폐오가노이드 개발 현황과 임상적용

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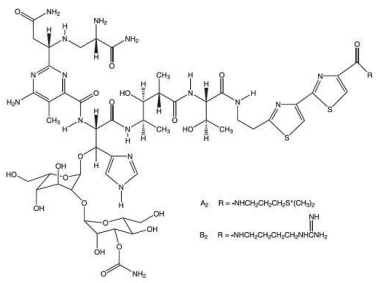
https://gladstone.org/news/lung-organoids-mini-models-mega-answers

Experimental *in vivo* model for pulmonary fibrosis



Bleomycin

Blenoxane®, Anti-tumor antibiotics
Melanoma, Sarcoma, Ova cancer …

Side effects: fever, skin redness, hair loss, anaphylaxis, pulmonary fibrosis

Resembling acute lung injury

Bleomycin causes an inflammatory response with induction of pro-inflammatory cytokines and activation of macrophages and neutrophils

Reversibility

The development of fibrosis is at least partially reversible, independent from any intervention. The aspect of slow and irreversible progression of IPF in patients is not reproduced in the bleomycin model. One of the most critical hallmarks of human IPF is therefore not present in animals, which has to be considered when this model is used for drug intervention studies.

Strain specificity

Another disadvantage is that bleomycin induced fibrosis is limited in certain mouse strains, namely Balb/c mice. This difference is due primarily to variability in the production of the inactivating enzyme, bleomycin hydrolase across strains.

동물대체시험법

The FDA no longer requires all drugs to be tested on animals before human trials

JANUARY 12, 2023 · 6:03 AM ET

By Joe Hernandez

A staff member for Sen. Rand Paul takes photos of her puppy, Jefferson, before a 2021 press conference on the FDA Modernization Act.

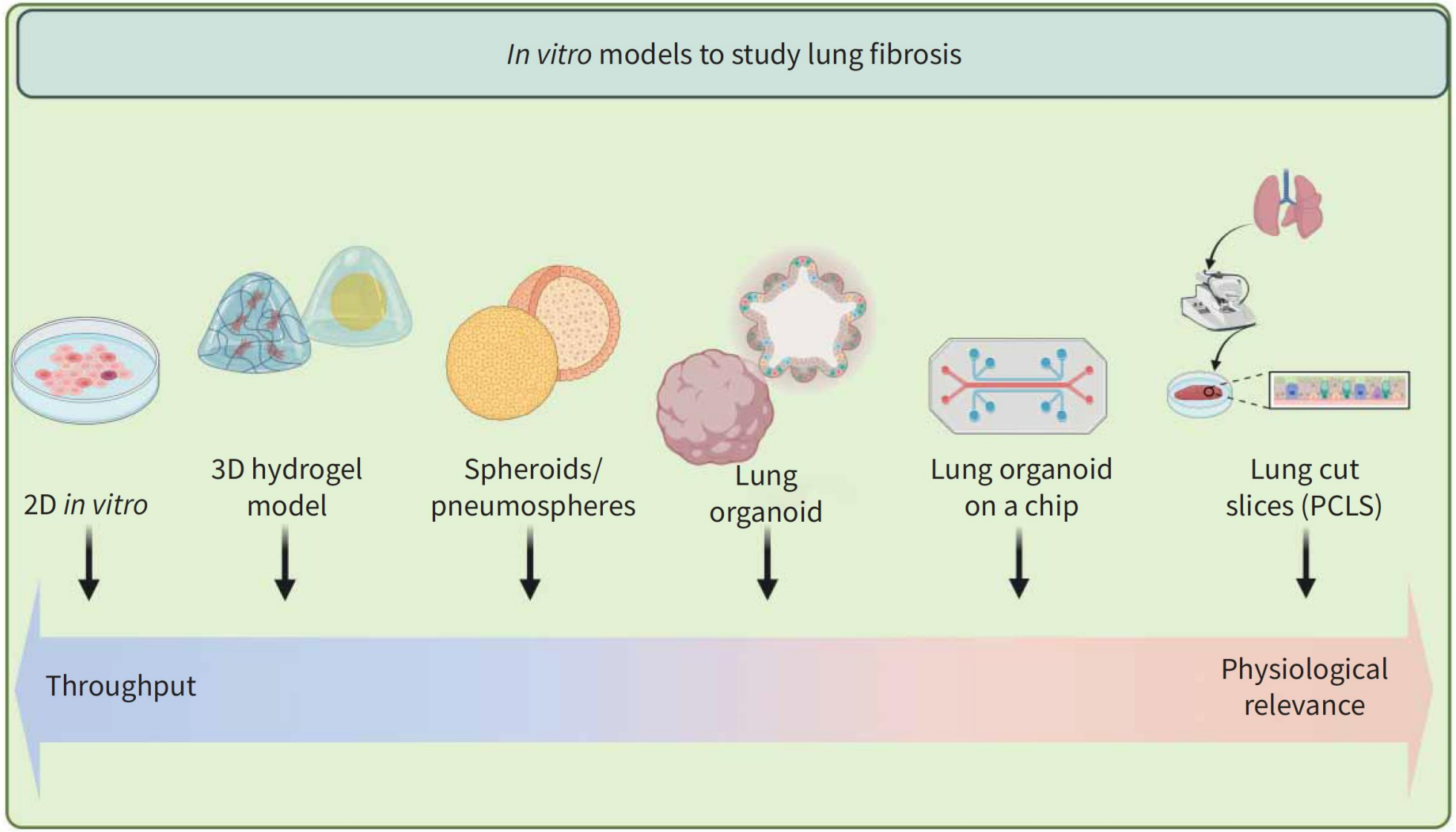
Anna Moneymaker/Getty Images

The new law – officially called the FDA Modernization Act 2.0 and part of a massive package of spending legislation signed into law by President Biden on Dec. 29, 2022 – has been long awaited by animal welfare organizations, consumers, and members of pharmaceutical companies.

For more than 40 years, these groups have advocated to move away from using animals such as rodents, monkeys, and dogs in scientific research and instead focus on using human cells and technology-powered models.

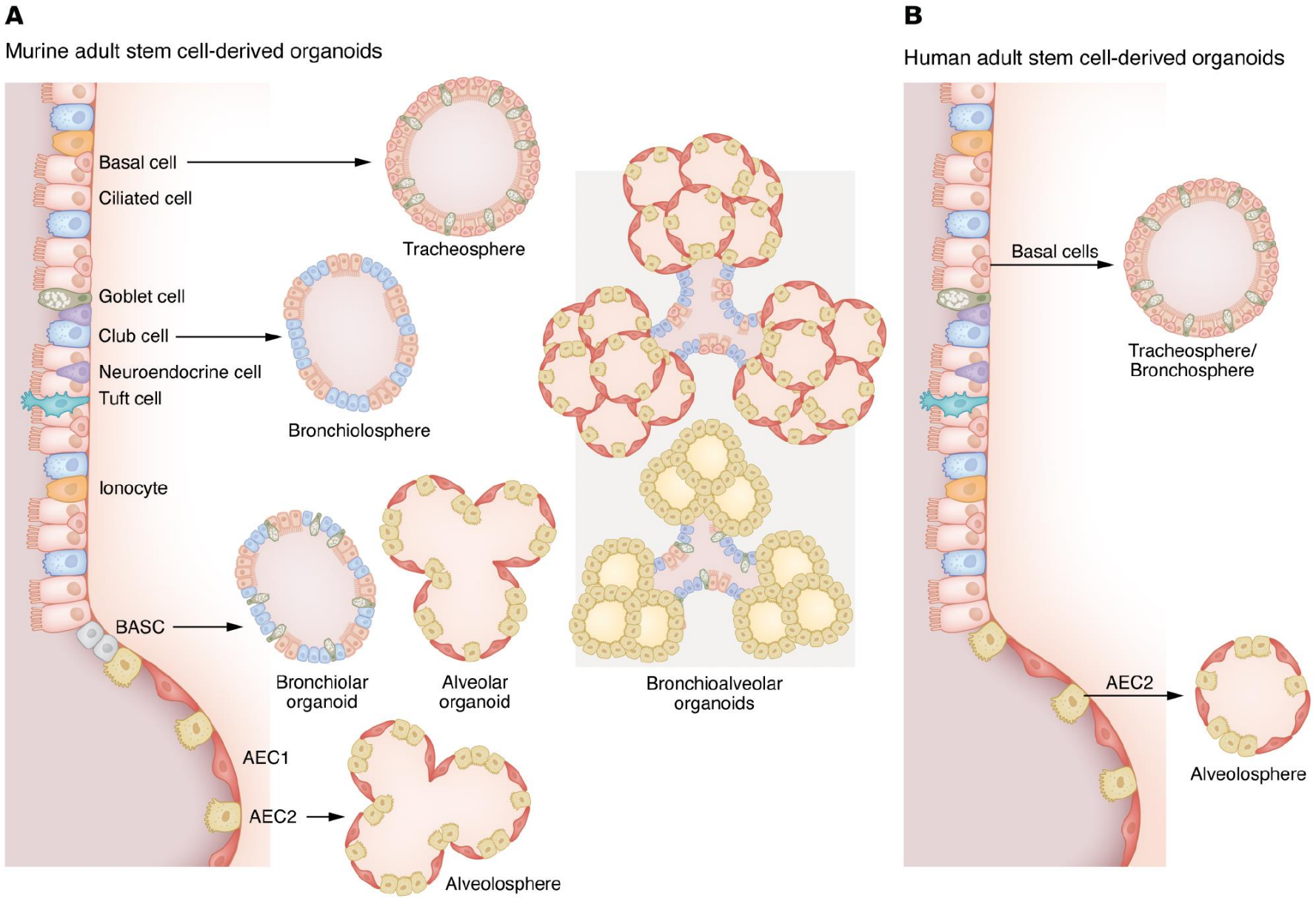
"The failure of the current system that relies on the use of animals for the first round of testing is an open secret,"

Experimental *in vitro* models for respiratory diseases



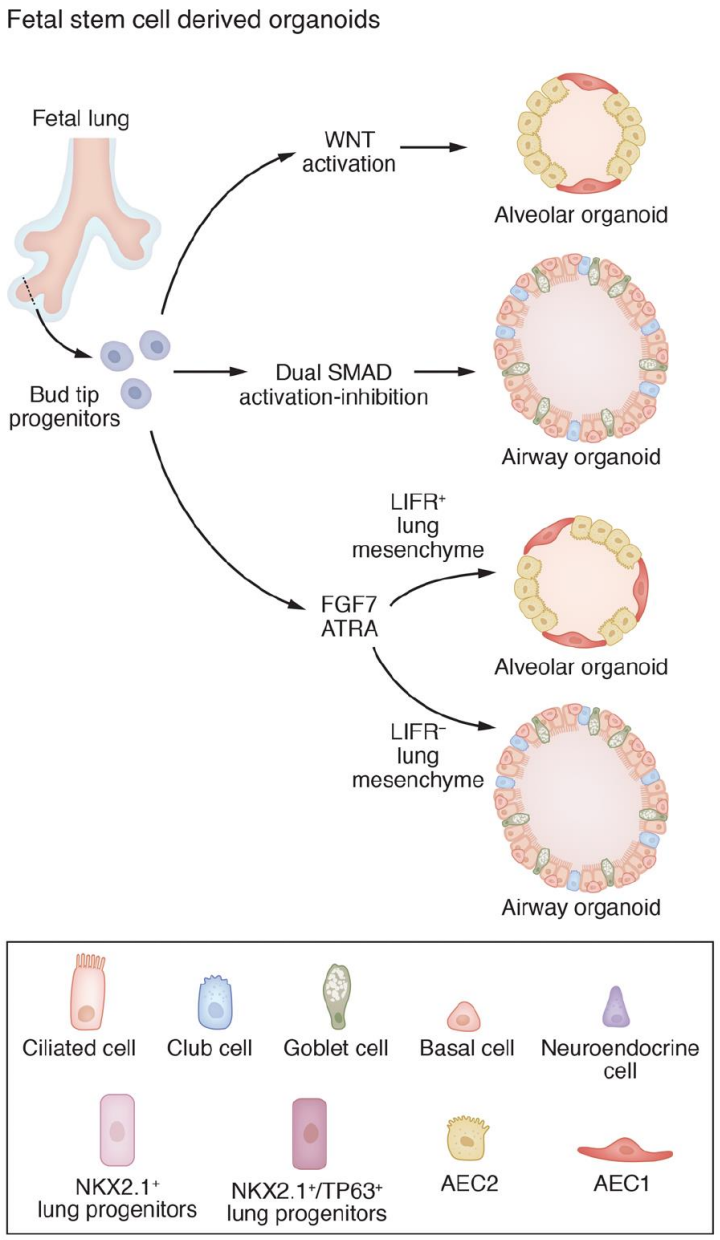
Kolanko et al. (2024) Eur Respir Rev

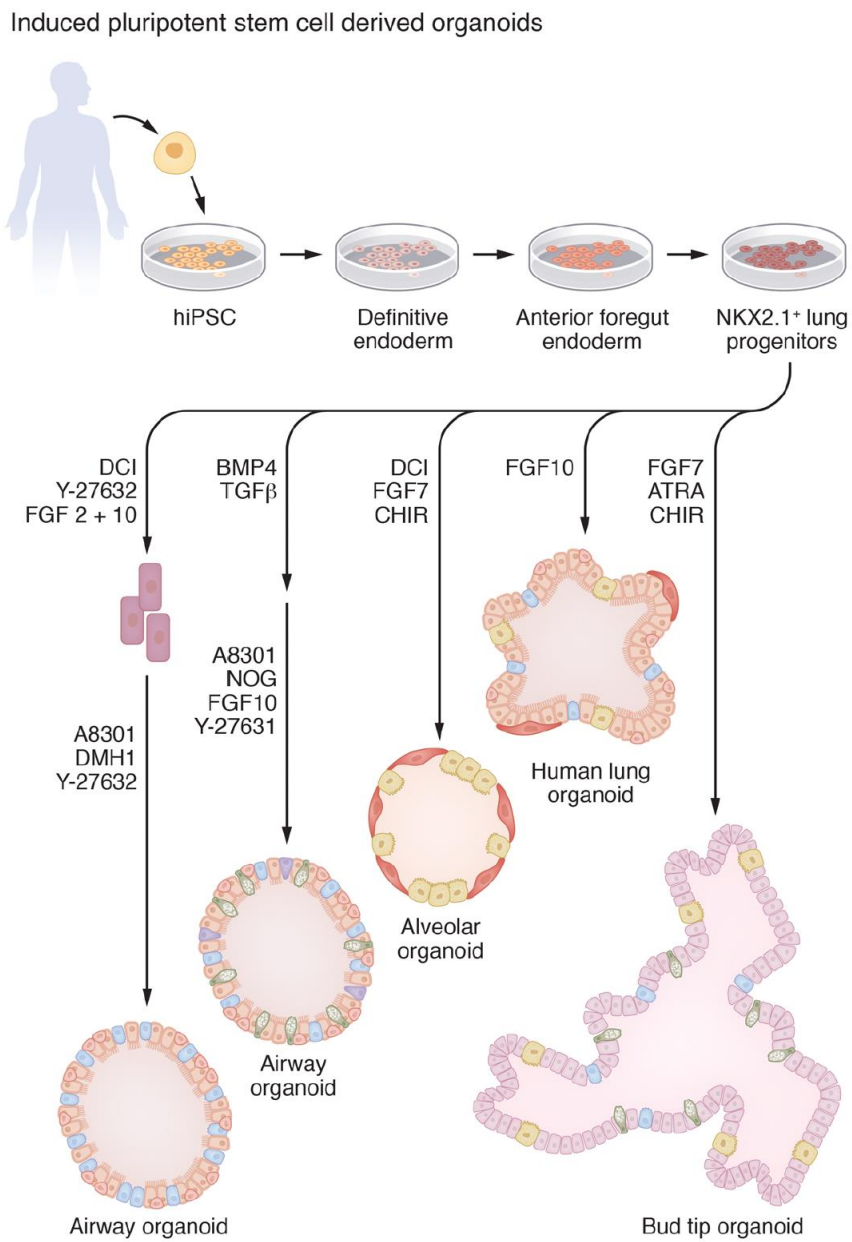
Types of lung organoids within different respiratory compartments



Vazquez-Armendariz *et al*. JCI (2023)

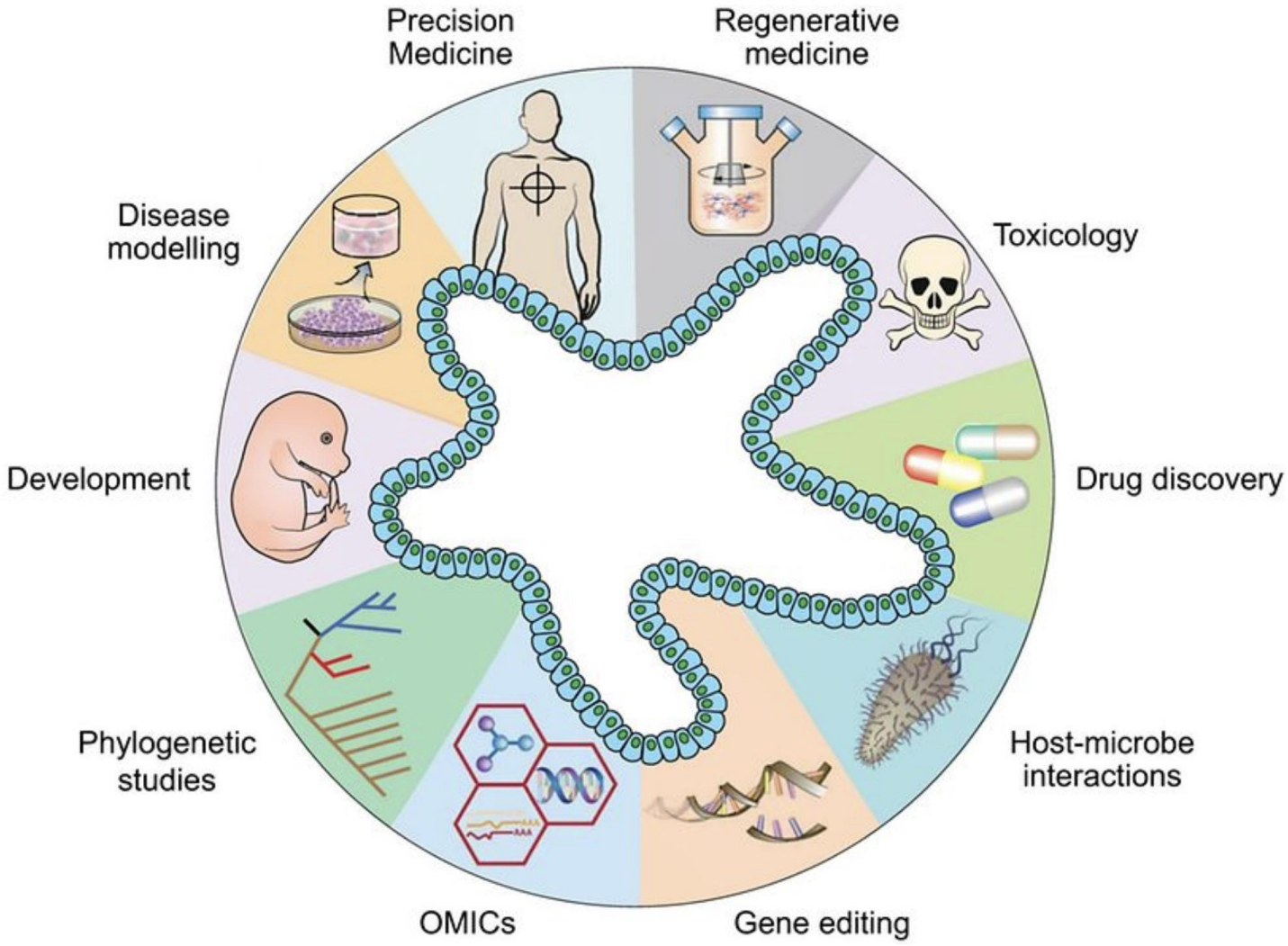
Sources of human lung organoid: Fetal stem cell vs huma pluripotent stem cell





