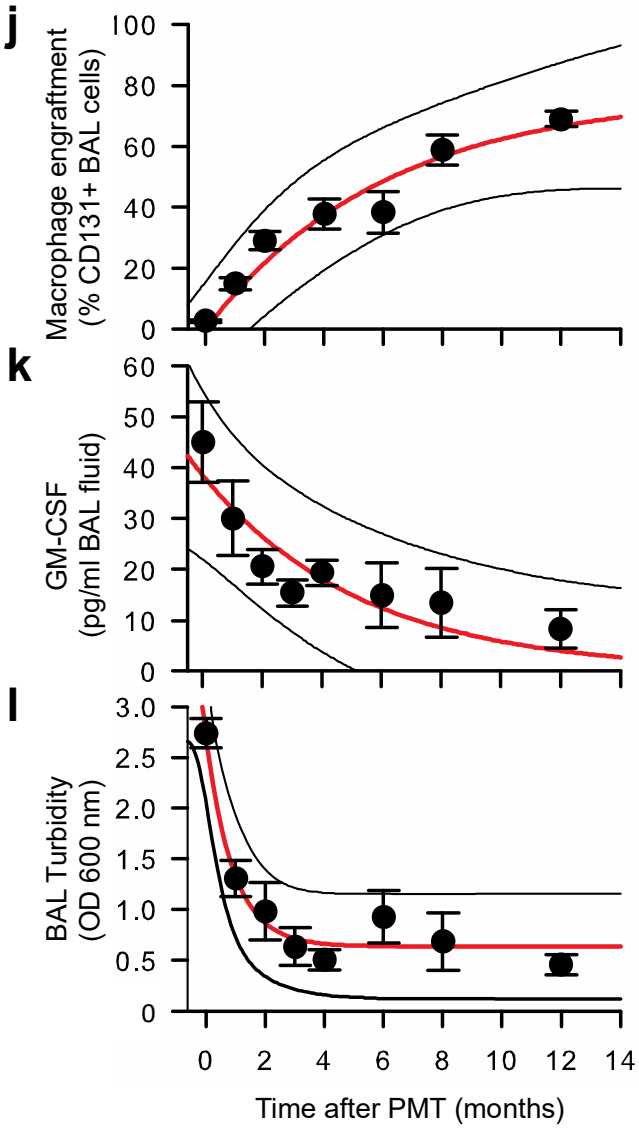
Transplanted macrophages localize to alveoli

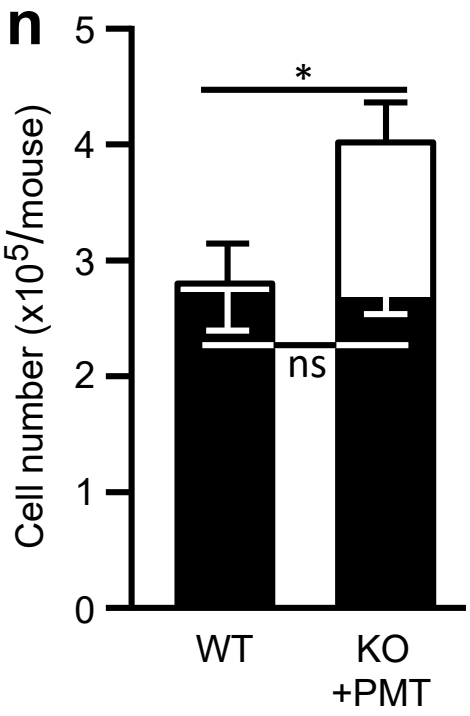
PMT: Lys-M^{GPF} Knock-in BMDMs



Suzuki… *Nature*, 2014.

