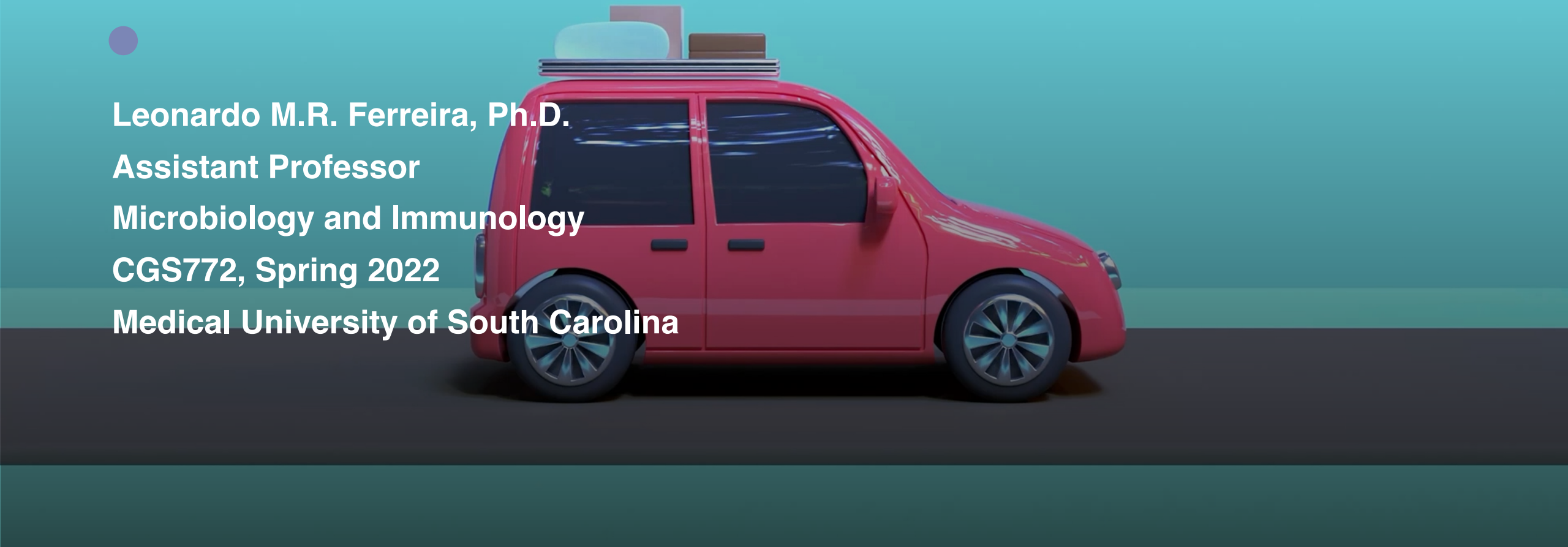
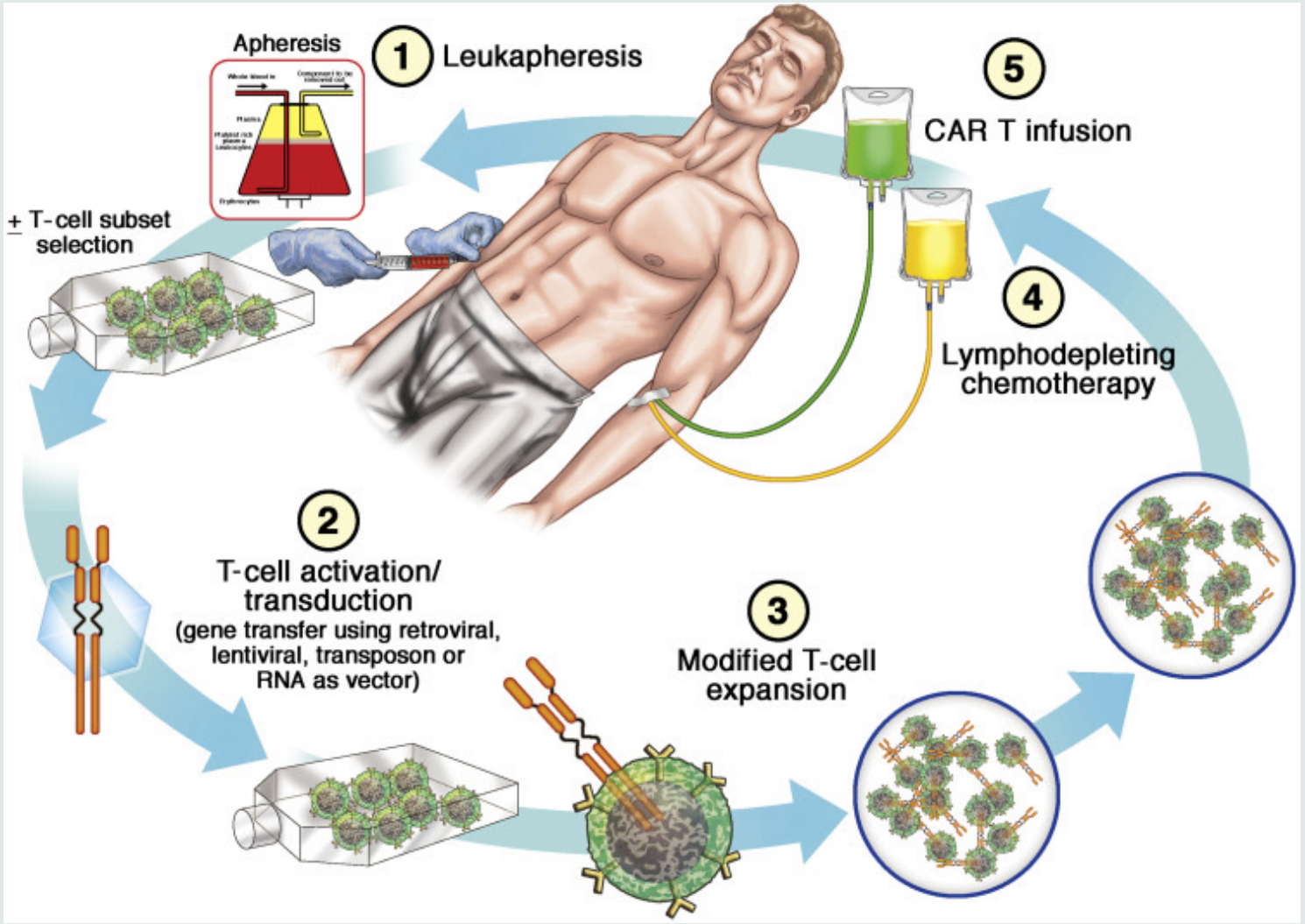
CAR T cells: Is there any disease they can't help with?