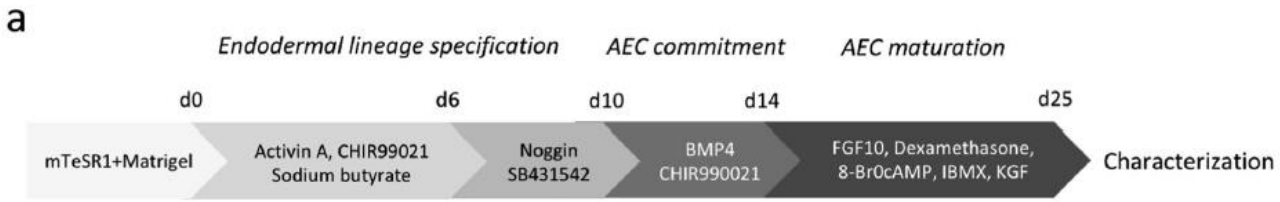
Vazquez-Armendariz *et al*. JCI (2023)

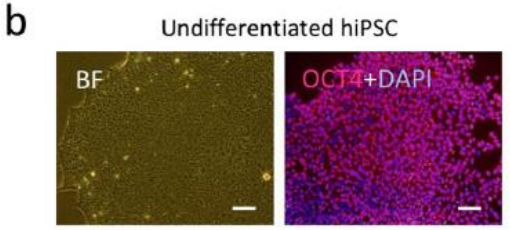
Applications of human lung organoids

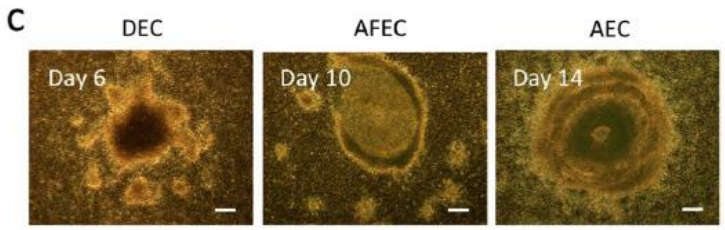


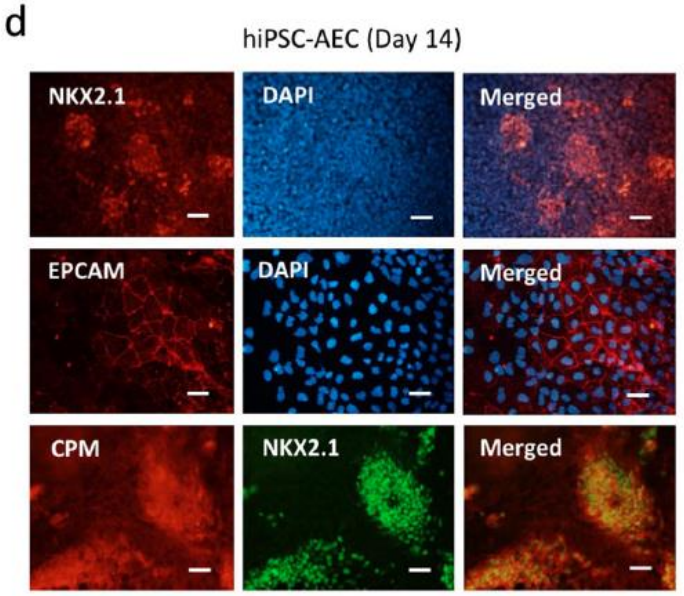
https://www.sartorius.com/en/knowledge/science-snippets/the-story-of-organoids-1062204

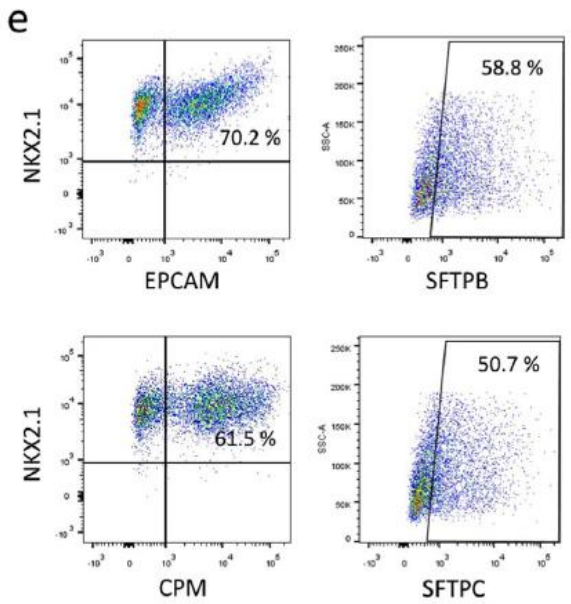
Generation of alveolar epithelial cells (AECs) from hPSCs

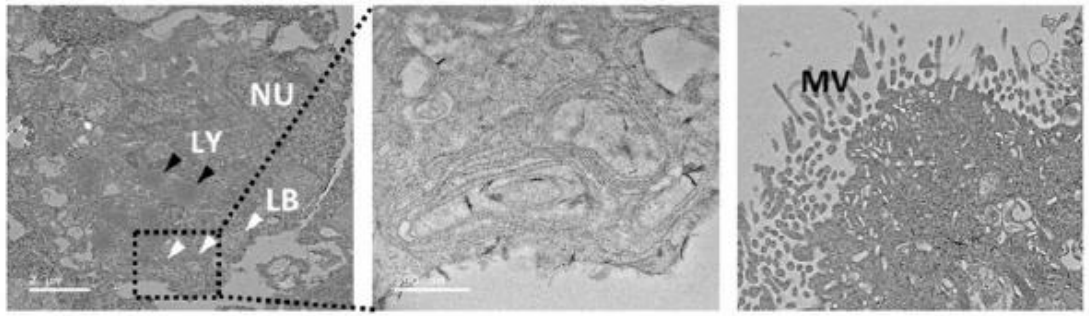






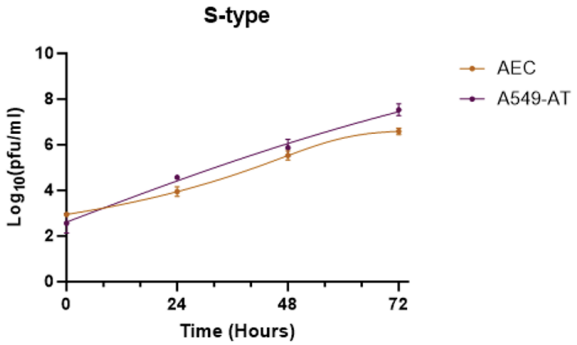


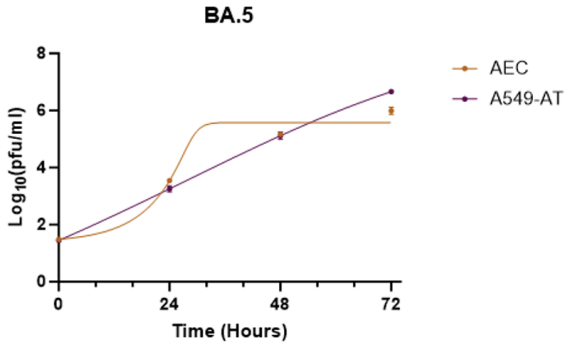


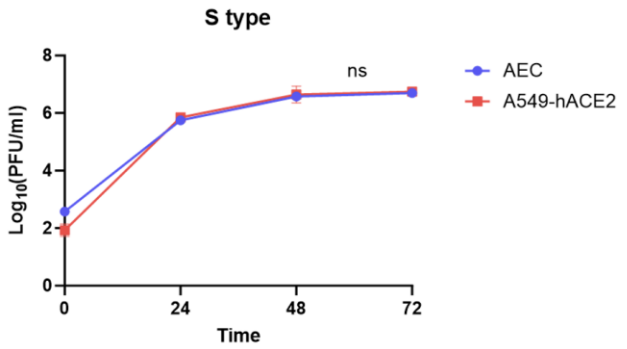


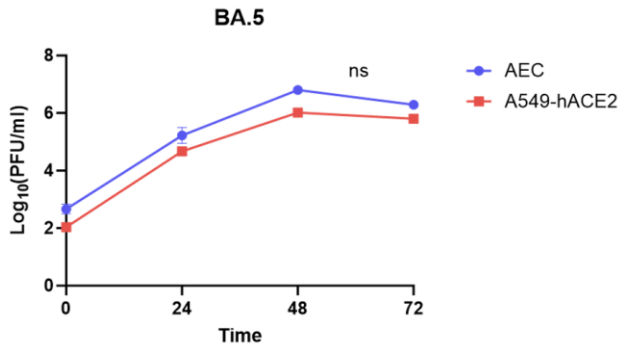
Heo *et al*. Scientific Reports (2019)

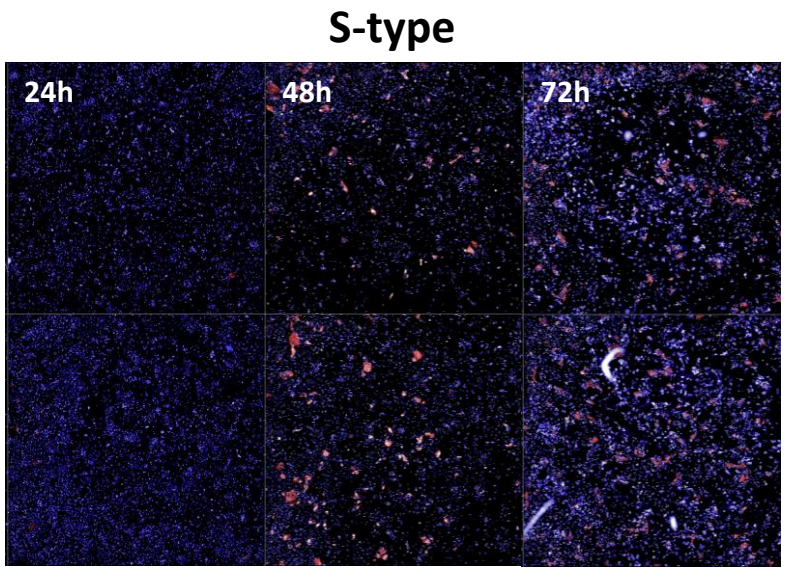
SARS-CoV-2 infectivity of hPSC-derived AECs

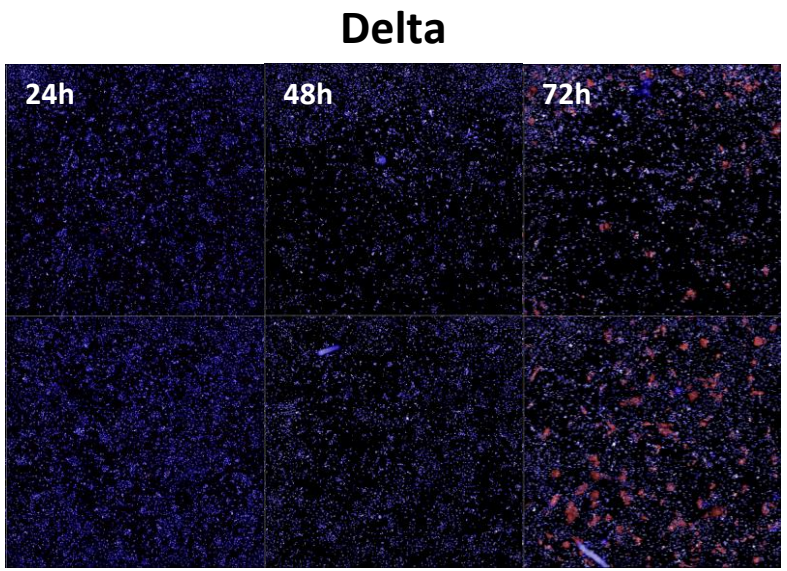


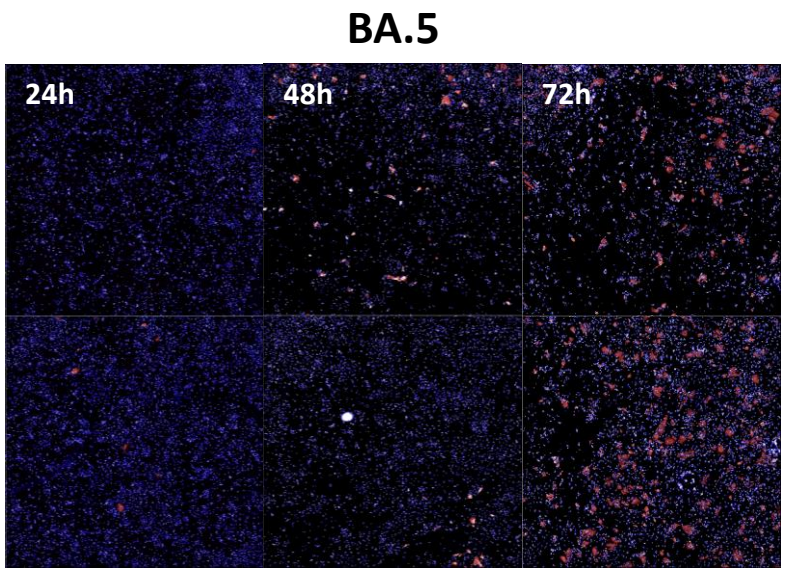






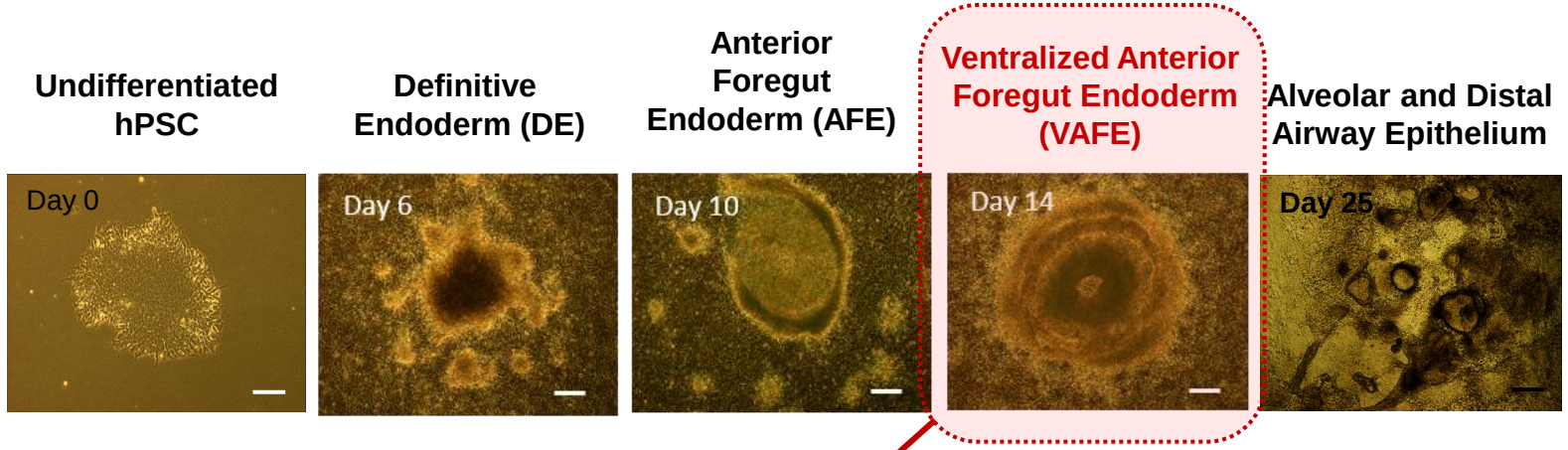






hPSC-AECs are SARS-CoV-2 susceptible and display similar growth kinetics patterns to A549-hACE2 cells

Generation of alveolar organoid (AO) from hPSC



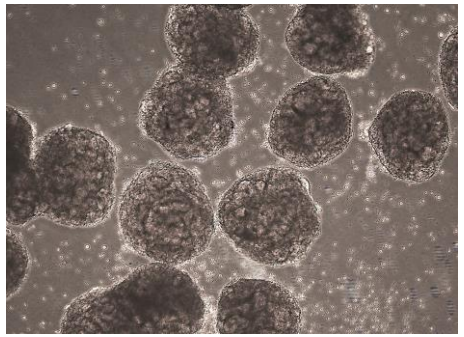
Alveolar epithelial progenitor cells

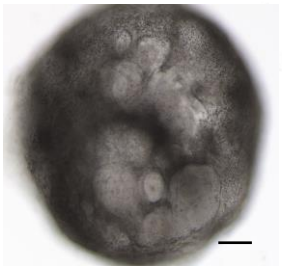
Single cell dissociation

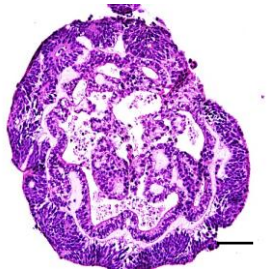
Forced aggregation (FA)

