

# Senolytic CAR T cells reverse senescence-associated pathologies

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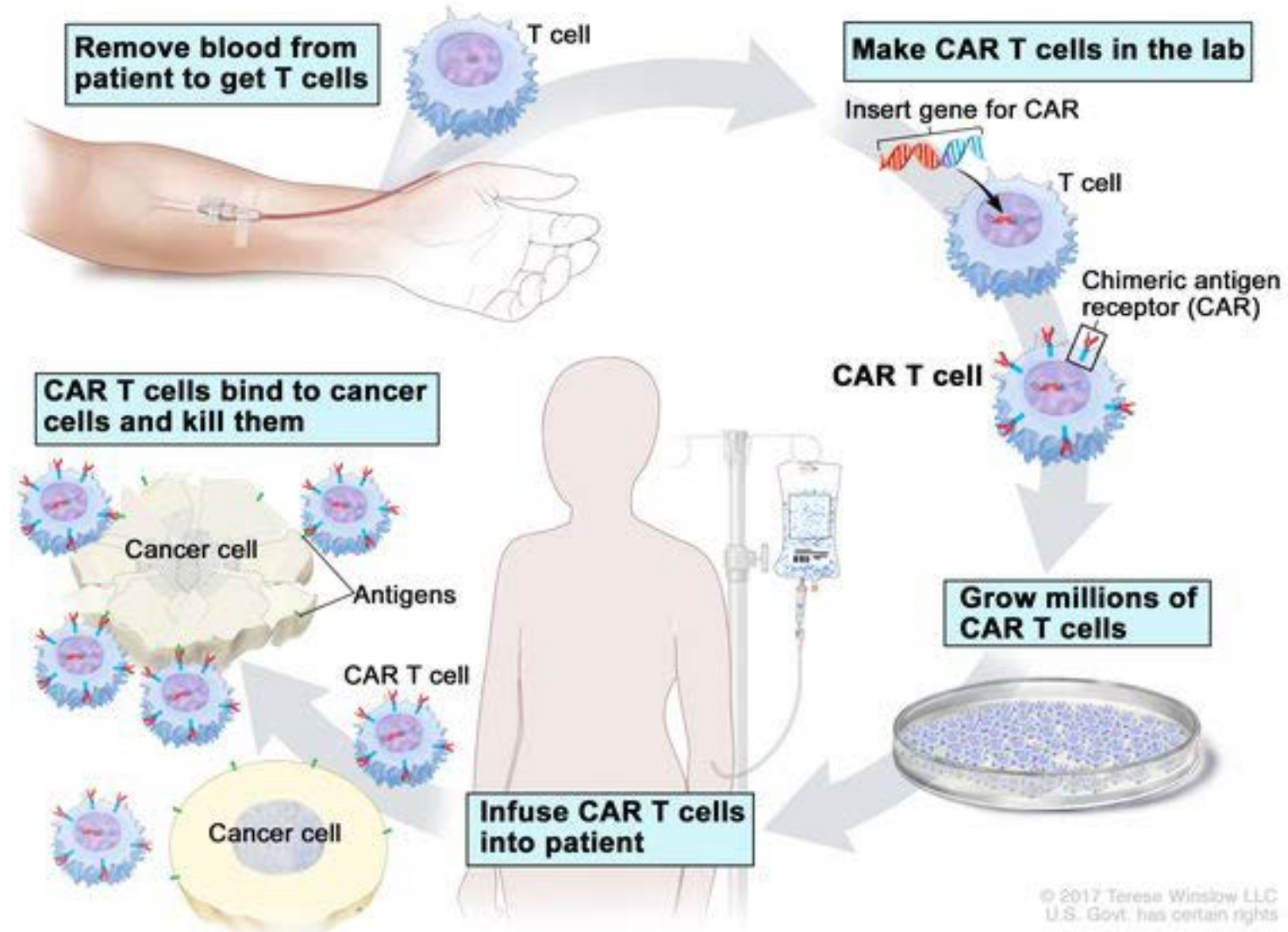