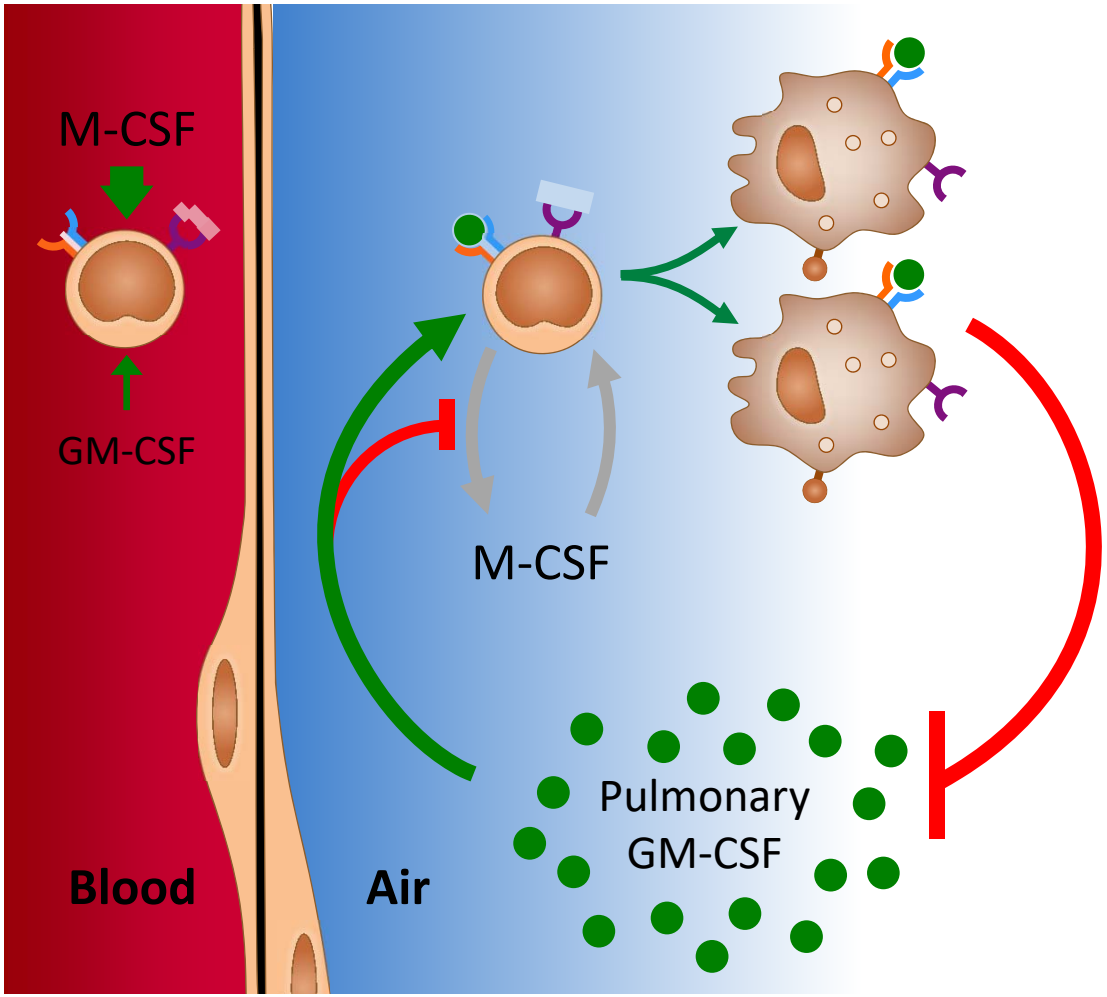
Transplanted macrophages engraft efficiently





Suzuki… *Nature*, 2014.

GM-CSF regulates alveolar macrophage population size via a reciprocal feedback mechanism



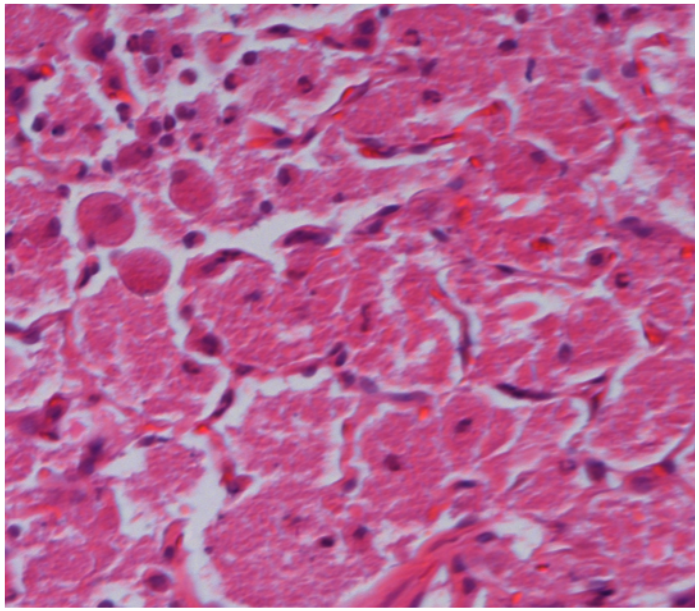
Alveolar macrophage
- Survival
- Differentiation
- Population size