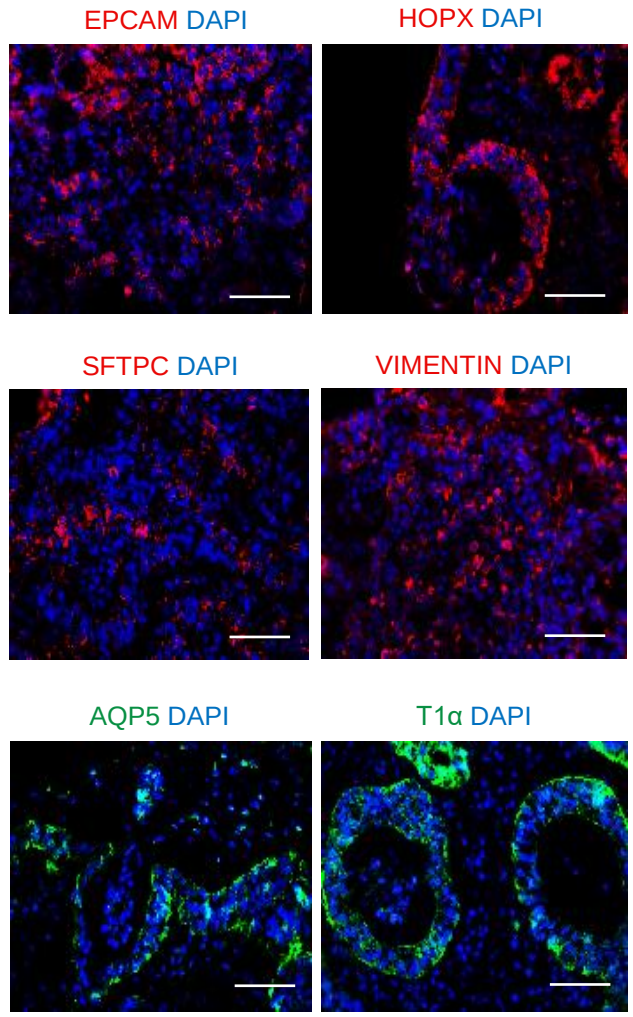
Seeding | **Aggregation (1,200 rpm, 5 min)** | **Sphere formation**

AO





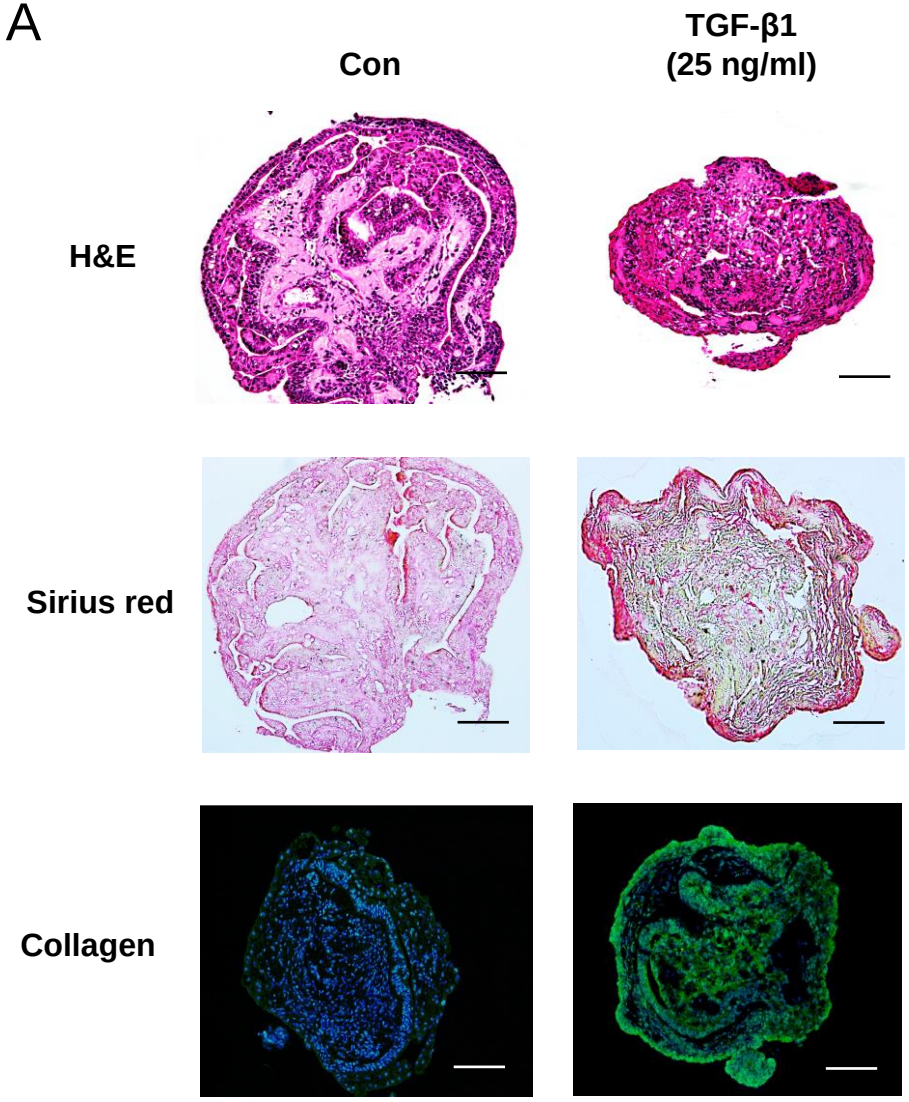




Rasaei *et al*. Biomedicine (2020)

Disease modeling: TGF-β1 or BLM-induced pulmonary fibrosis modeling of hPSC-AO

A



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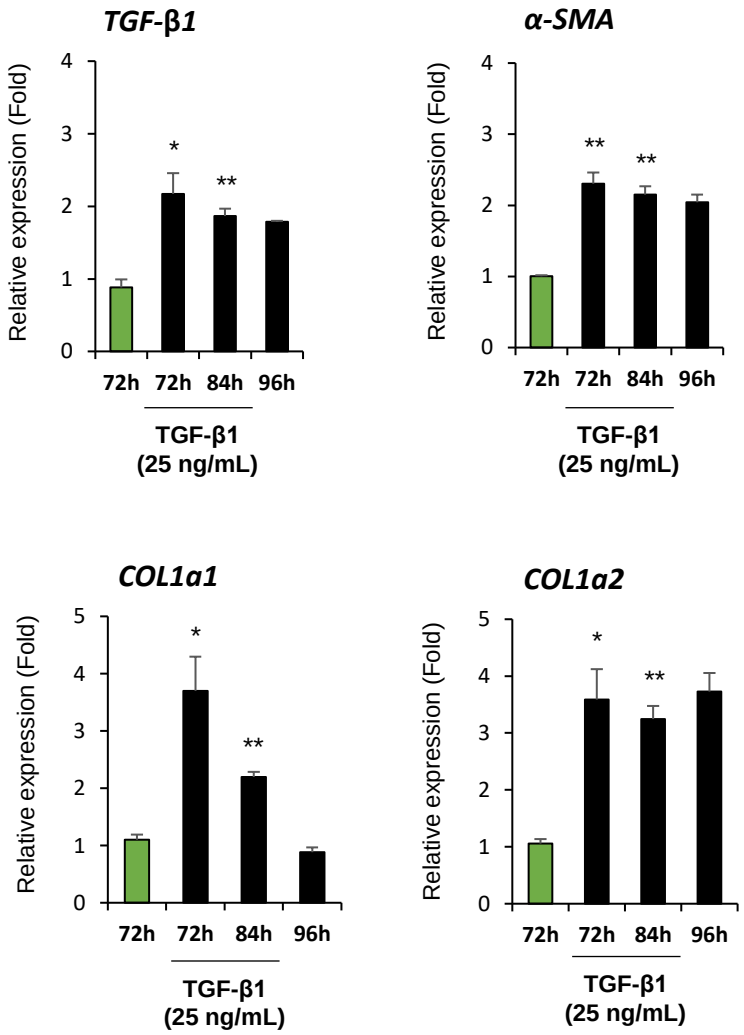

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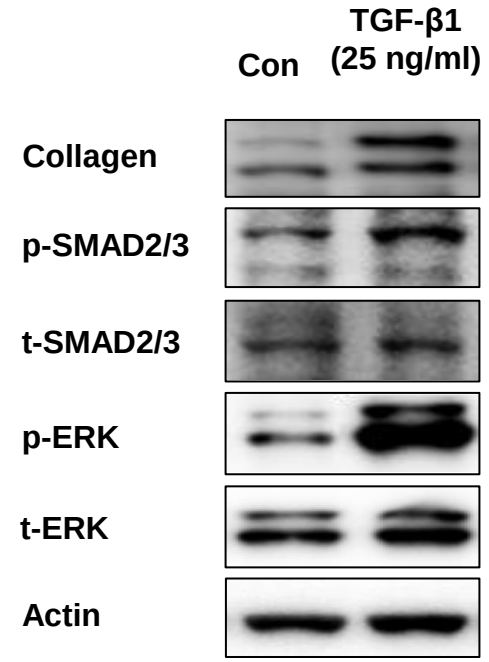
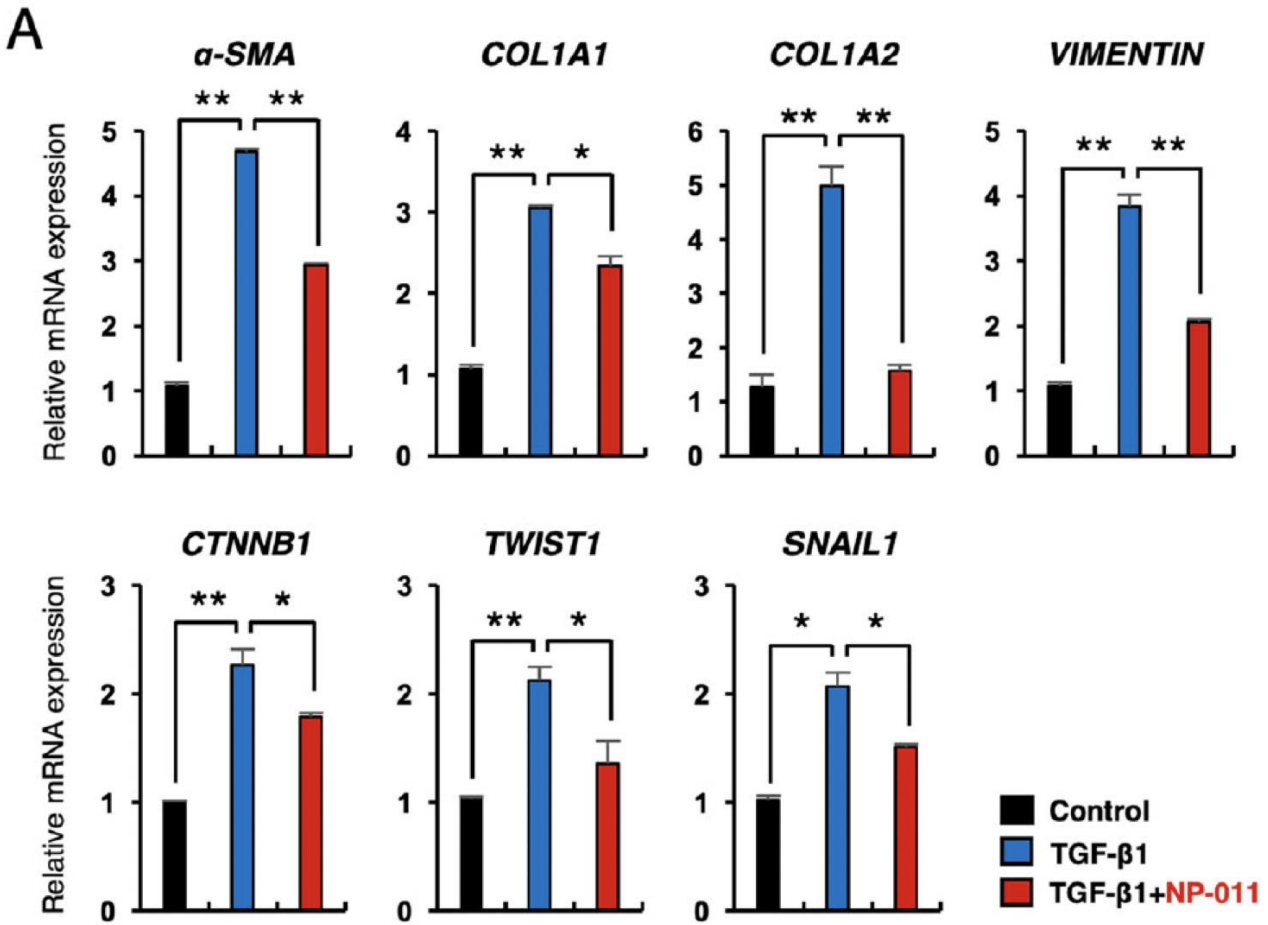
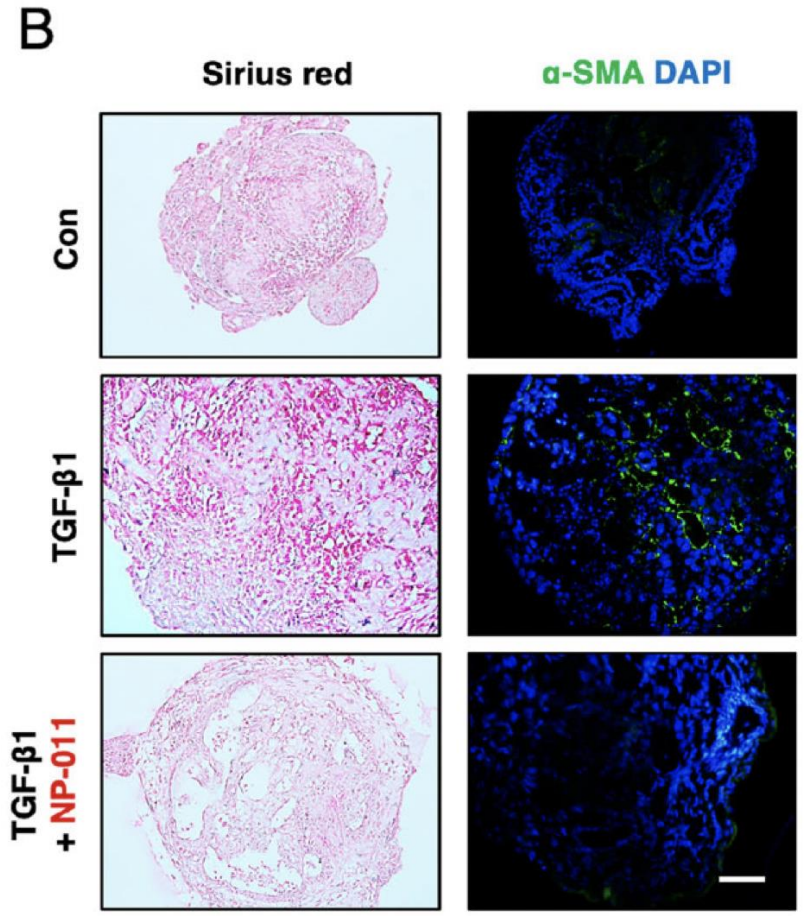


Kim *et al*. Cell Death Discovery (2021)

Drug efficacy testing: NP-011 ameliorates TGF-β1-induced fibrotic changes in AO





NEXEL NP-011, A truncated (deletion of C2 domain) form of MFG-E8

Kim *et al*. Cell Death Discovery (2021)

Harmful effects of fine particulate matter (PM2.5) on human health

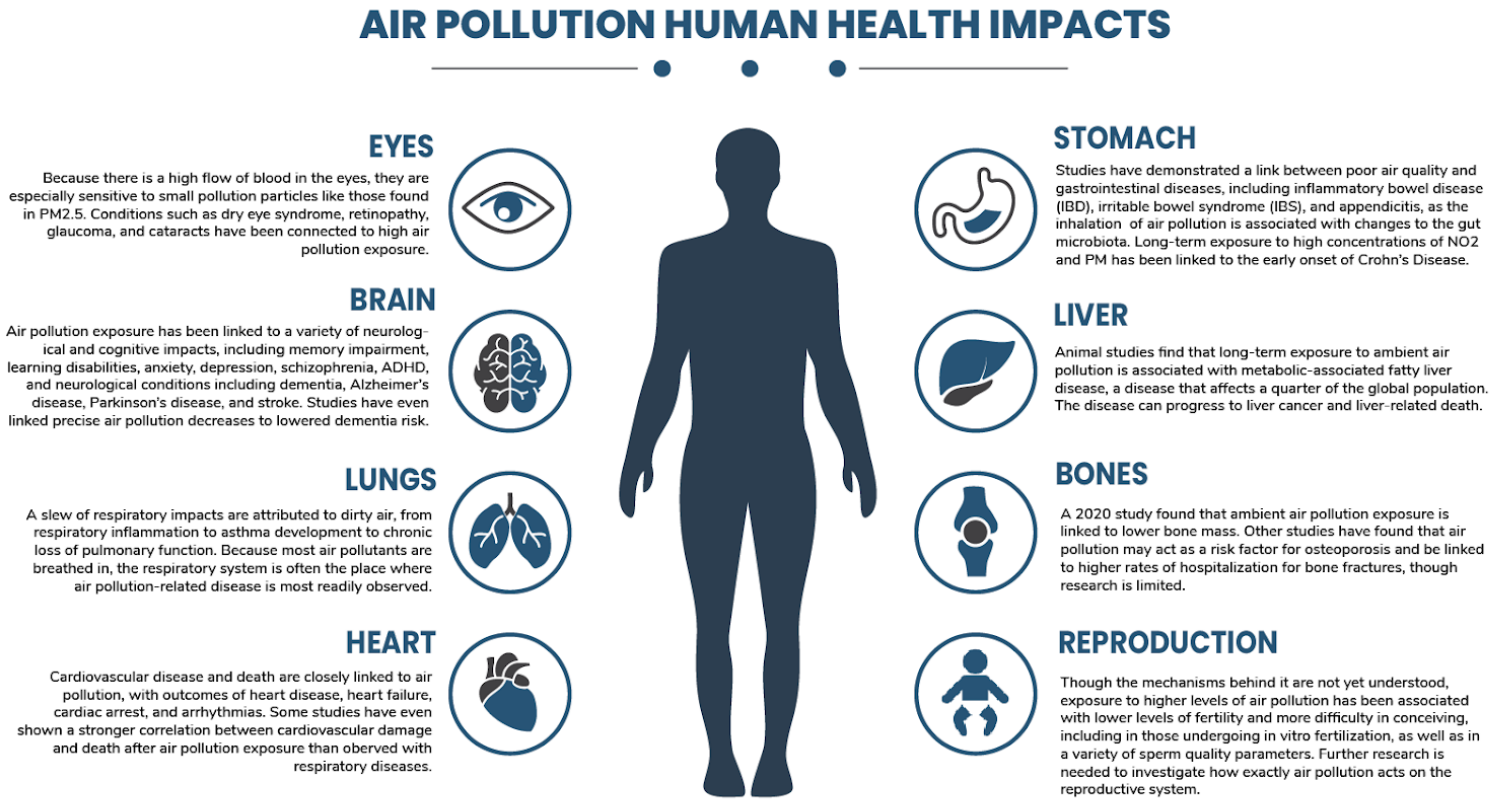
- **Terms for a mixture of solid particles and liquid droplets**
- **PM is classified as Group 1 carcinogen (WHO, 2013)**