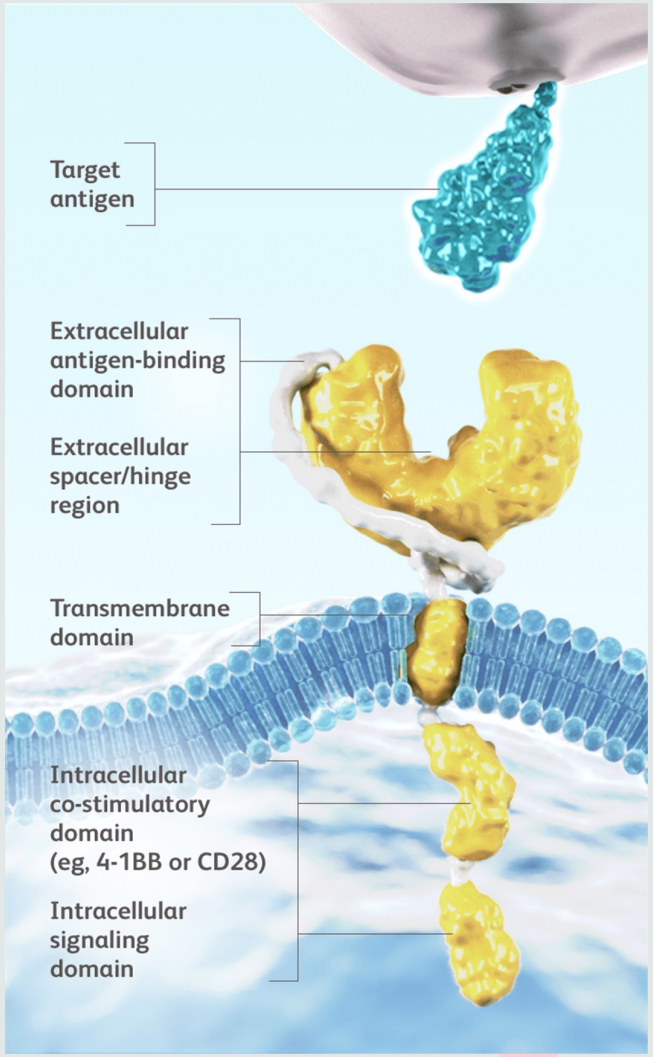


Leonardo M.R. Ferreira, Ph.D.
Assistant Professor
Microbiology and Immunology
CGS772, Spring 2022
Medical University of South Carolina