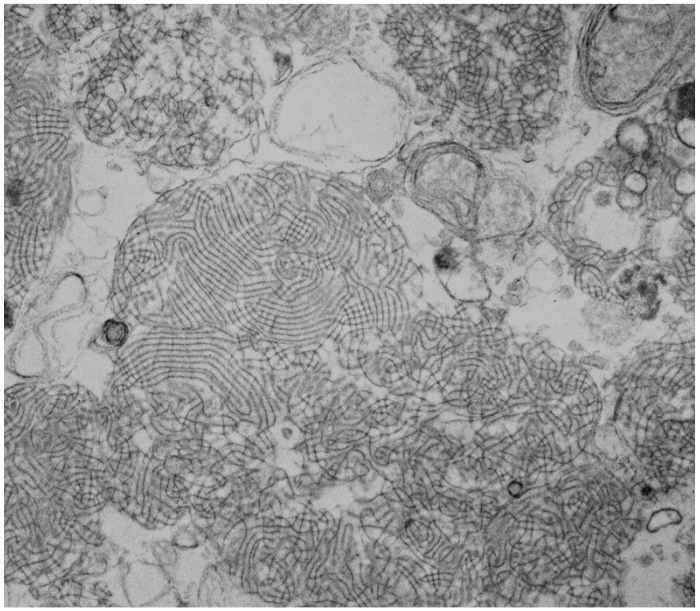
Lung
- Surfactant homeostasis
- Alveolar stability
- Oxygen uptake

Suzuki… *Nature*, 2014.

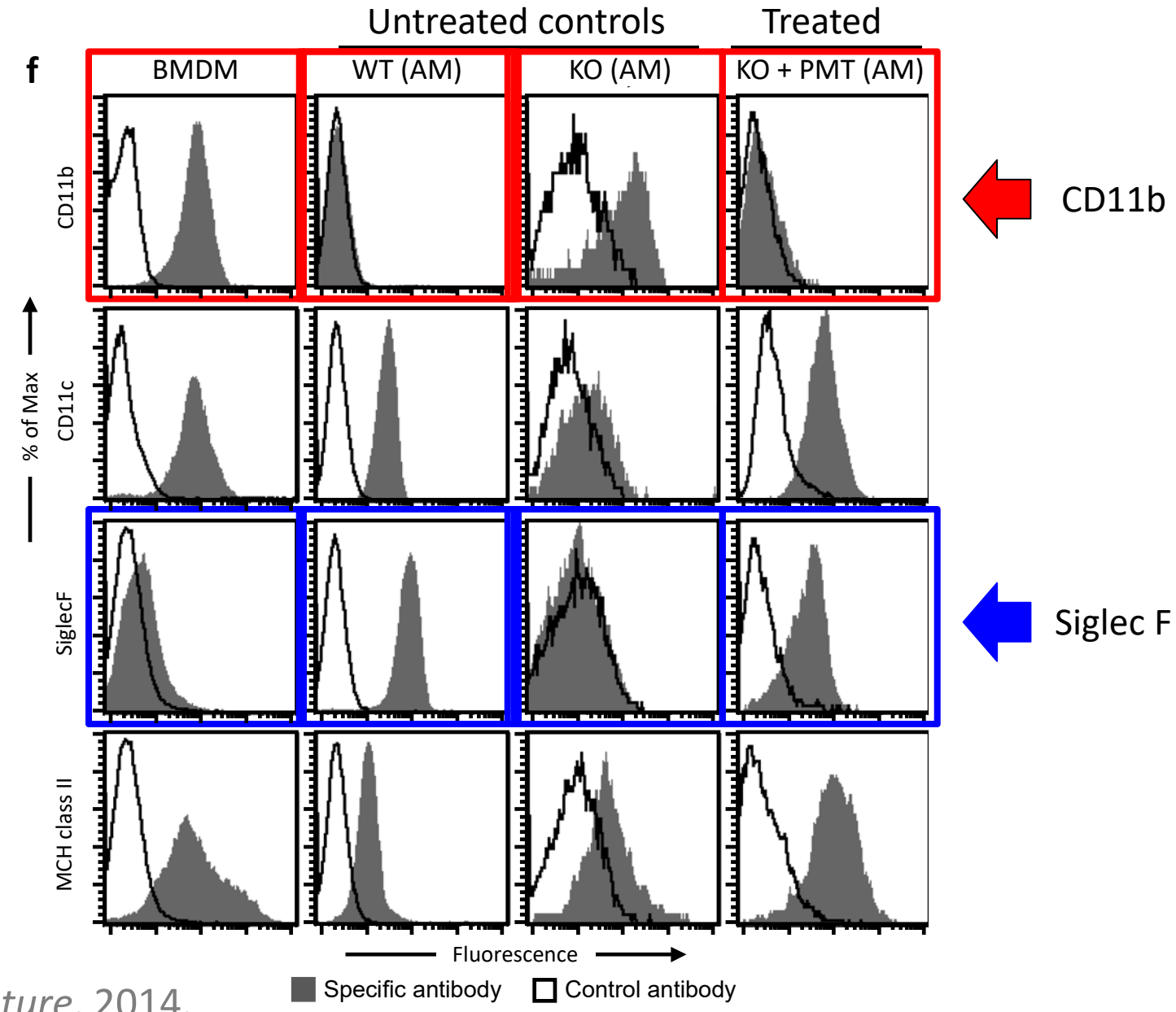
Importance of pulmonary GM-CSF concentration