PM_{10}

– 20μg/m^3 annual mean
– 50μg/m^3 24–hours mean

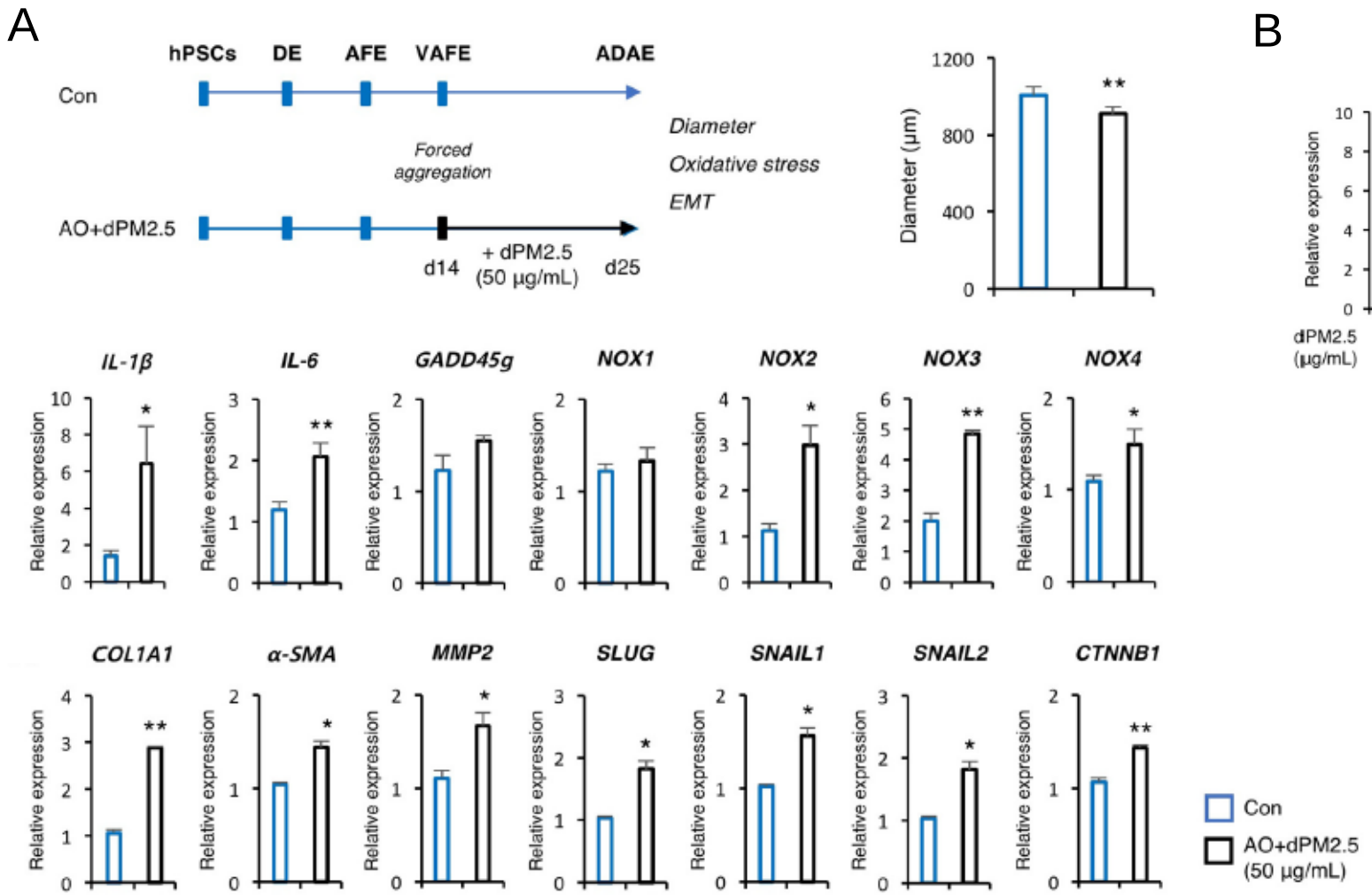
$PM_{2.5}$

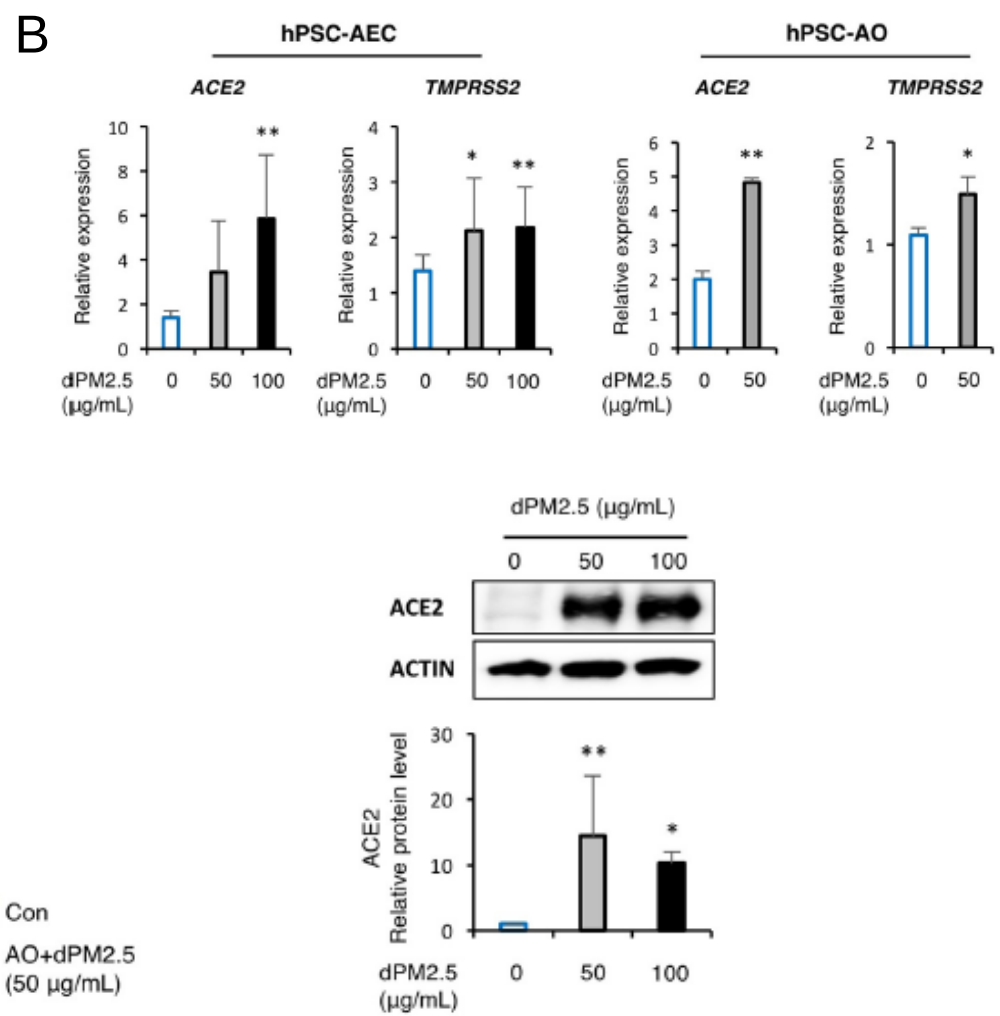
– 10μg/m^3 annual mean
– 25μg/m^3 24–hours mean



https://www.clarity.io/blog/deep-dive-health-impacts-of-air-pollution

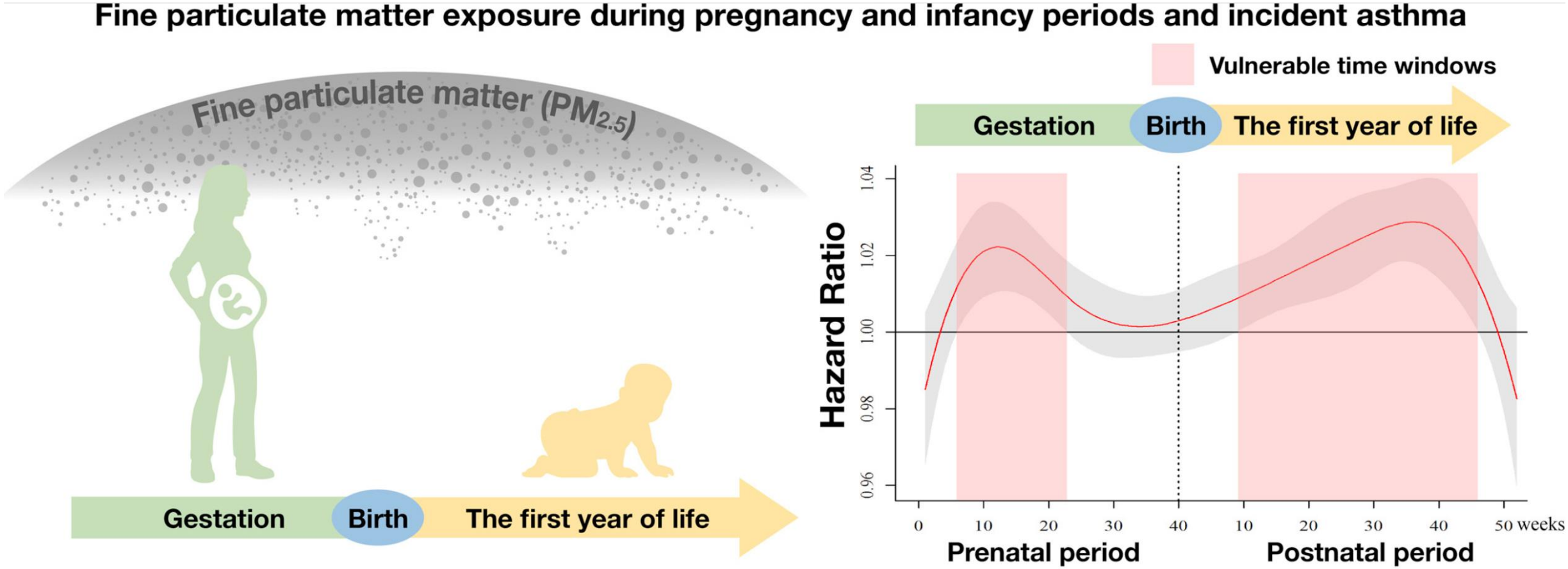
Environmental toxicology: Effects of PM2.5 on alveolar organoid





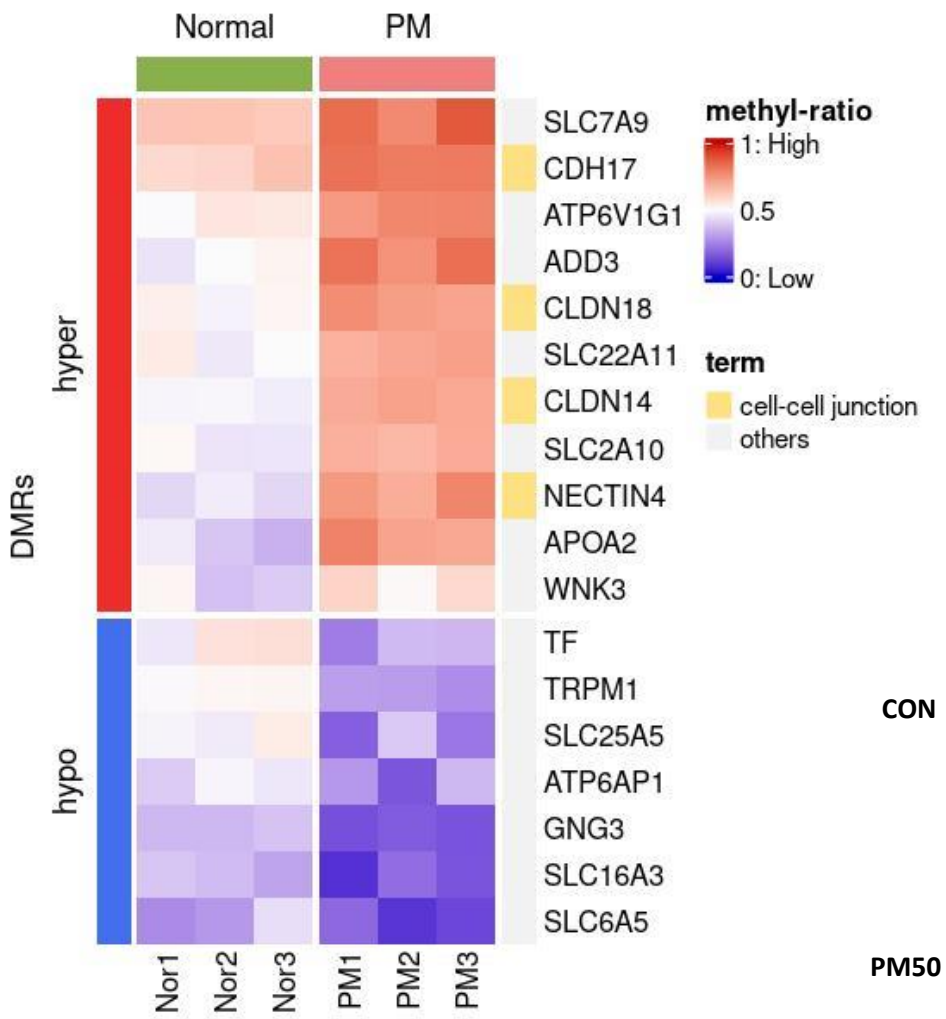
Kim *et al*. Int J Env Res & Pub Health (2021)

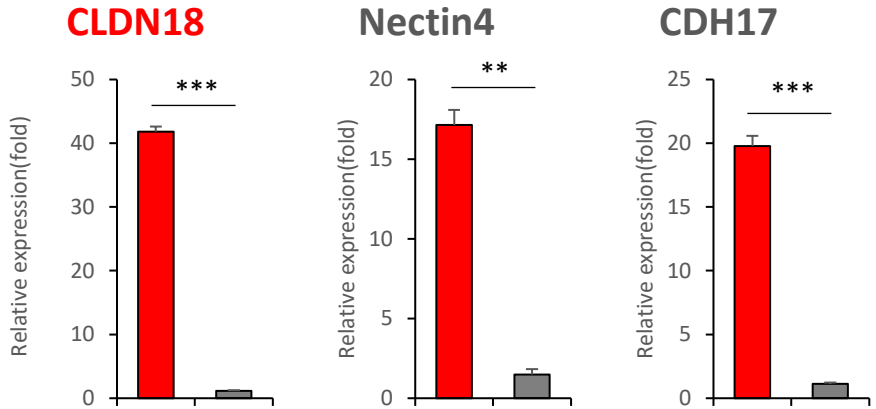
PM exposure during pregnancy affects lung functions after the birth

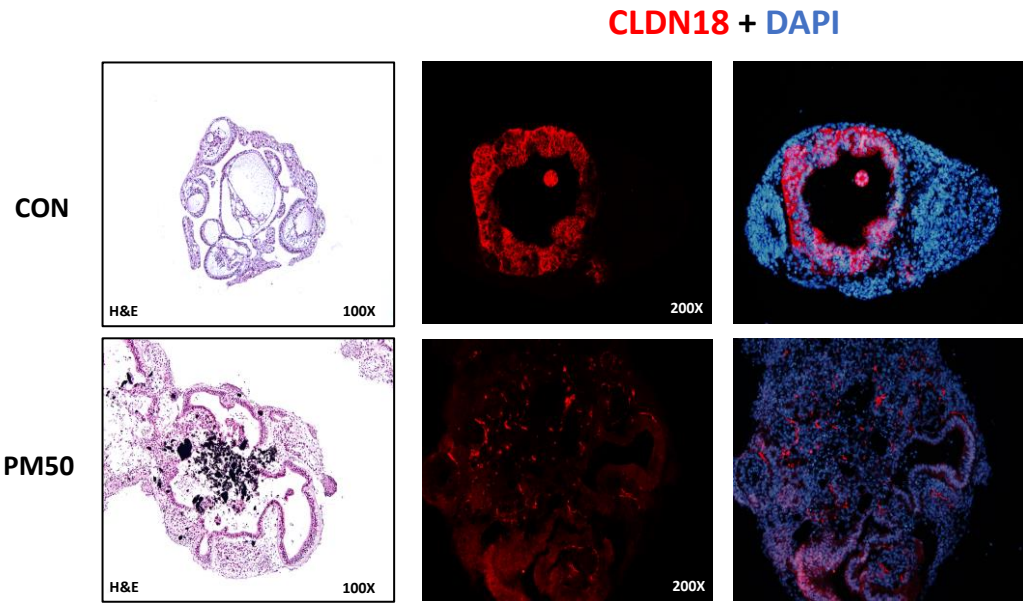


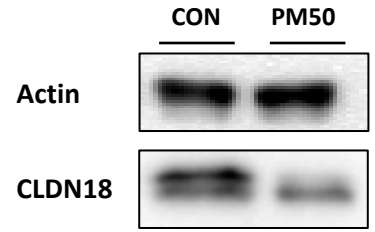
Jung *et al*. J Alle Clin & Immunol (2019)