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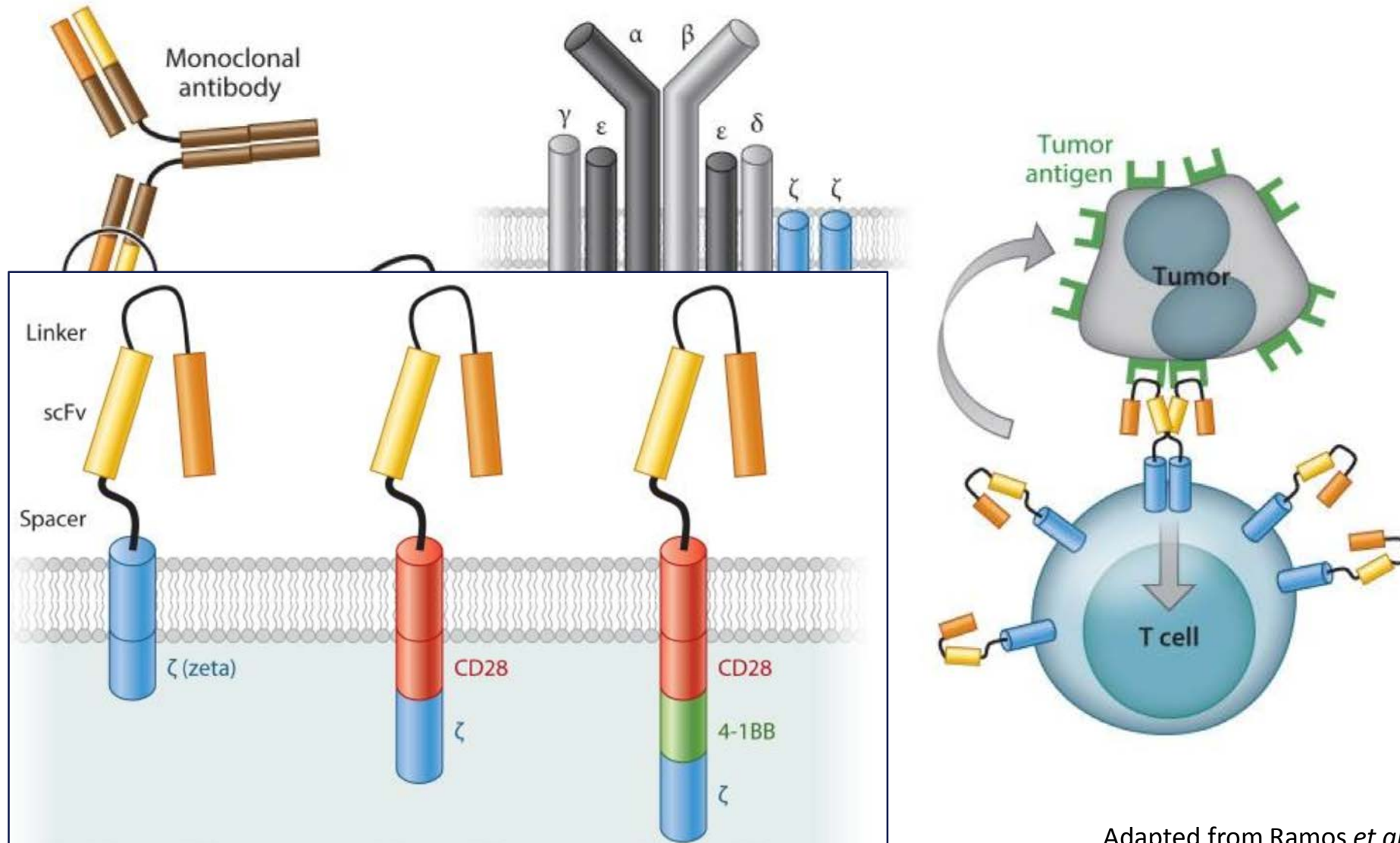
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# Chimeric antigen receptor (CAR) T cell therapy