GM-CSF
Absent



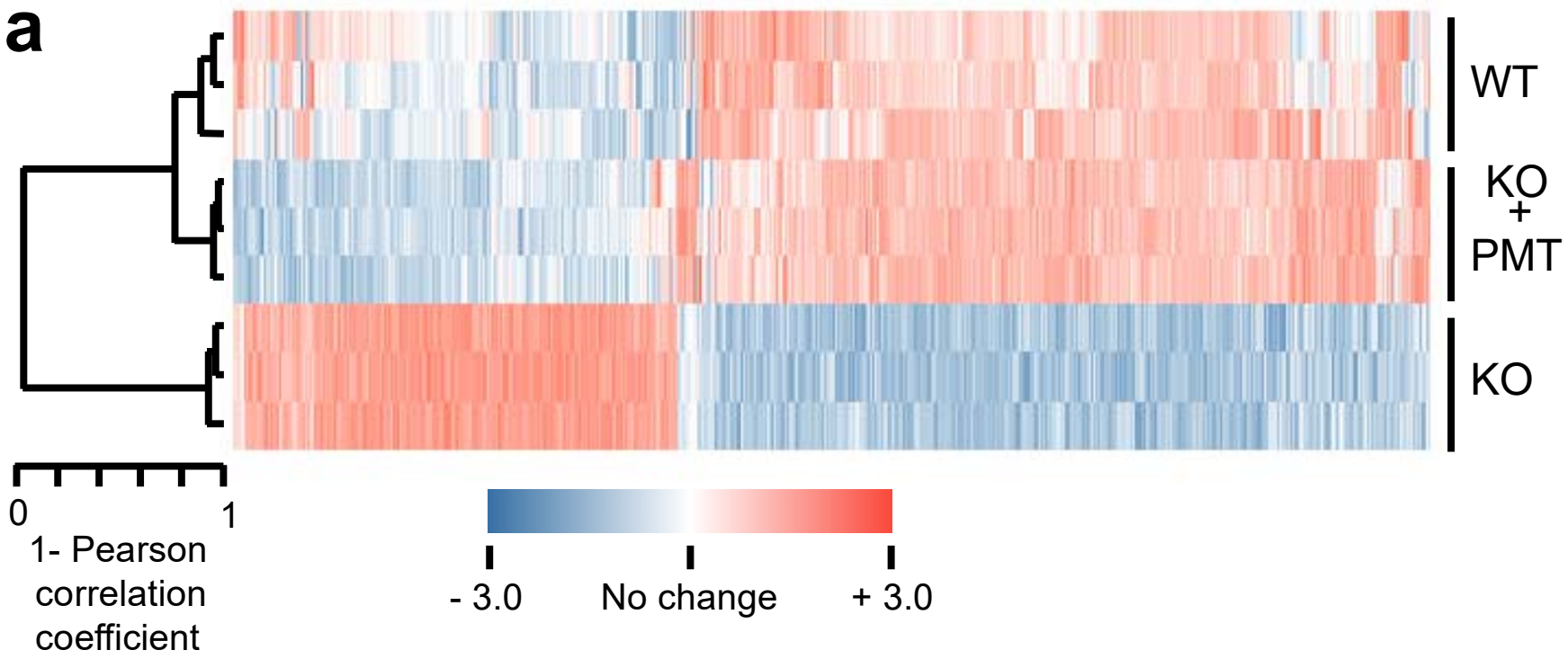


Transplanted macrophages adopt a normal phenotype



Suzuki… *Nature*, 2014.