Developmental toxicology: dPM2.5 exposure triggers alterations in cell to cell junction in AO



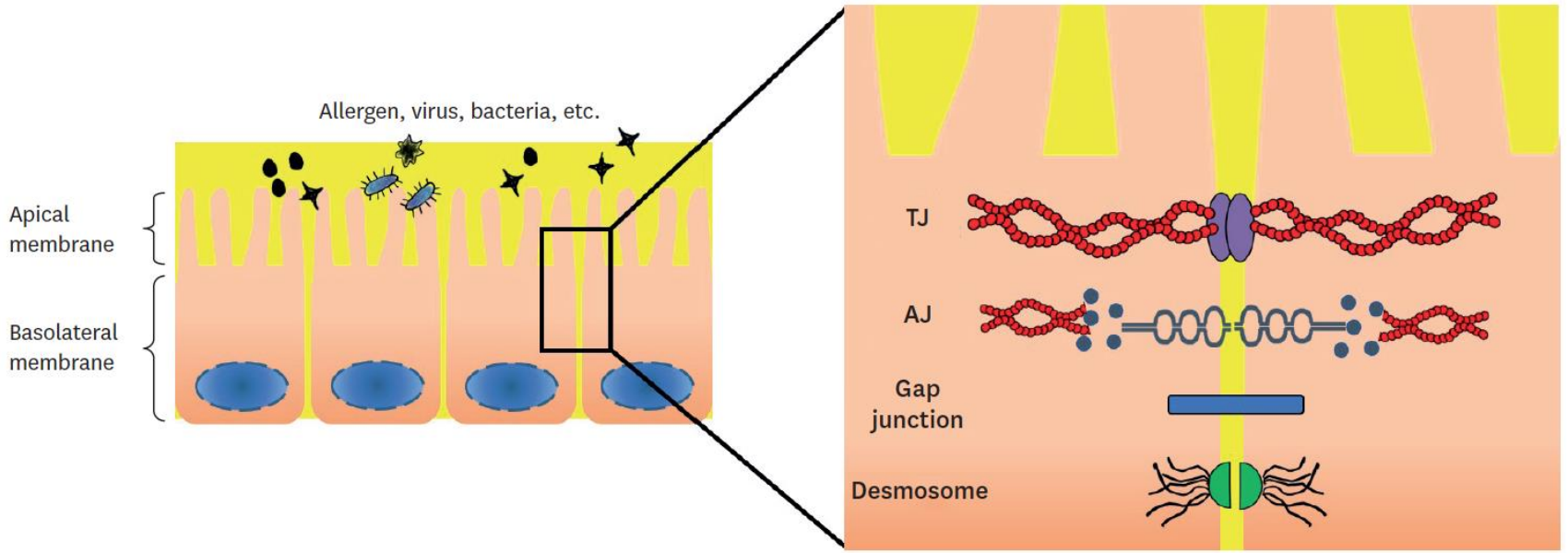






Unpublished

PM exposure during pregnancy is associated with a higher risk of respiratory tract infection



Lee et al. AAIR (2021)

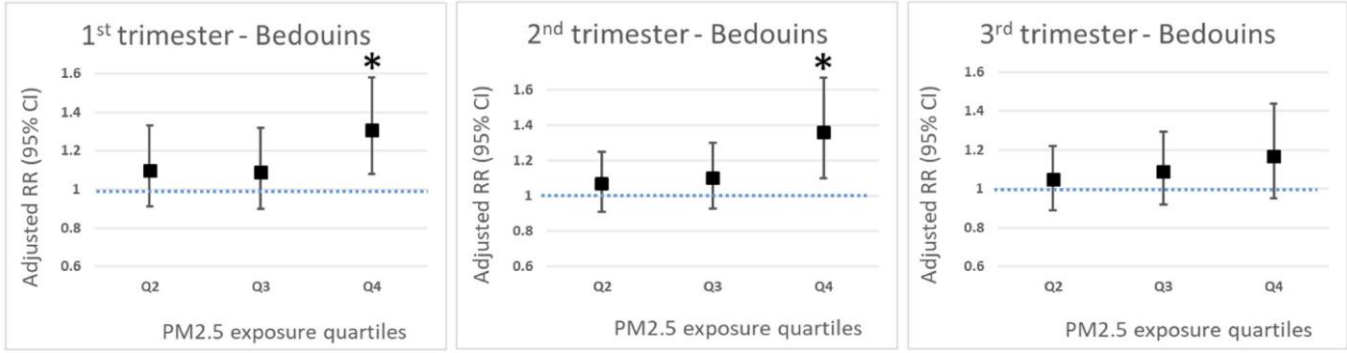
Goshen *et al. Environmental Health* (2020) 19:90
https://doi.org/10.1186/s12940-020-00645-3

Environmental Health

RESEARCH Open Access

The effect of exposure to particulate matter during pregnancy on lower respiratory tract infection hospitalizations during first year of life

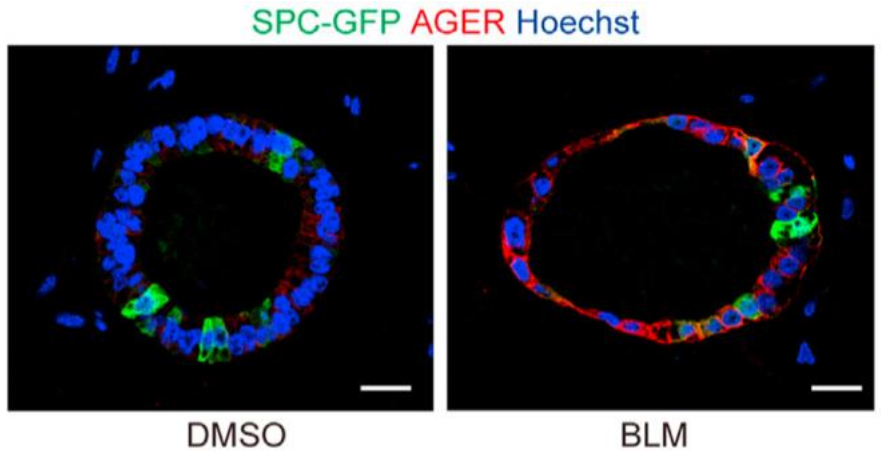
Sharon Goshen[1*], Lena Novack[1,2], Offer Erez[3], Maayan Yitshak-Sade[4], Itai Kloog[5], Alexandra Shtein[5] and Eilon Shany[6]

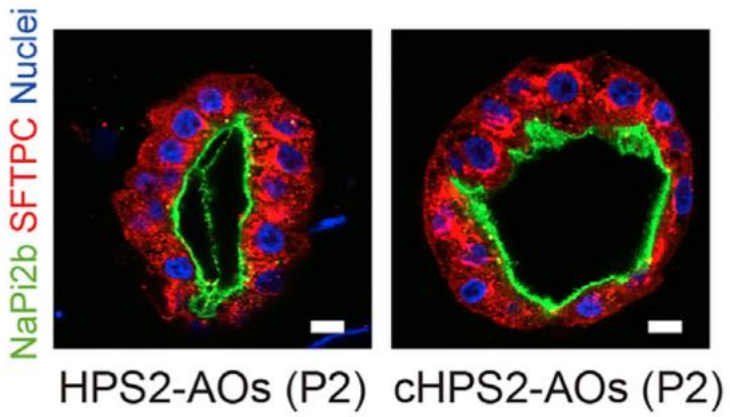


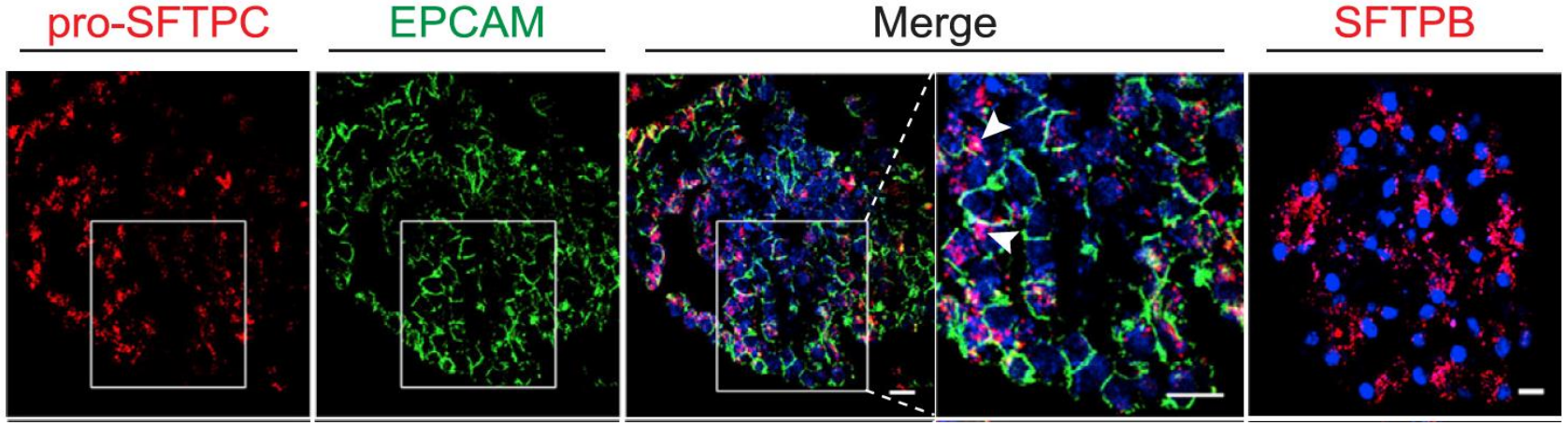
Limitations yet to be overcome (1)

- **Heterogeneity**

Most of AOs are comprised of fibroblast, type 1 and 2 AECs lack of key components such as immune cells and blood vessel.







Limitations yet to be overcome (2)

- **Maturity: similar to fetal lung**

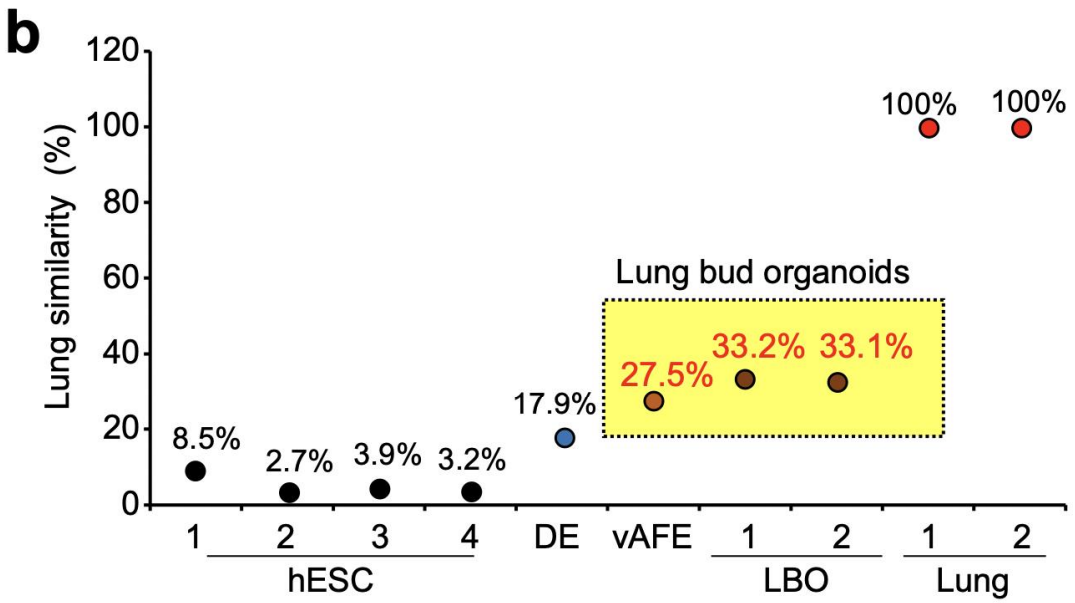
ARTICLE

https://doi.org/10.1038/s41467-021-24746-w OPEN

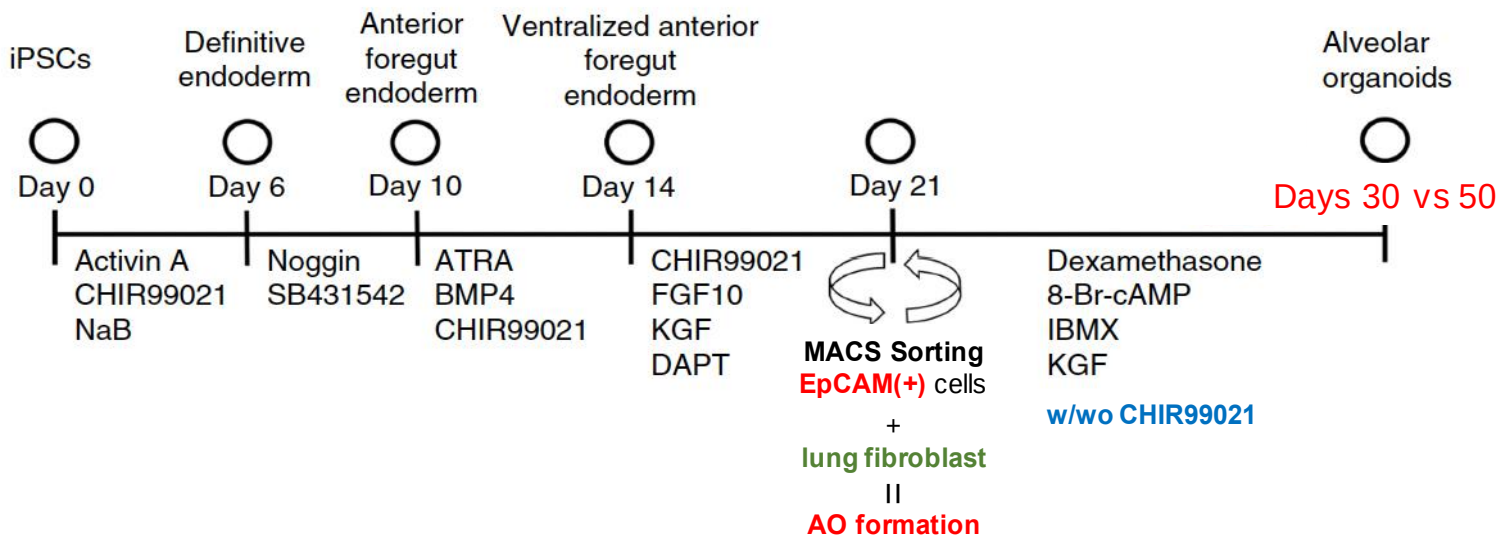
Check for updates

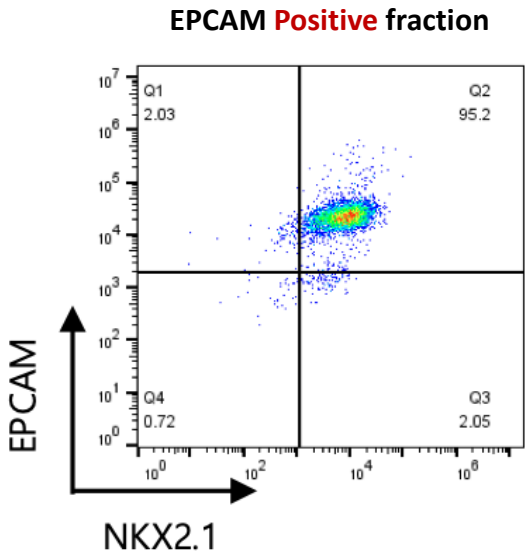
Development of a quantitative prediction algorithm for target organ-specific similarity of human pluripotent stem cell-derived organoids and cells

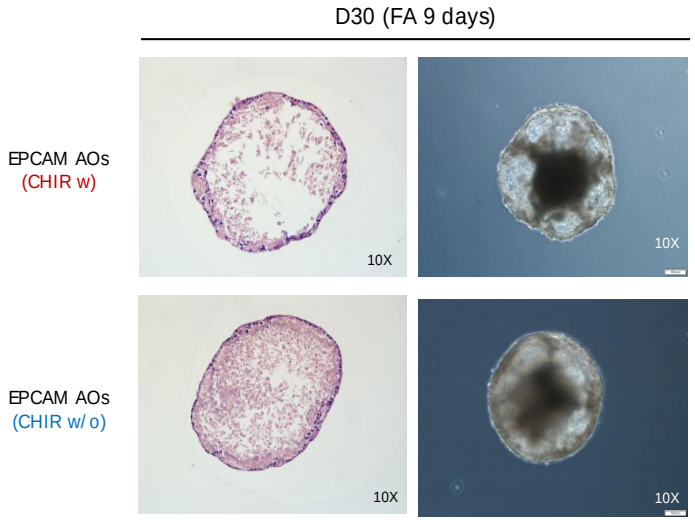
Mi-Ok Lee[1,2,4], Su-gi Lee[1,2,4], Cho-Rok Jung[1,2,4], Ye Seul Son[1,2,4], Jae-Woon Ryu[1], Kwang Bo Jung[1,2], Jun-Ho Ahn[3], Jung-Hwa Oh[3], Hyang-Ae Lee[3], Jung Hwa Lim[1], Janghwan Kim[1,2], Insu Jang[1], Jinhyuk Choi[1], Jaeeun Jung[1], Kunhyang Park[1], Byungwook Lee[1], Dae-Soo Kim[1,2,5✉], Mi-Young Son[1,2,5✉] & Hyun-Soo Cho[1,2,5✉]