<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy>

# Structure of chimeric antigen receptors



Adapted from Ramos *et al.*, *Annu Rev Med.* (2016)

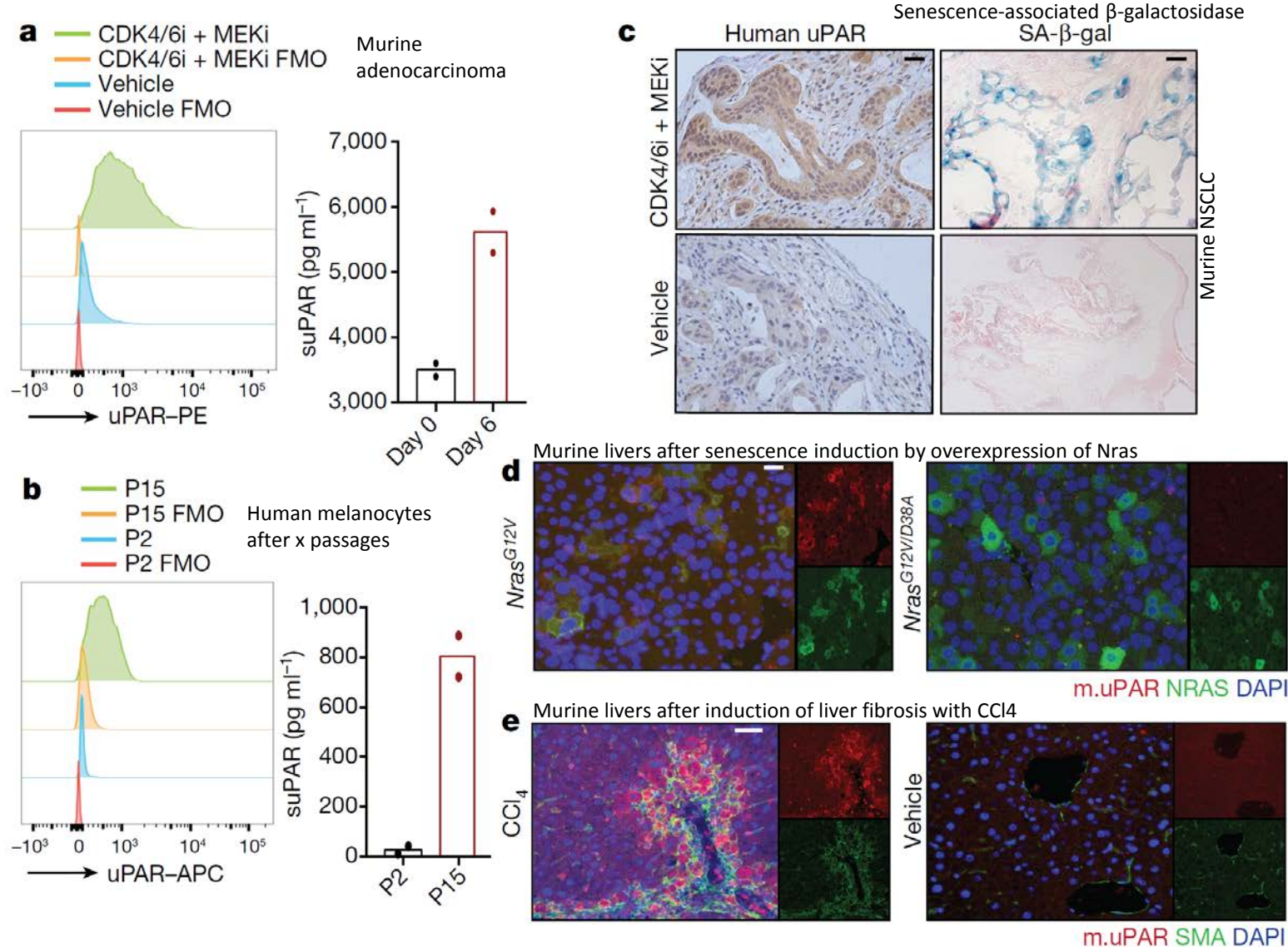
# Rationale of the study

- Age-related pathologies such as liver and lung fibrosis, atherosclerosis, DM2 and osteoarthritis
- In these diseases, aberrant accumulation of senescent cells generates an inflammatory milieu

## Proposed solution:

Elimination of senescent cells via CAR T cells

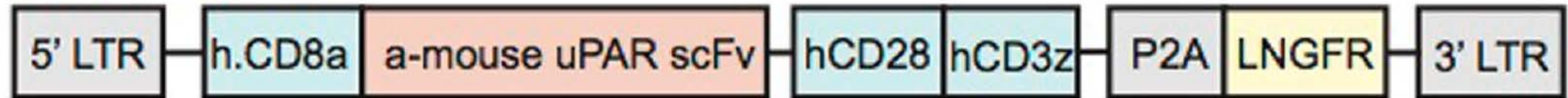
# Identification of a cell senescence-specific target



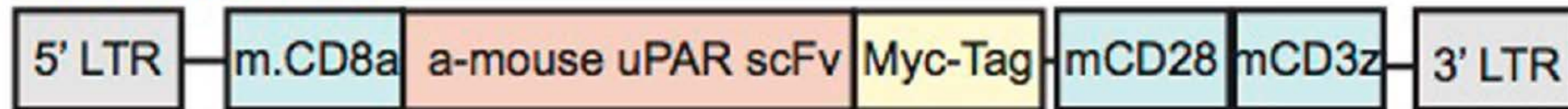
- **uPAR** (urokinase-type plasminogen activator receptor)
- High expression on senescent cells but also on bronchial epithelium, monocytes, macrophages and neutrophils
- Promotes processes in wound healing but also tumorigenesis
- suPAR (soluble uPAR)