Alveolar macrophage transcriptome 1 year after PMT



Suzuki… *Nature*, 2014.

Results of preclinical safety studies

- PMT using WT or KO gene-corrected macrophages into KO mice:
  - No behavioral changes
  - No cellular inflammation in the lungs
  - No pro-inflammatory cytokine increase in the lungs (TNFα, IL-1β, IL-6)
  - No changes in baseline hematologic parameters
  - Reduction in PAP biomarkers: M-CSF, GM-CSF, MCP-1
  - Doses of 5,000,000 cells/mouse were safe and well-tolerated providing a 10-fold safety margin for cell dose

Suzuki… *Nature*, 2014.

Estimating the cell dose for PMT in humans

Calculation method	Human cell dose	% AM #
Alveolar number (relative) ¶	0.03 x 10e9	0.5%
Body weight (relative) ¶	1.1 x 10e9	14%
AM number (relative) ¶	1.1 x 10e9	19%
Alveolar surface area (relative) ¶	4.4 x 10e9	78%
AM number (absolute)§	5.6 x 10e9	100%

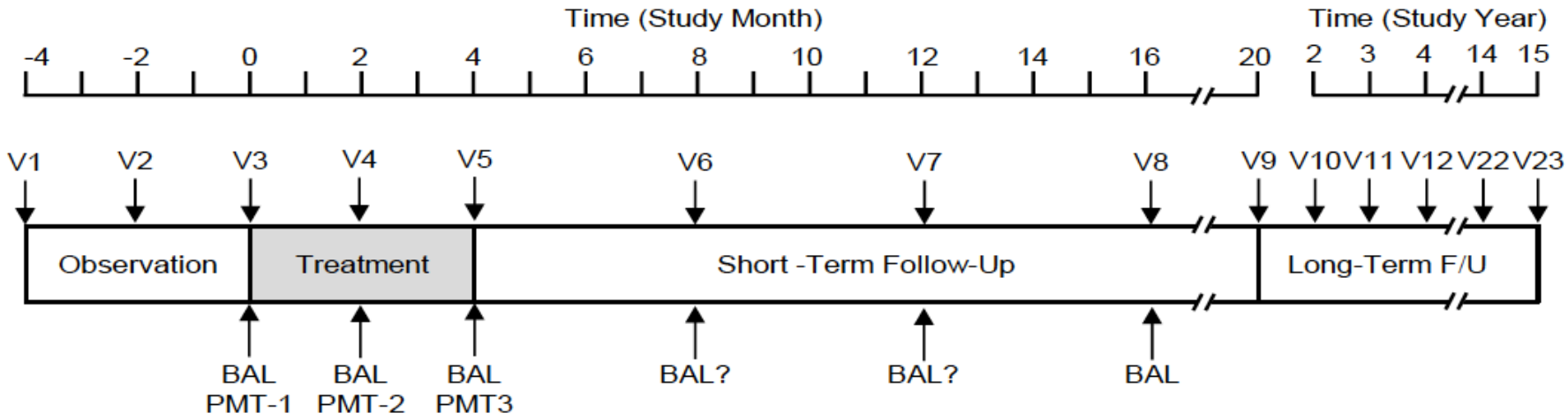
- Based on values for corresponding mouse and human parameters
  500,000 cells/mouse gives good/maximum efficacy at 1 year
  100,000 cells/mouse gives detectable therapeutic efficacy at 2 months
  4 x 10e6 cells/mouse was well-tolerated and safe without adverse events

¶ Calculated from corresponding mouse and human parameter

§ Calculate from the absolute human parameter

Translating PMT therapy to humans with hPAP

Dose No.	Dose (40 kg human)	Safety margin	Delivery site
1	12 x 10e6	293	1 segment
2	24 x 10e6	146	1 segment
3	400 x 10e6	8.8	All remaining segments



Trapnell, Pre-Pre-IND information package

Conclusions

- Pulmonary GM-CSF:
  - Regulates alveolar macrophage population size, surfactant homeostasis, alveolar stability, and lung function
  - GM-CSF is a critical pulmonary hormone

- Pulmonary macrophage transplantation (preclinical):
  - Myeloablation not required
  - Safe and well-tolerated
  - High therapeutic efficacy
  - Durable treatment effect (>1 year)
  - Prolongs lifespan by 20%
  - A strong survival advantage drives efficacy

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