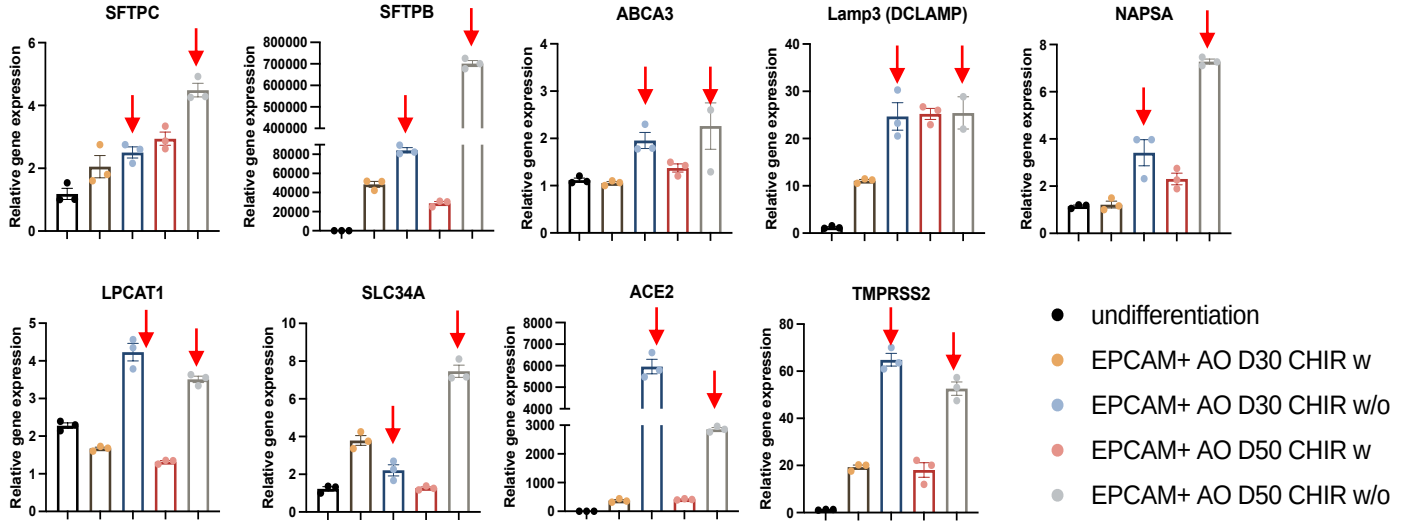


Improvement of maturity and heterogeneity of AO





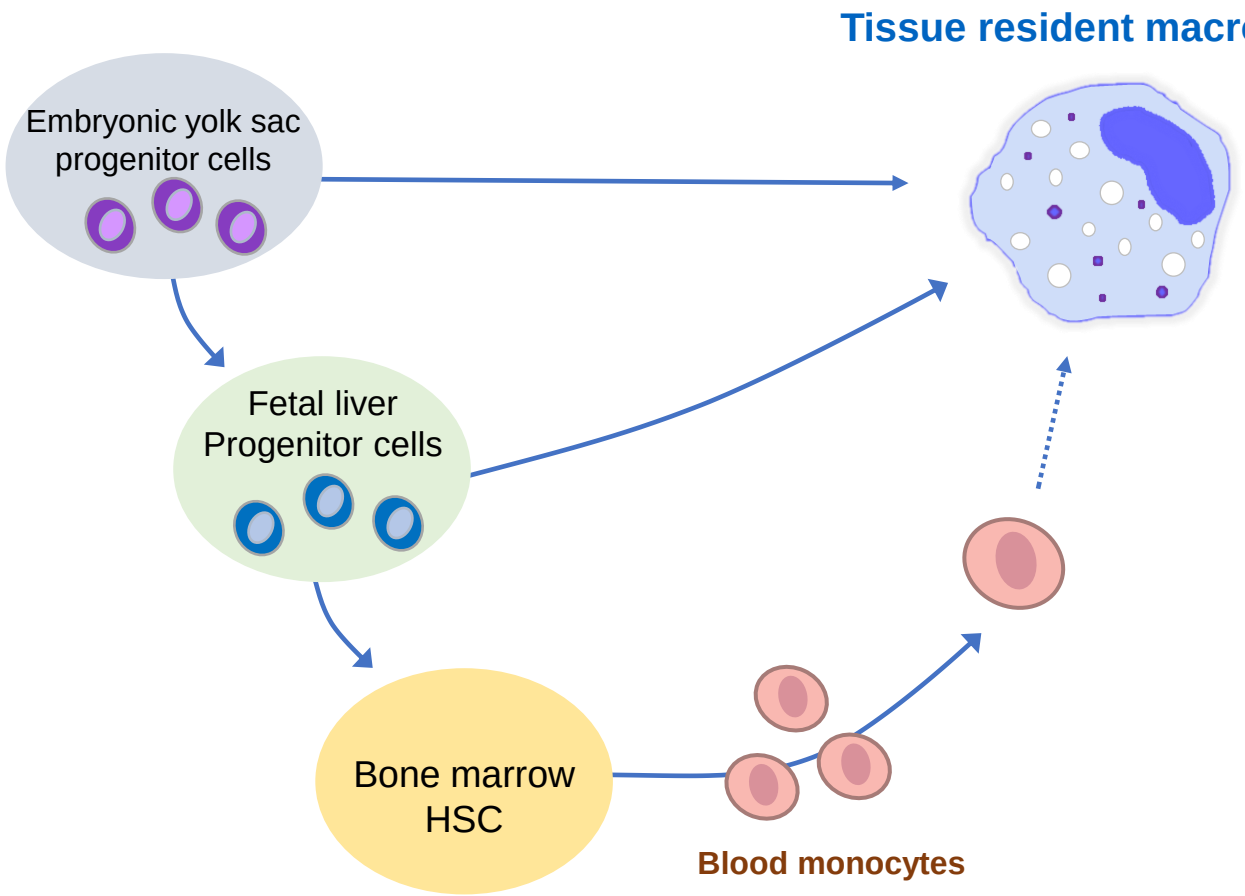


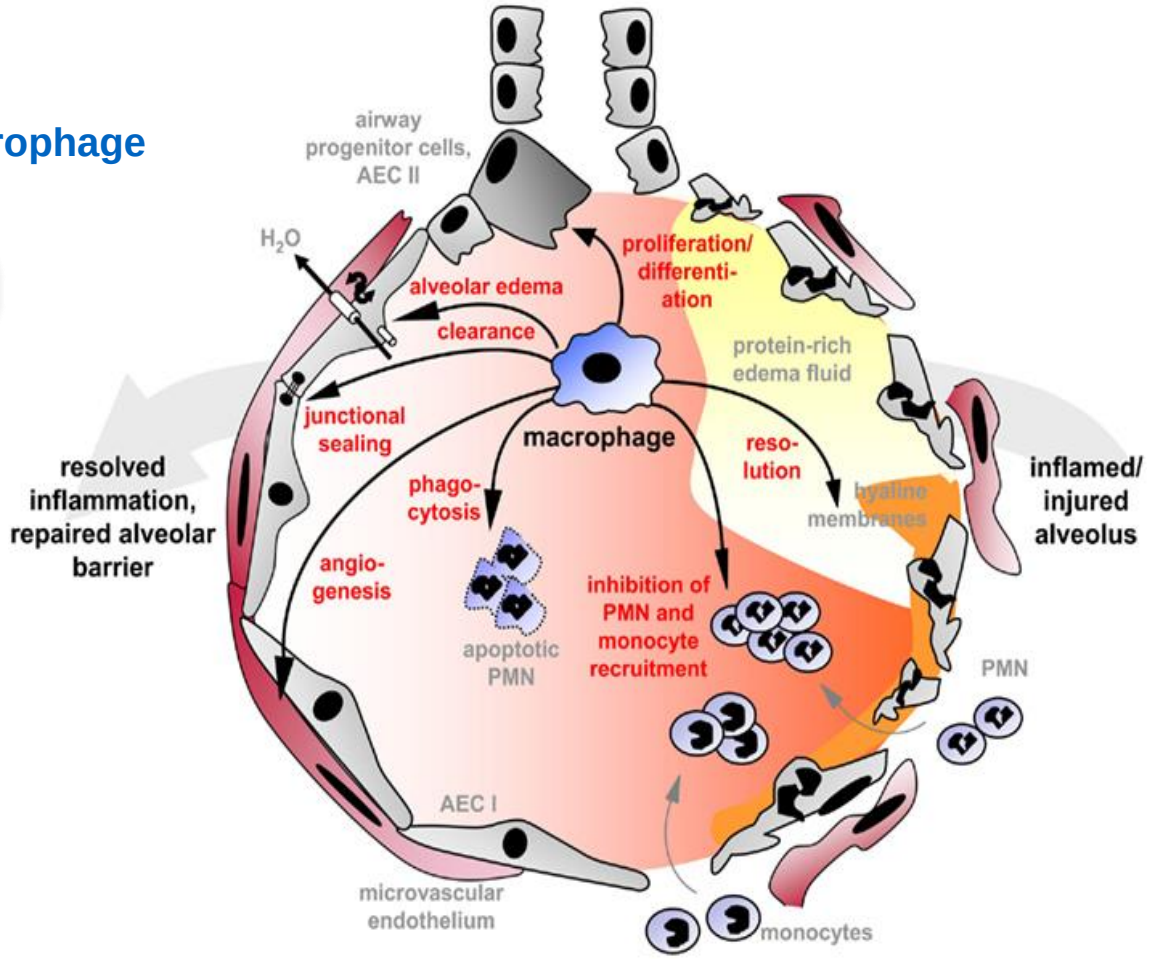


Unpublished

Regulatory functions of macrophages in injured lung

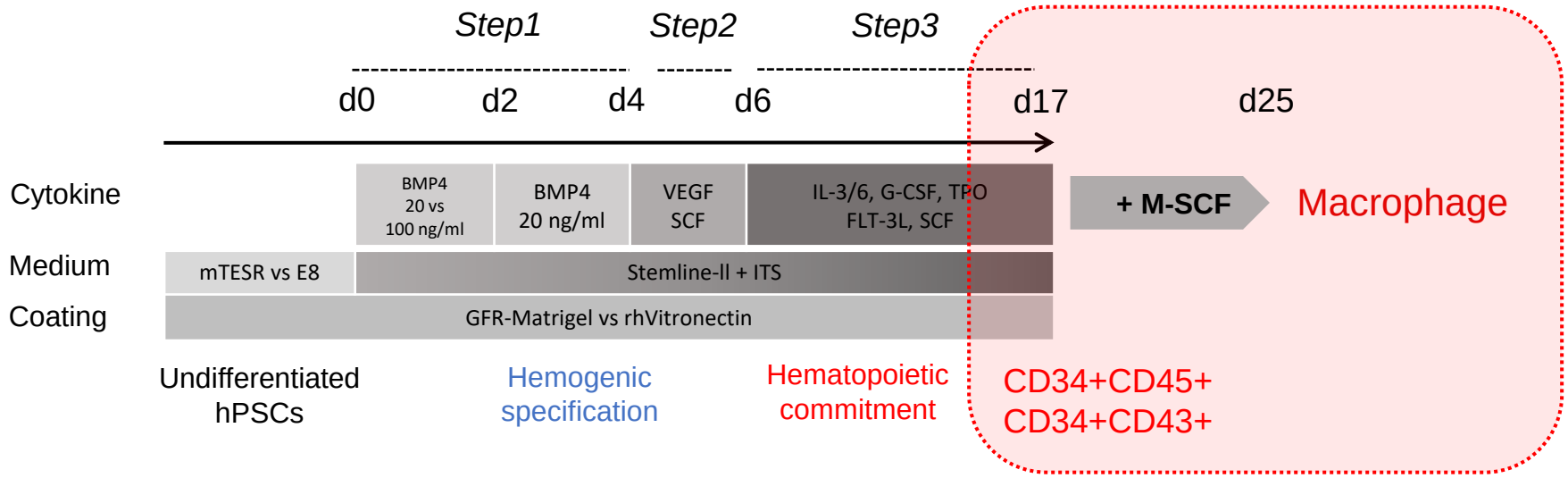
Origin of tissue resident macrophage



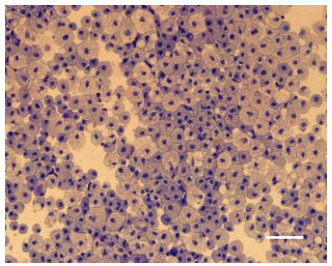


Rasaei *et al*. Int J Mol Sci (2020)

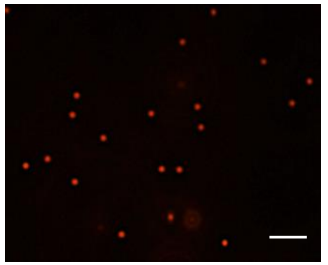
Scalable production of functional macrophages from hPSCs

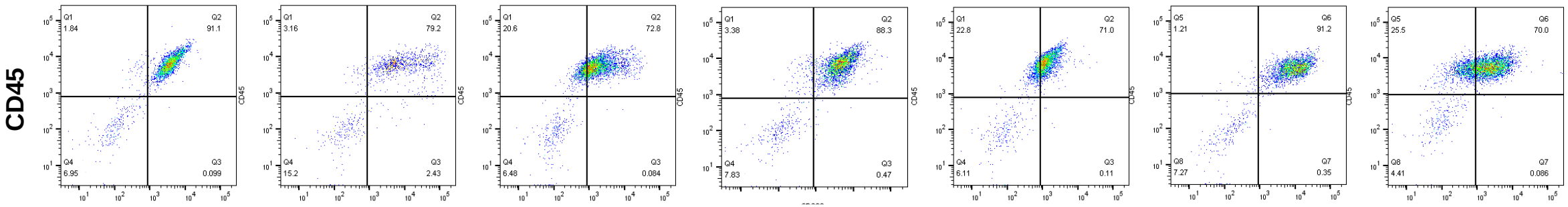


Diff-Quick



Phagocytosis





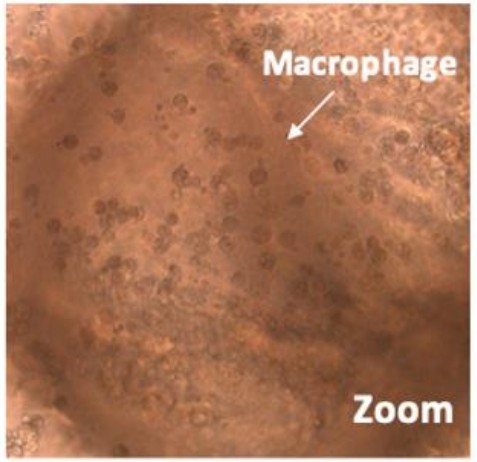
Heo *et al*. Cell and Bioscience (2021)

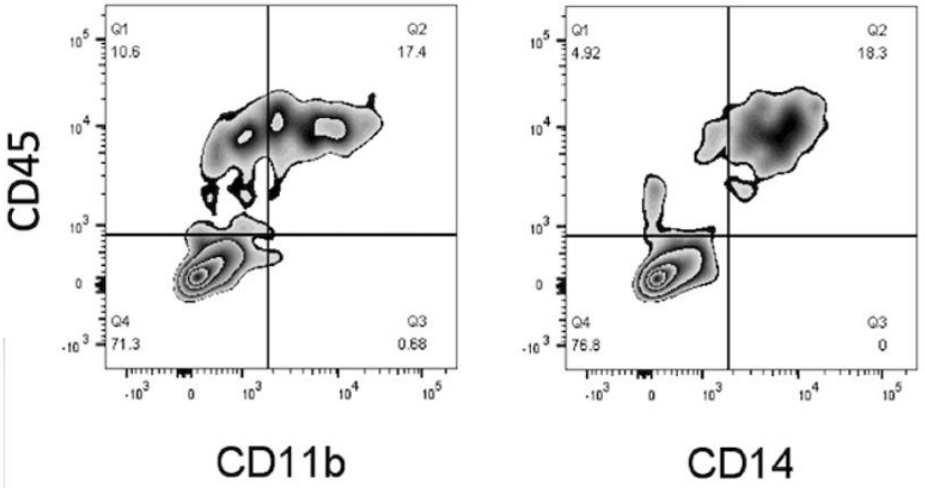
Generation of macrophage & fibroblast containing AO (Mac-FAO) from hPSCs