# Design of uPAR-specific CARs

## m.uPAR-h.28z



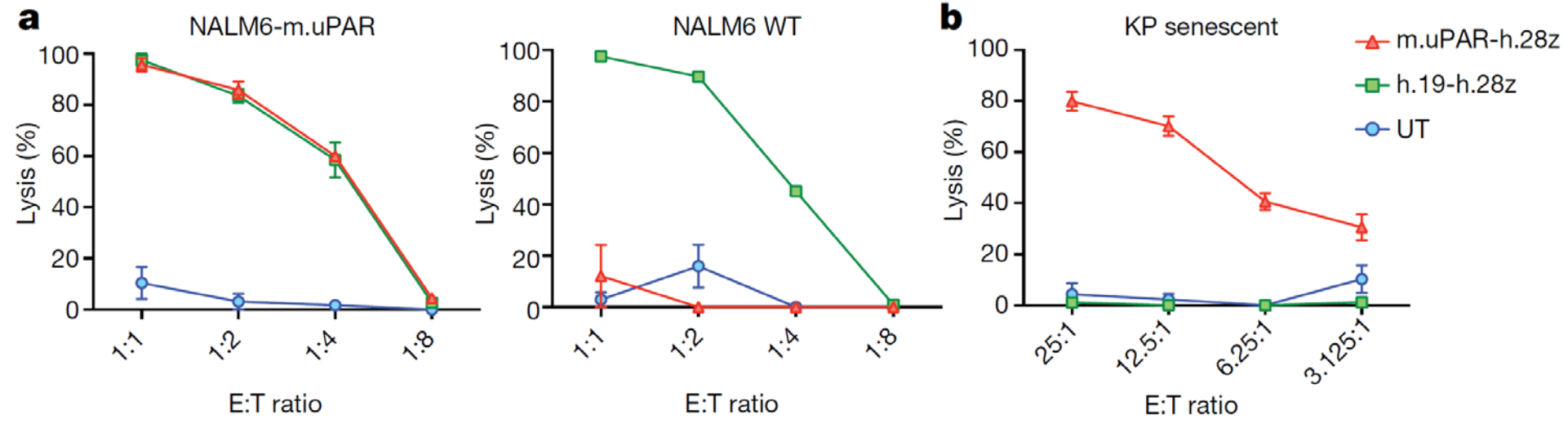
## m.uPAR-m.28z



# uPAR-specific CAR T cells remove senescent cells *in vitro* and *in vivo* (1/2)

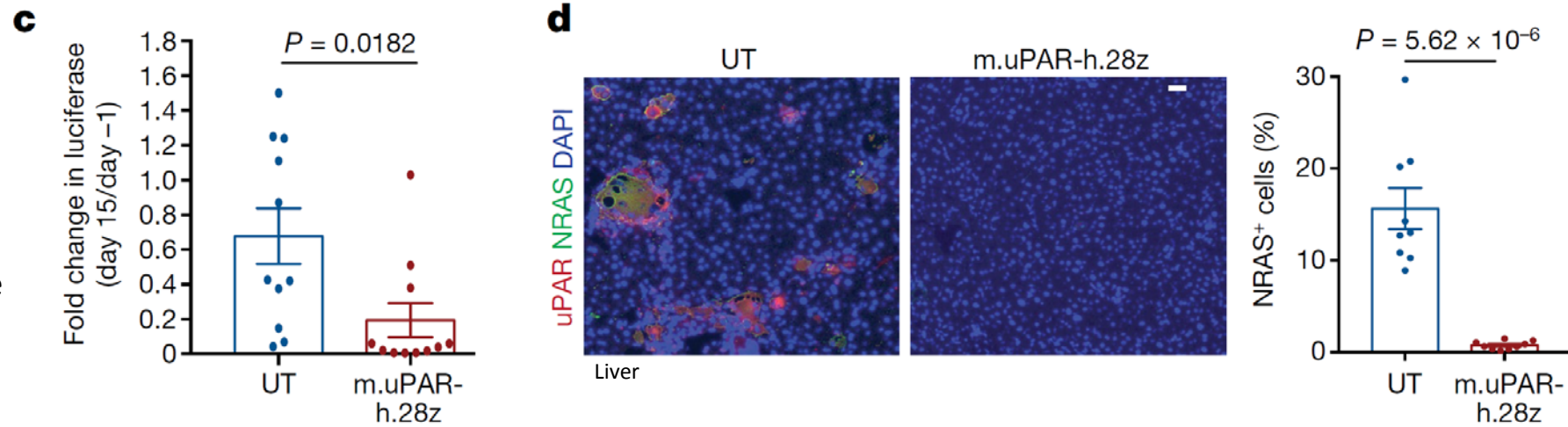
*In vitro*

Killing assays

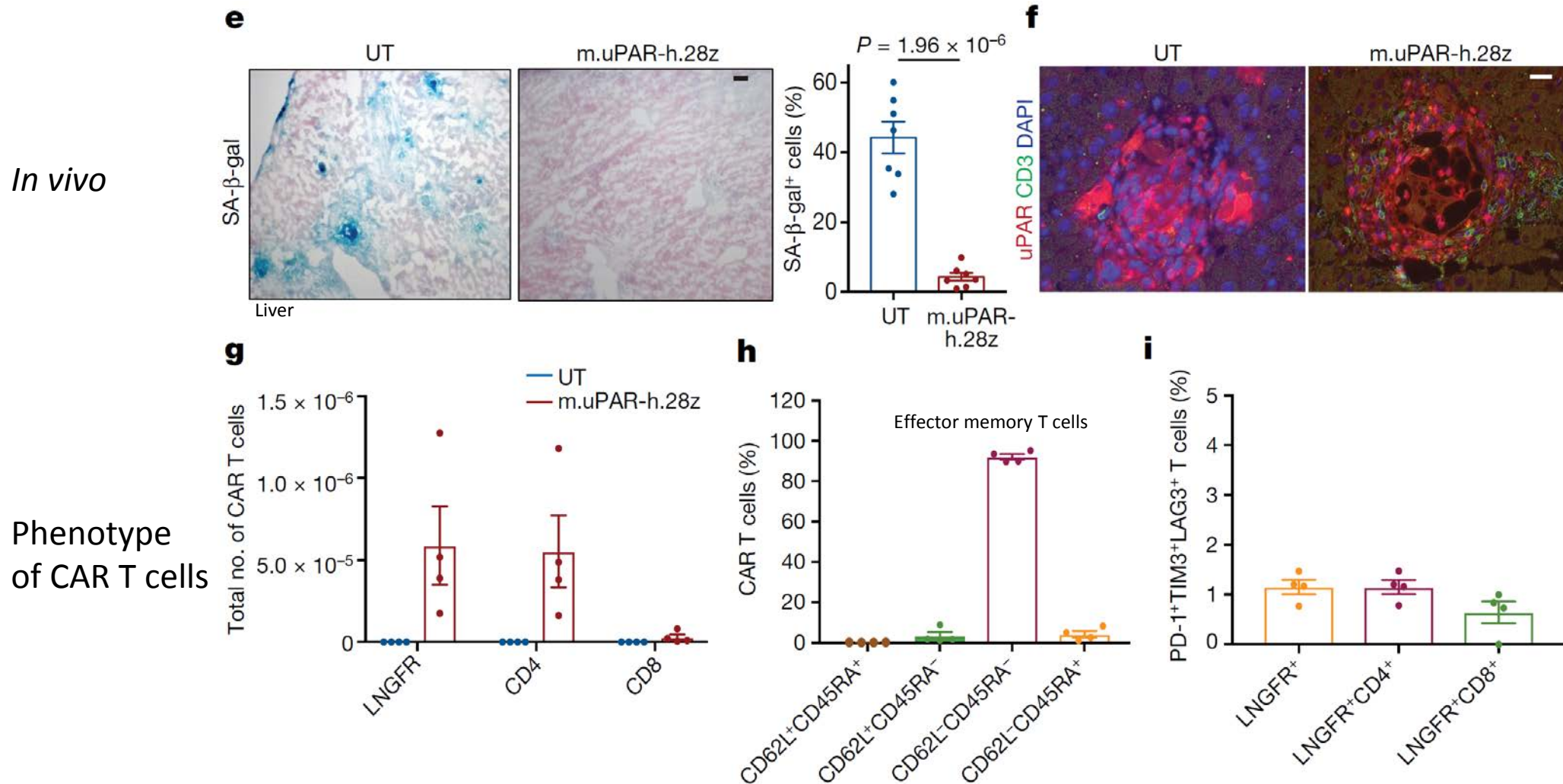


*In vivo*

Cell senescence in mice was induced by injection with Kras-encoding plasmid; then mice were treated with CAR T cells.



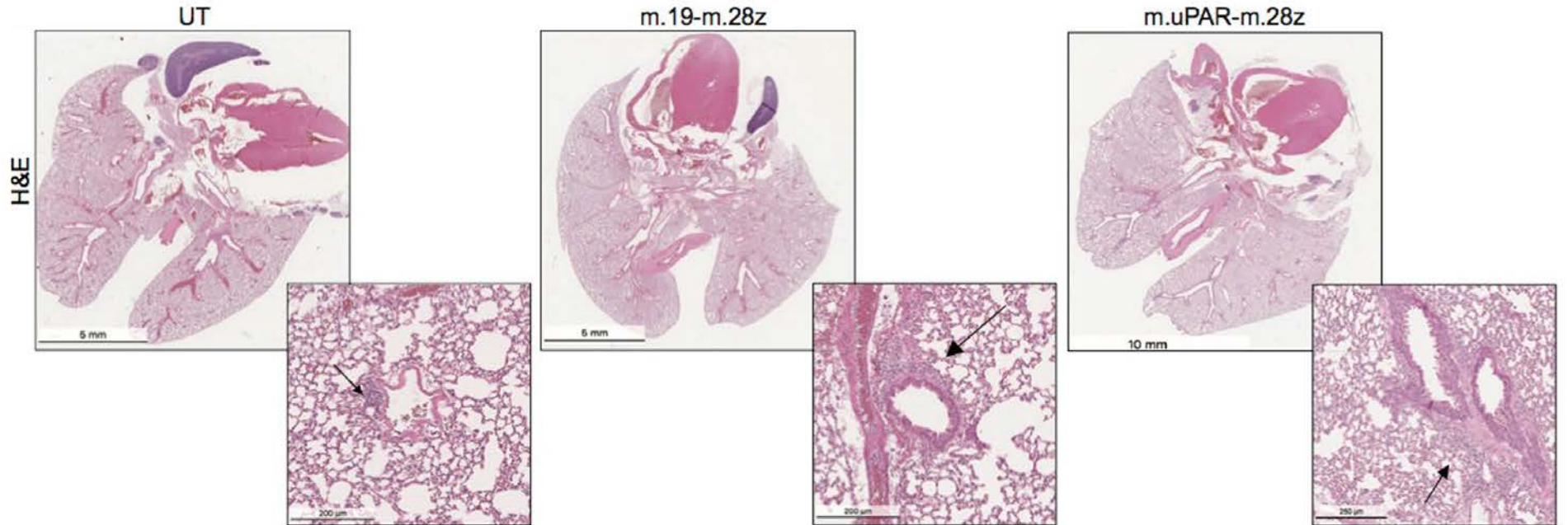
# uPAR-specific CAR T cells remove senescent cells *in vitro* and *in vivo* (2/2)