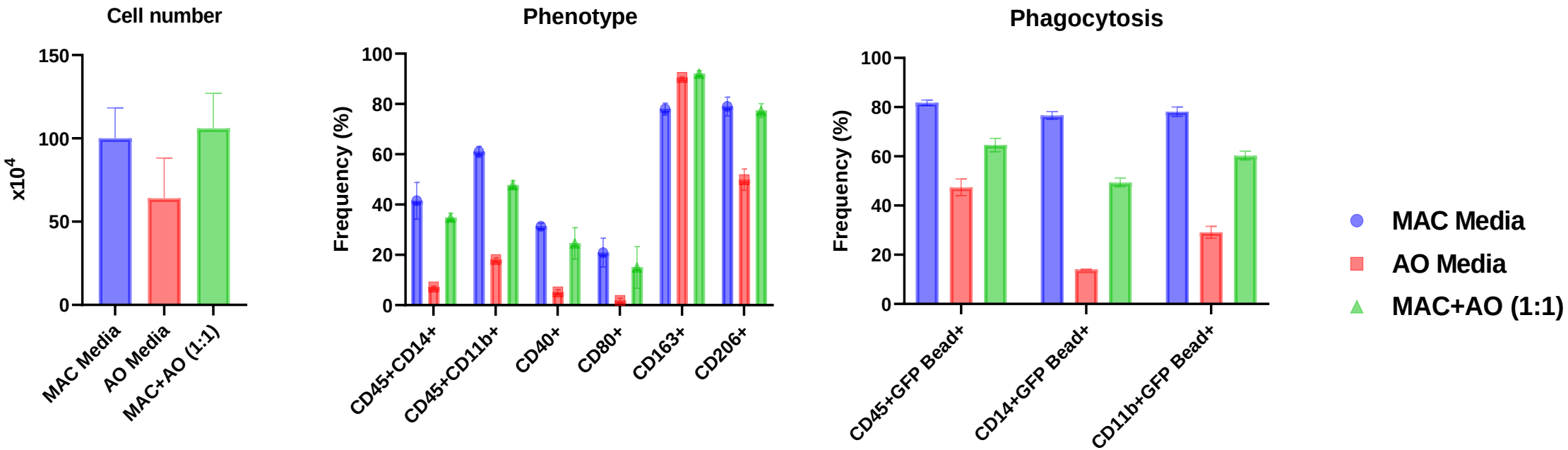
Epithelial : Mac : Fib = 3 : 1 : 1

D23 — 7days — D30 Sampling

EPCAM(+)+
Fibroblast+
Macrophage
} Forced aggreegation

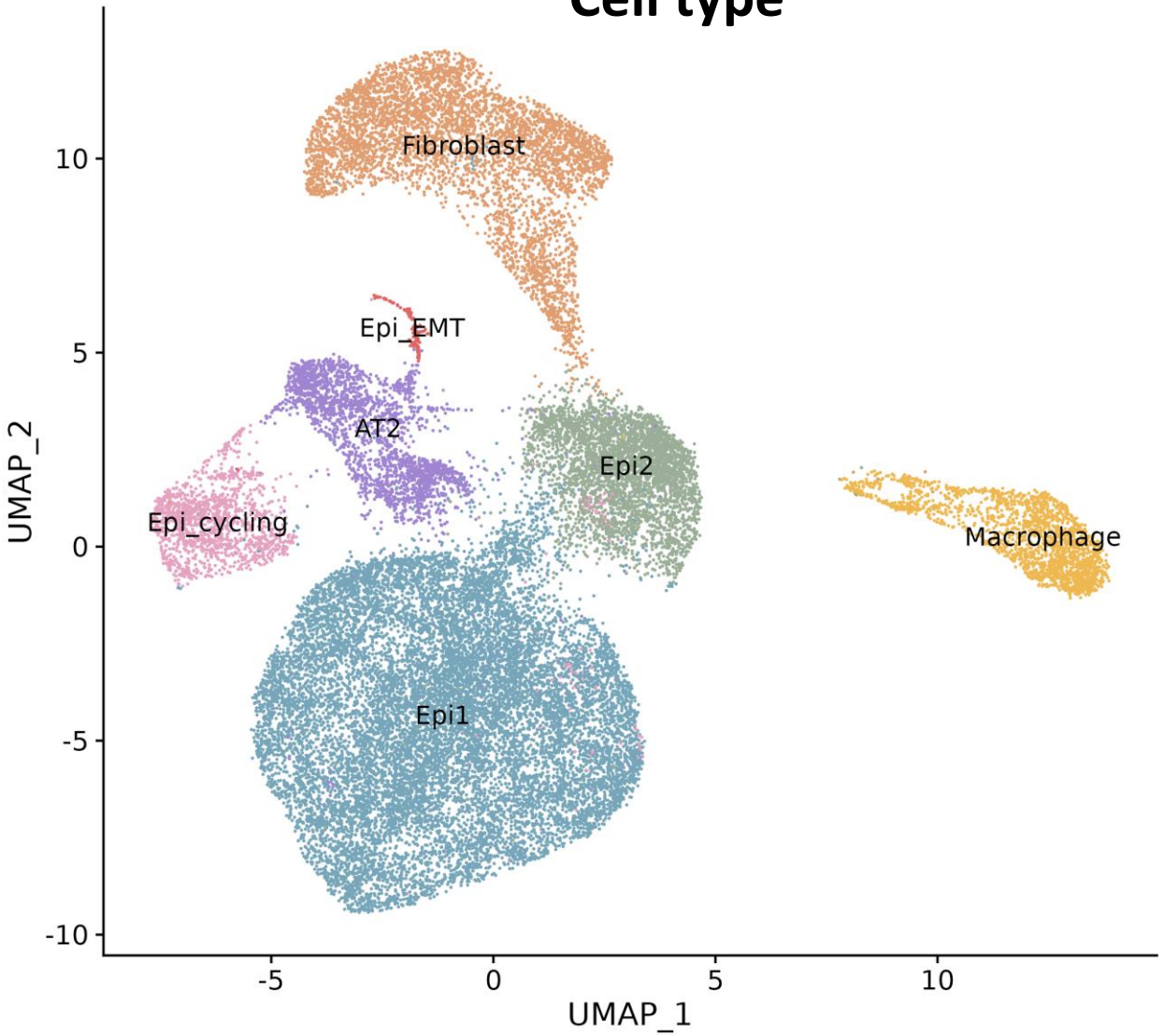






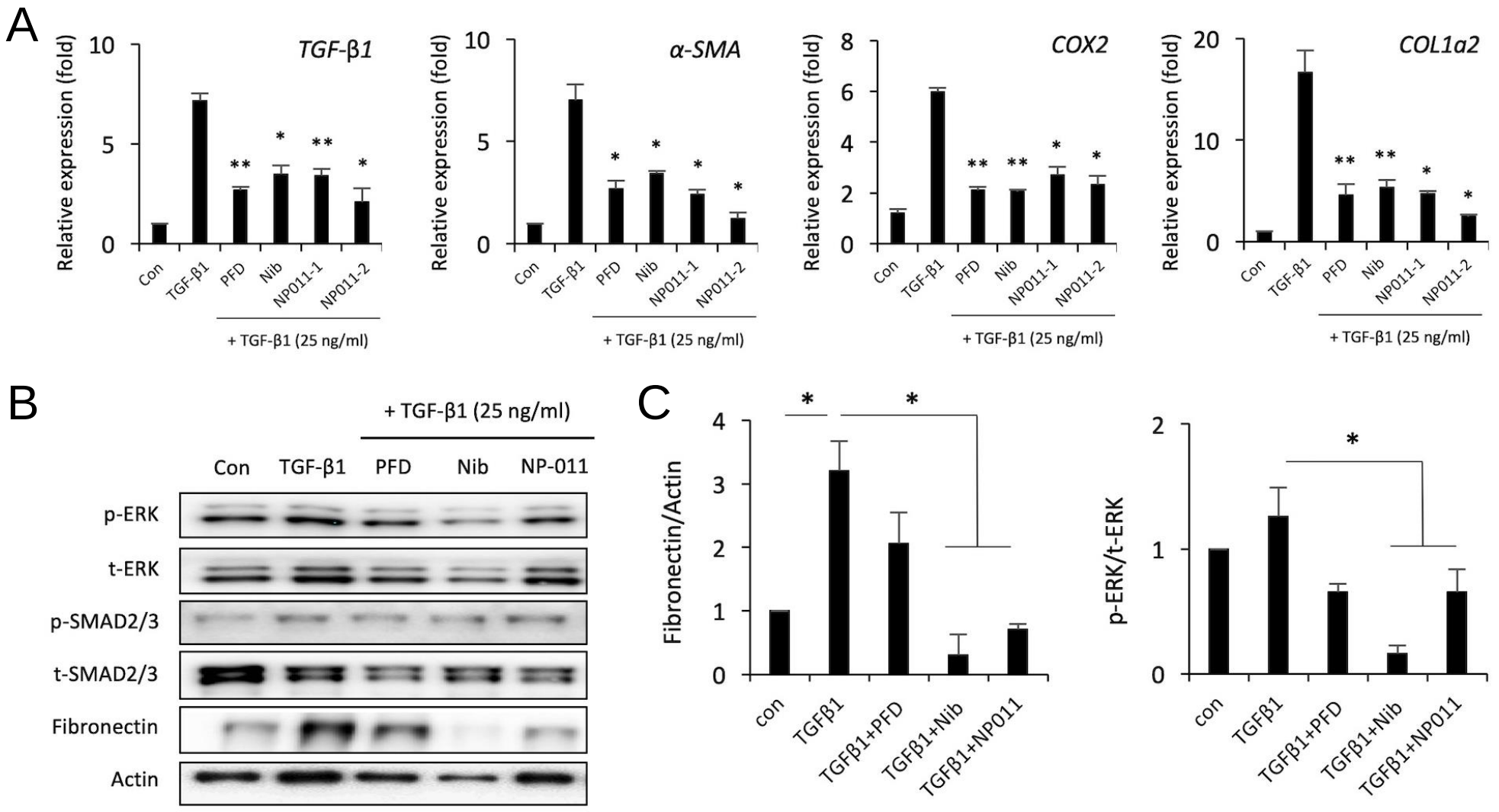
Single cell RNA seq analysis of Mac-FAO

Cell type



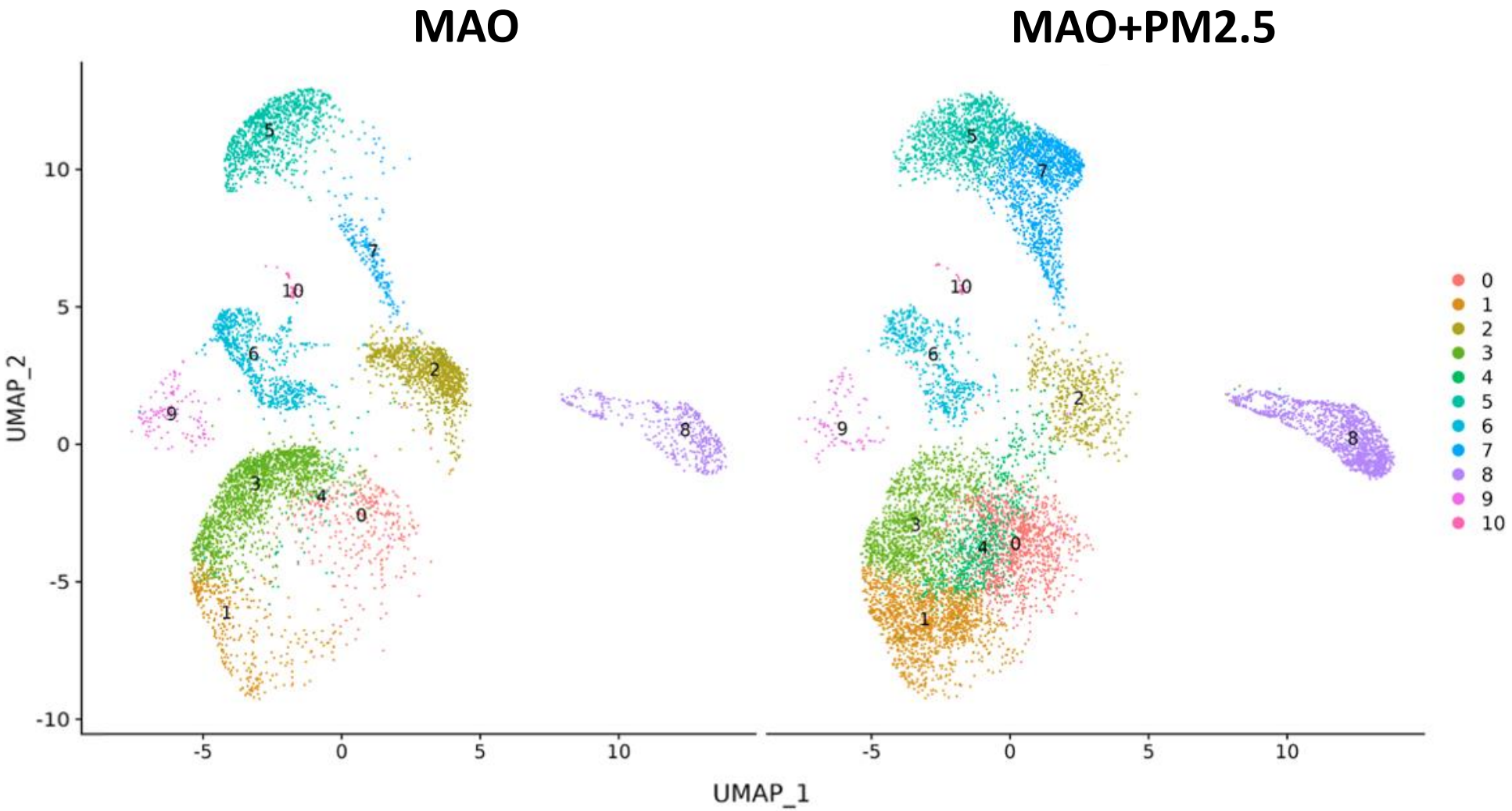
scVelo: RNA velocity analysis

Mac-FAO-based drug efficacy testing for pulmonary fibrosis

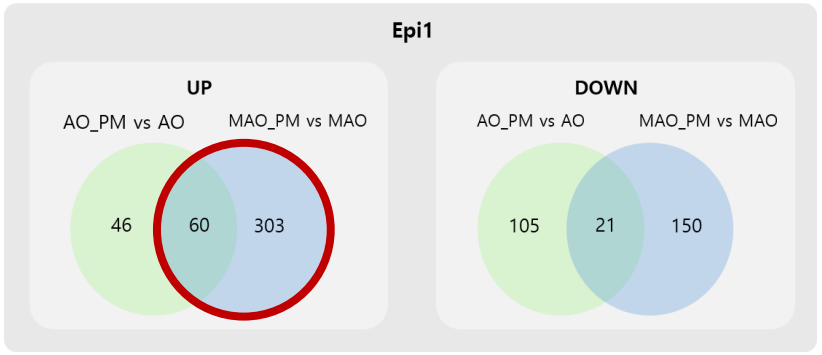


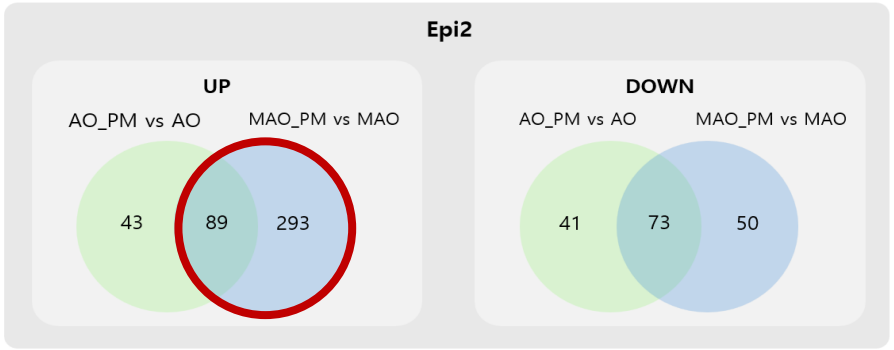
Heo *et al*. Cell and Bioscience (2021)