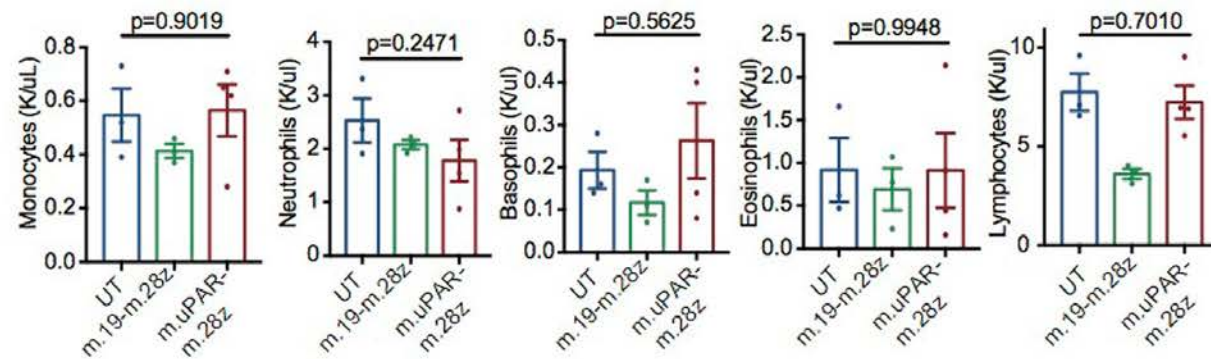


# No significant off-target effects of uPAR-specific CAR T cells

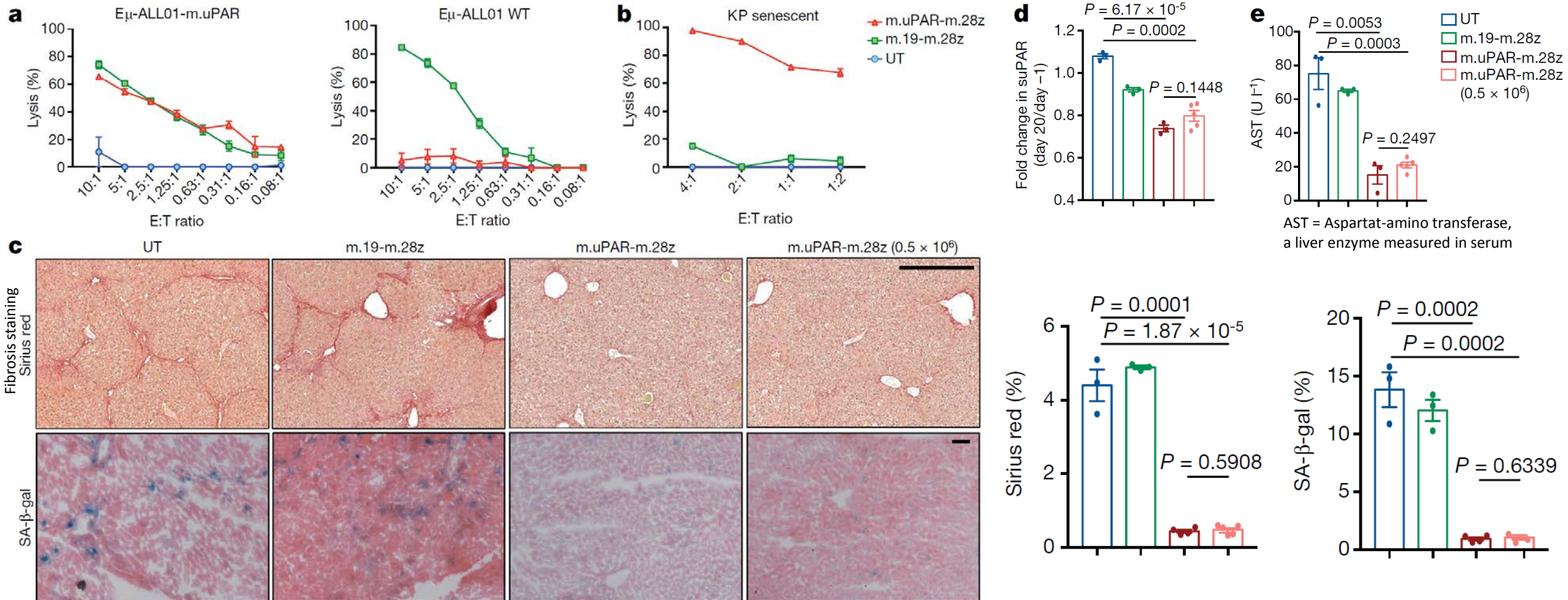
HE staining of lung tissue :