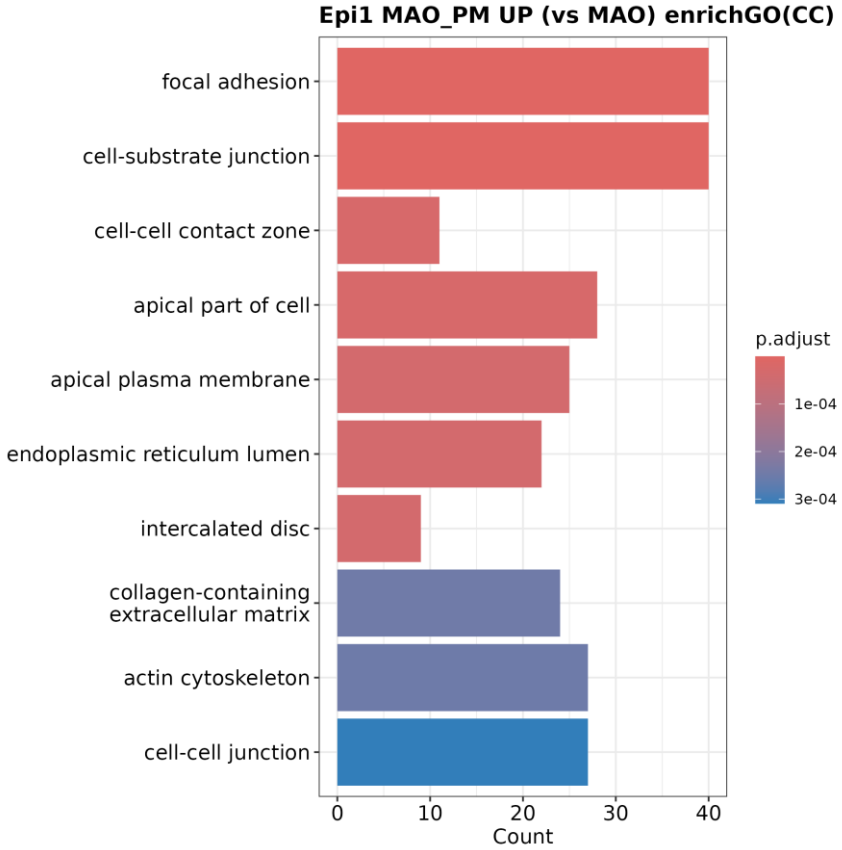
Effects of PM2.5 exposure to Mac-FAO

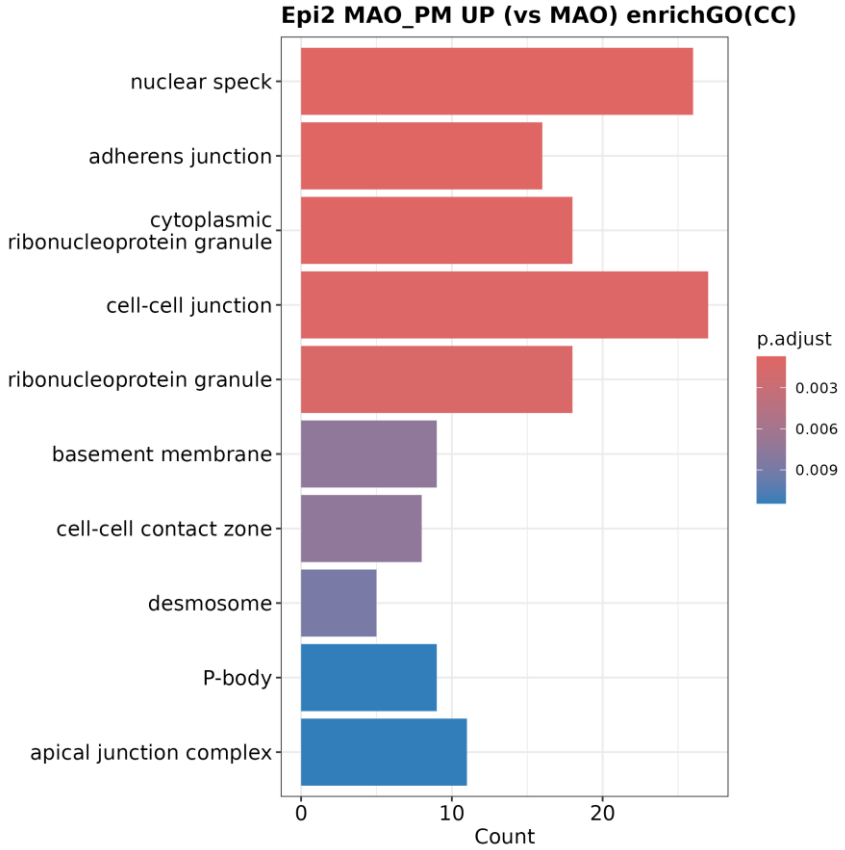


Effects of PM2.5 exposure to epithelial cells of Mac-FAO

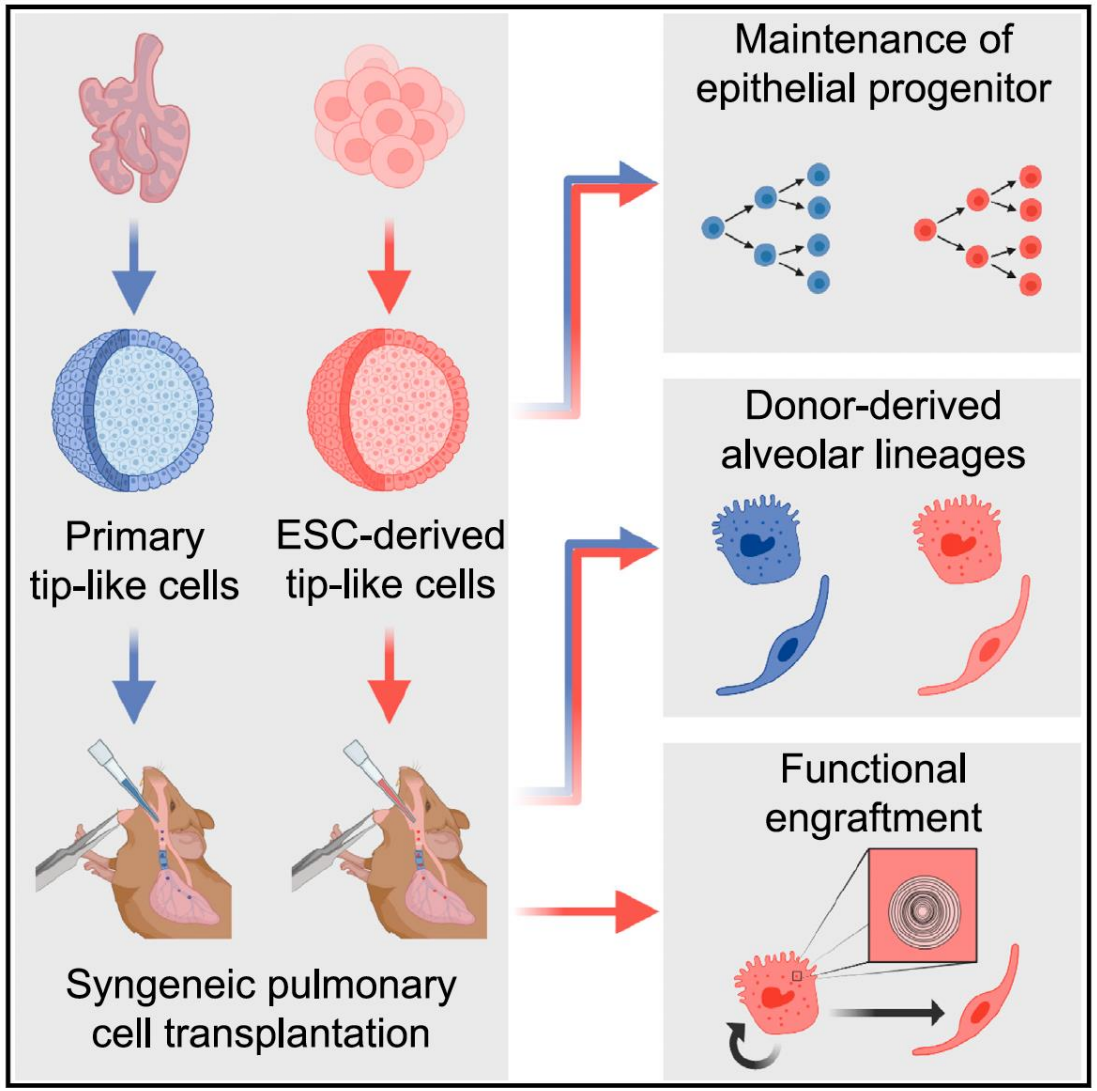




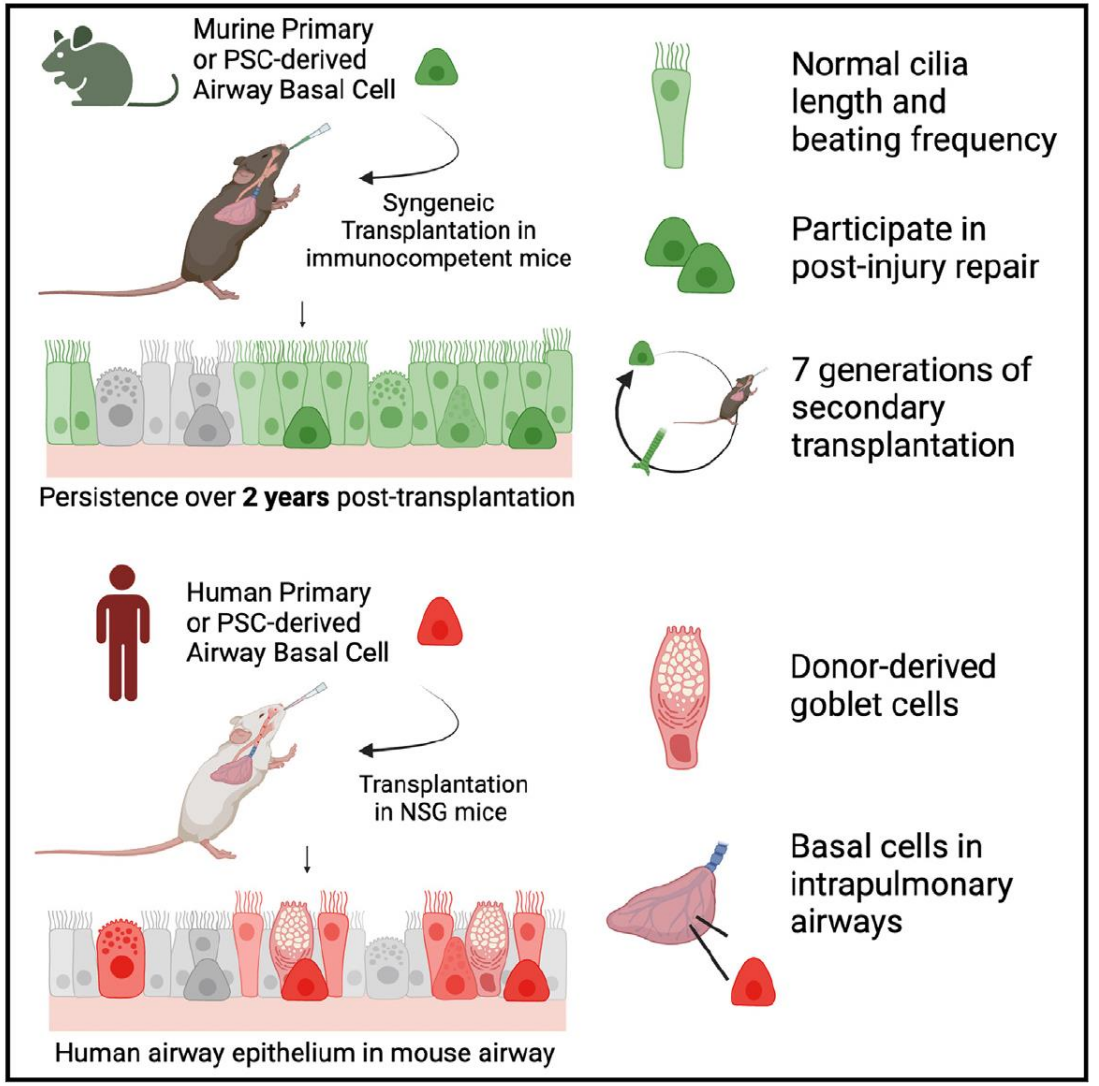




Regenerative medicine: Engraftment of PSC-derived lung epithelial and basal cells

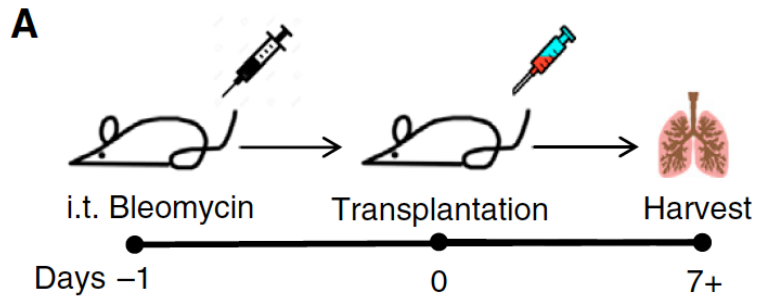


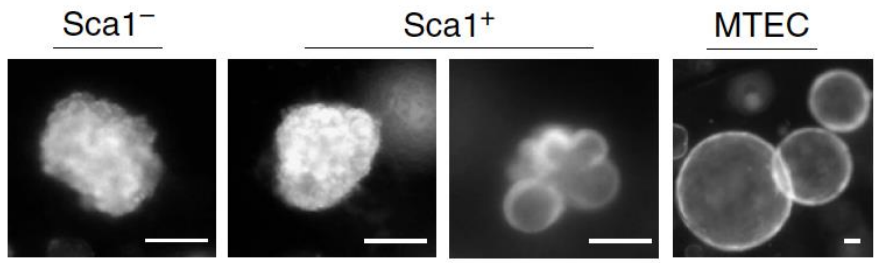
Herriges *et al*. Cell Stem Cell (2023)

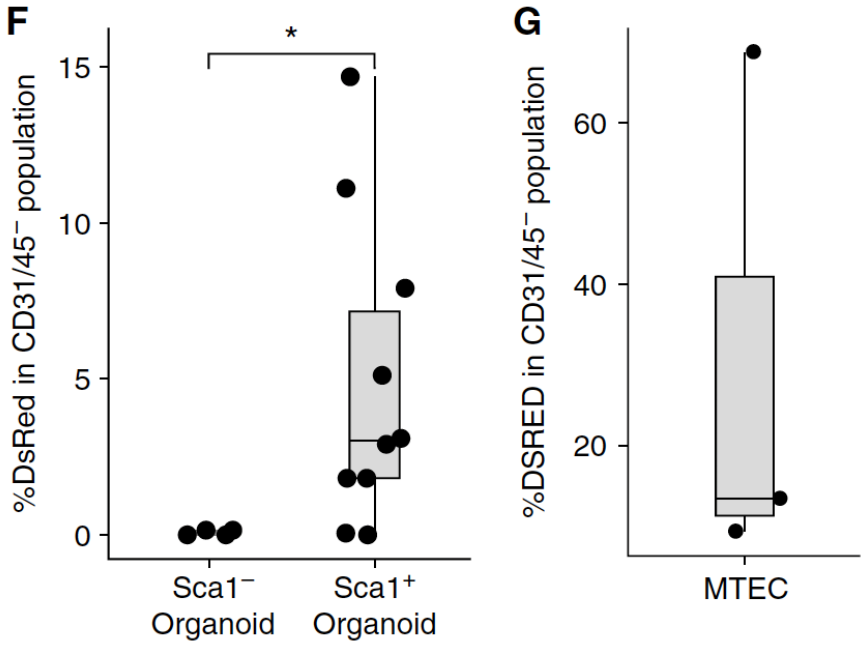


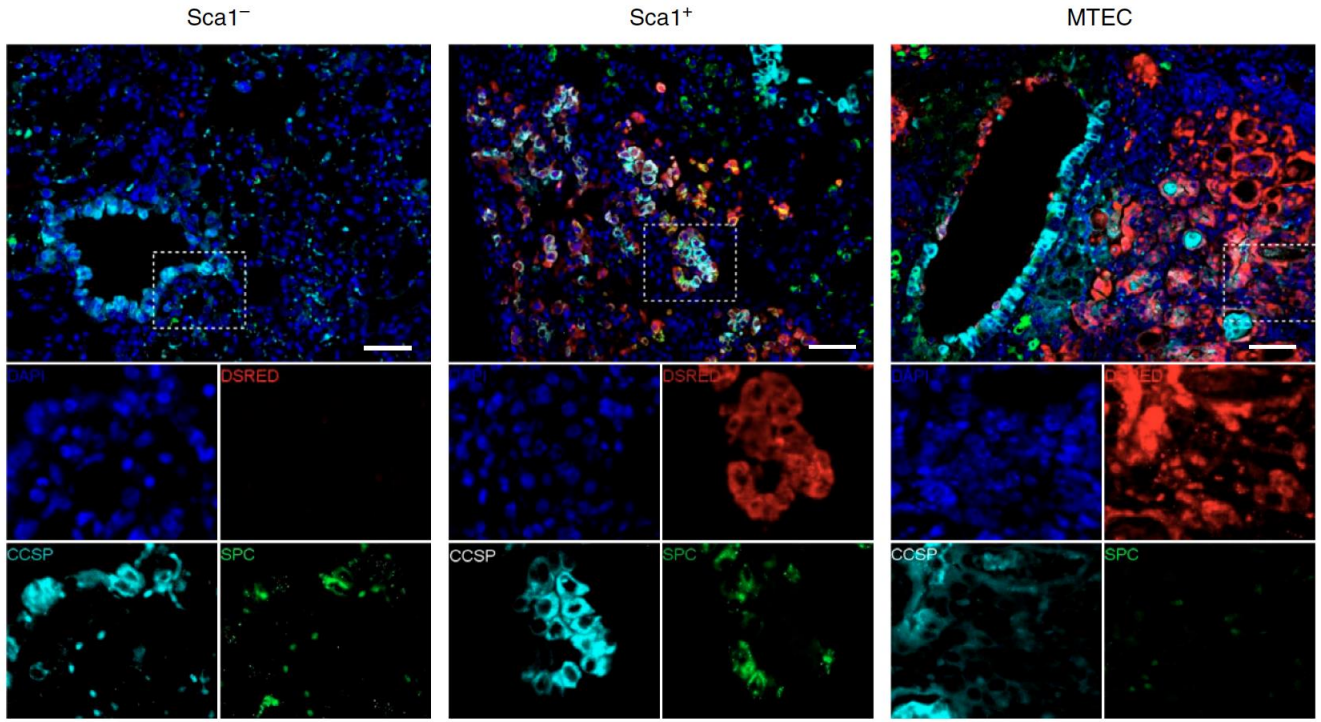
Ma et al. Cell Stem Cell (2023)

Comparison of transplantation of lung organoid cell types: *One Size Does Not Fit All*





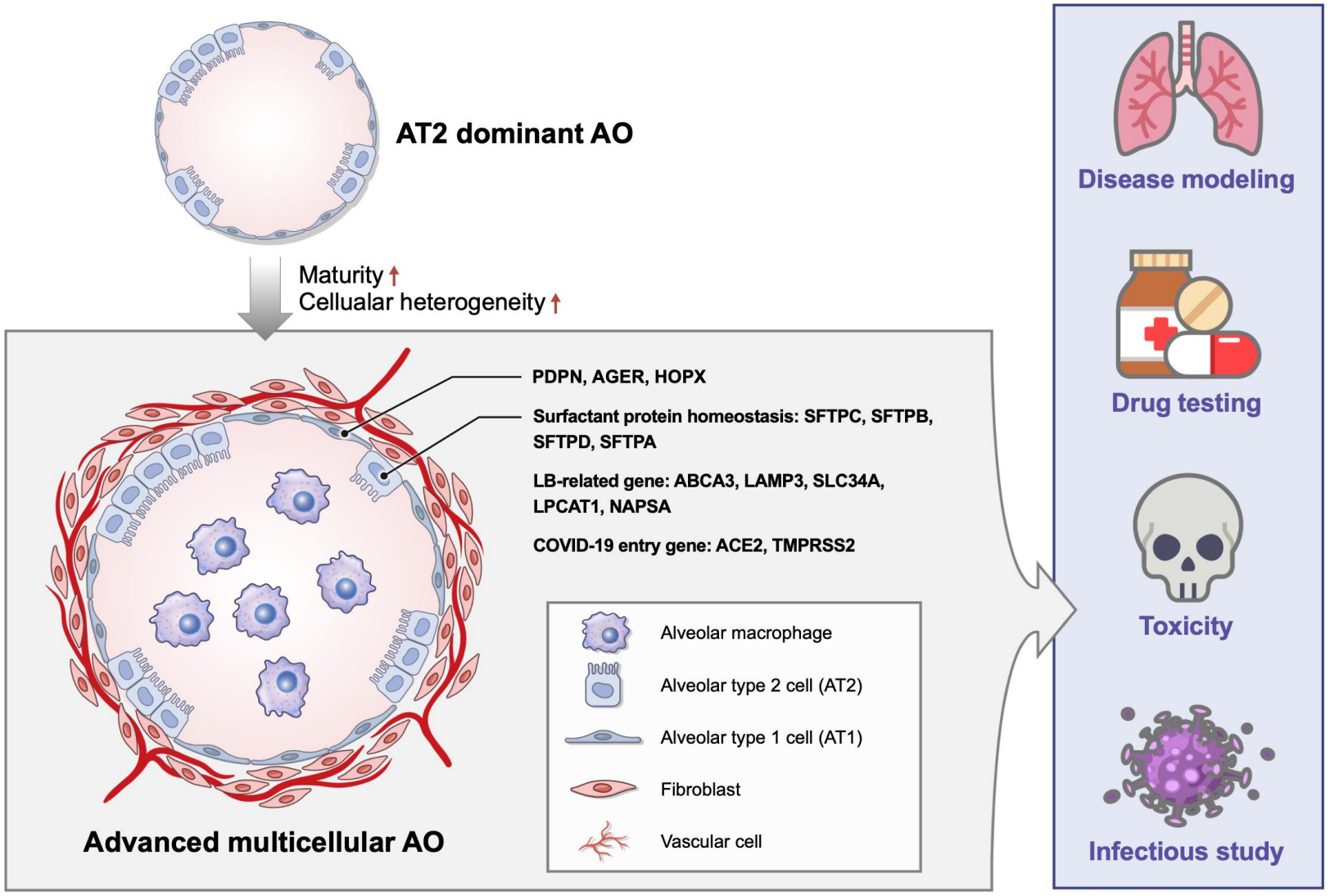




Cells grown in organoid cultures had more robust transplantation capacity than freshly sorted cells

Ararat *et al*. AJRCMB (2022)

Further optimization for better shape and function of human alveolar organoid



Limitations

Lack of tissue microenvironment

Limited long-term expansion

Suboptimal culture condition

Lack of complete maturation (vs adult tissues)

Jung *et al*. Tuber Res Dis (2024)

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