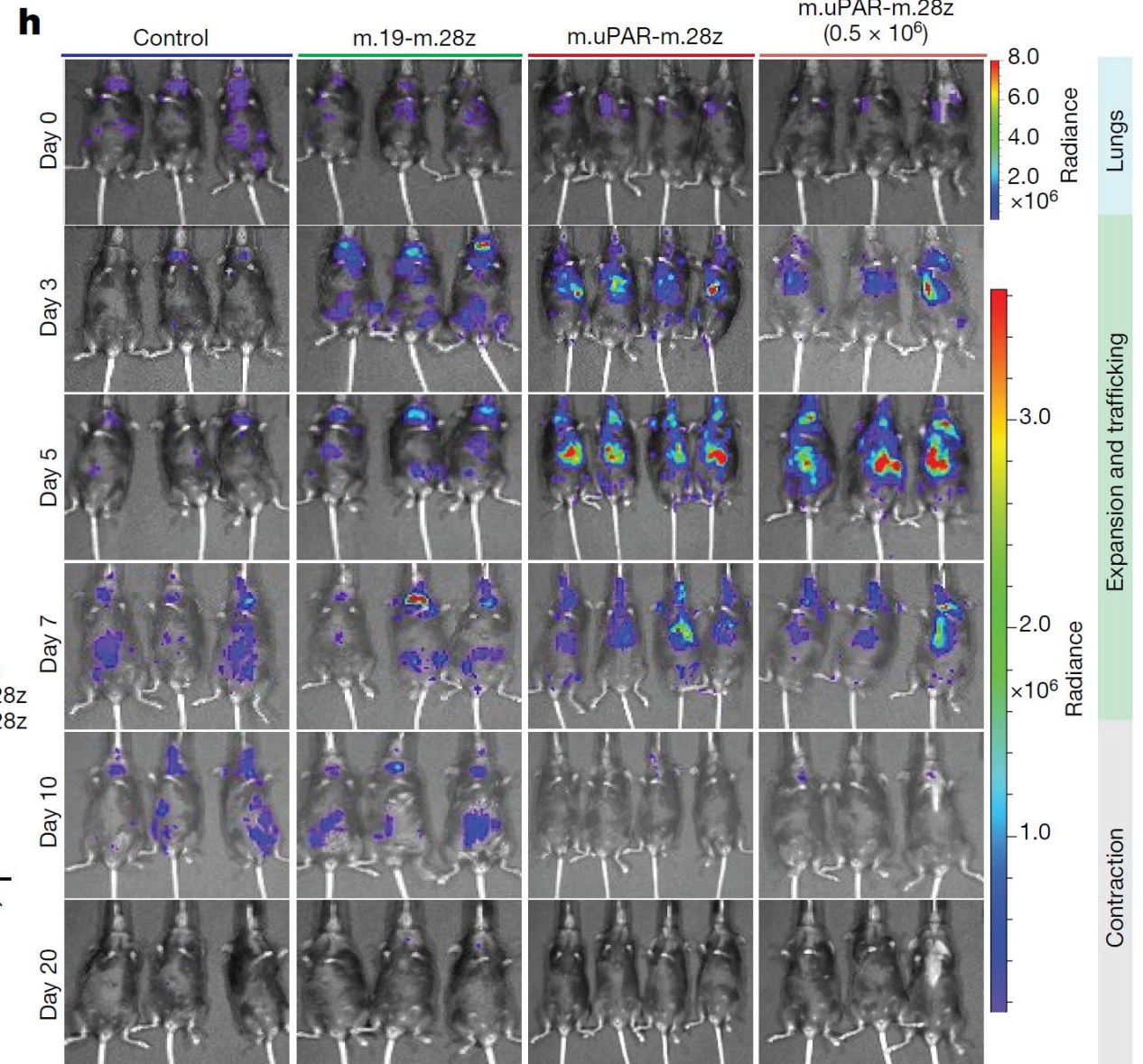
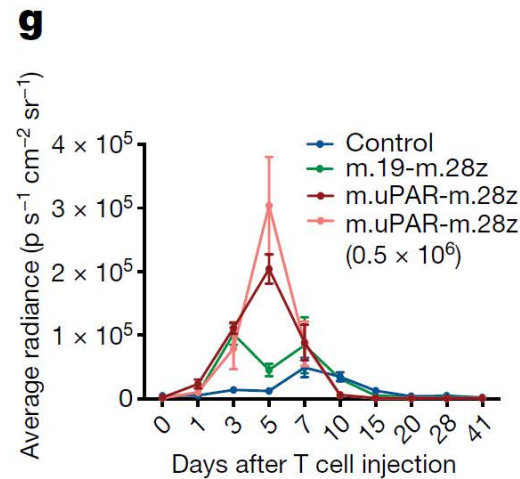
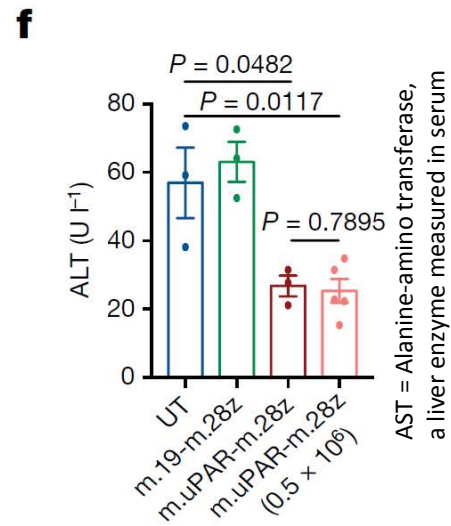
Blood counts:



# Senolytic CAR T cells show therapeutic efficacy in CCl4-induced liver fibrosis (1/2)

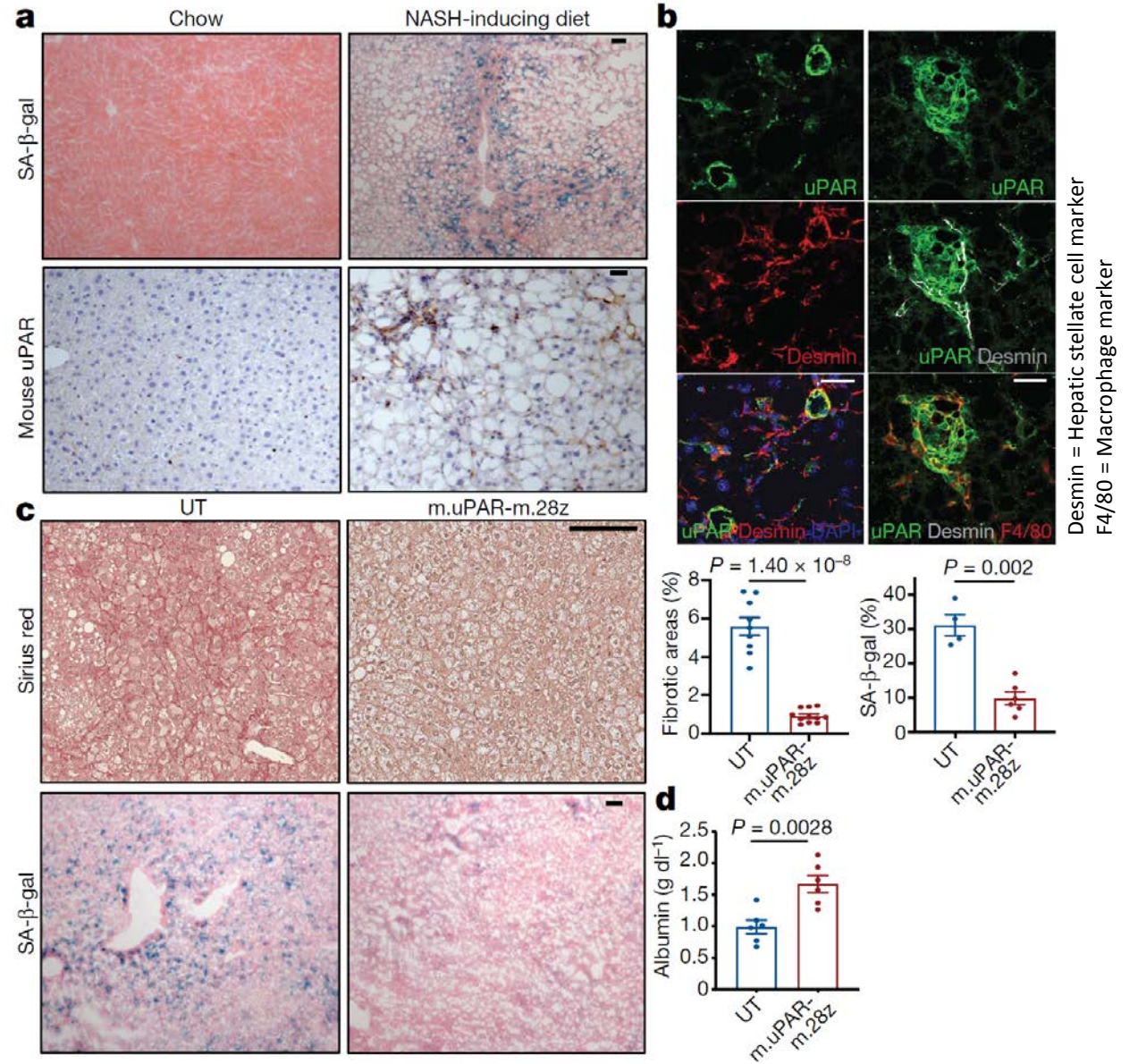


# Senolytic CAR T cells show therapeutic efficacy in CCl4-induced liver fibrosis (2/2)



# Senolytic CAR T cells show therapeutic efficacy in NASH *in vivo*

NASH = non-alcoholic steatohepatitis



# Discussion

- Senolytic CAR T cells **reverse** senescence-associated pathologies – REALLY?
- No studies on what happens after CAR T cell therapy in the tissues
- Really no off-target effects?
- Is the exorbitant price of CAR T cells justifiable for treatment of these non-life threatening diseases?
- There are other therapy options for senescence-related diseases that are more convenient for the patient and are more reasonably priced

**Thank you for your attention!**