The CAR T cell paradigm



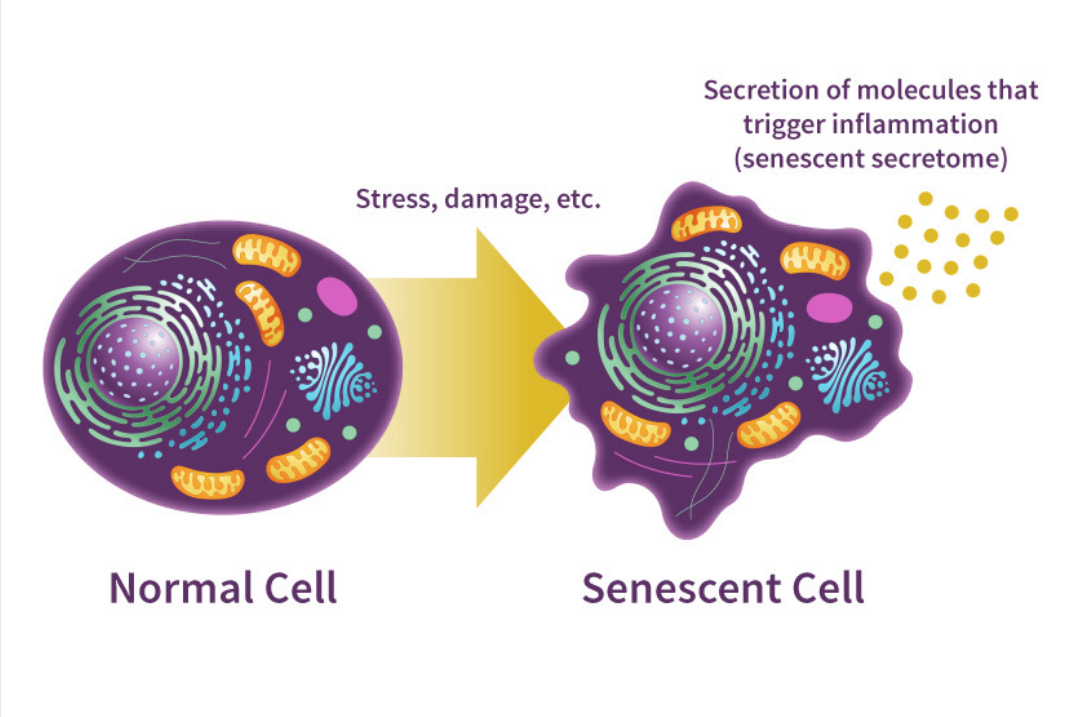
Freyer JACI 2020



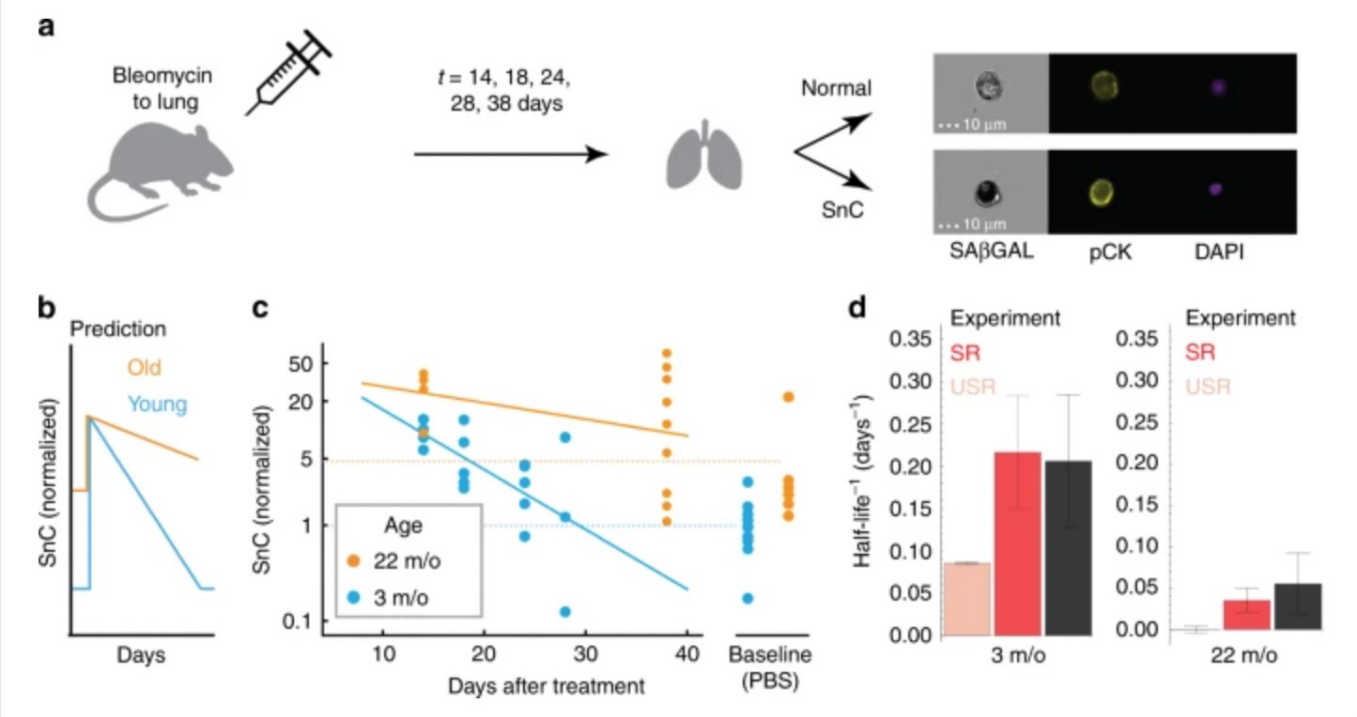
cartcellscience.com

Paradigm shift #1: can we use CAR T cells for non-cancer cells?

Aging: a disease of senescent cells?



National Institute on Aging



Karin Nat Comm 2019

Article

Senolytic CAR T cells reverse senescence-associated pathologies

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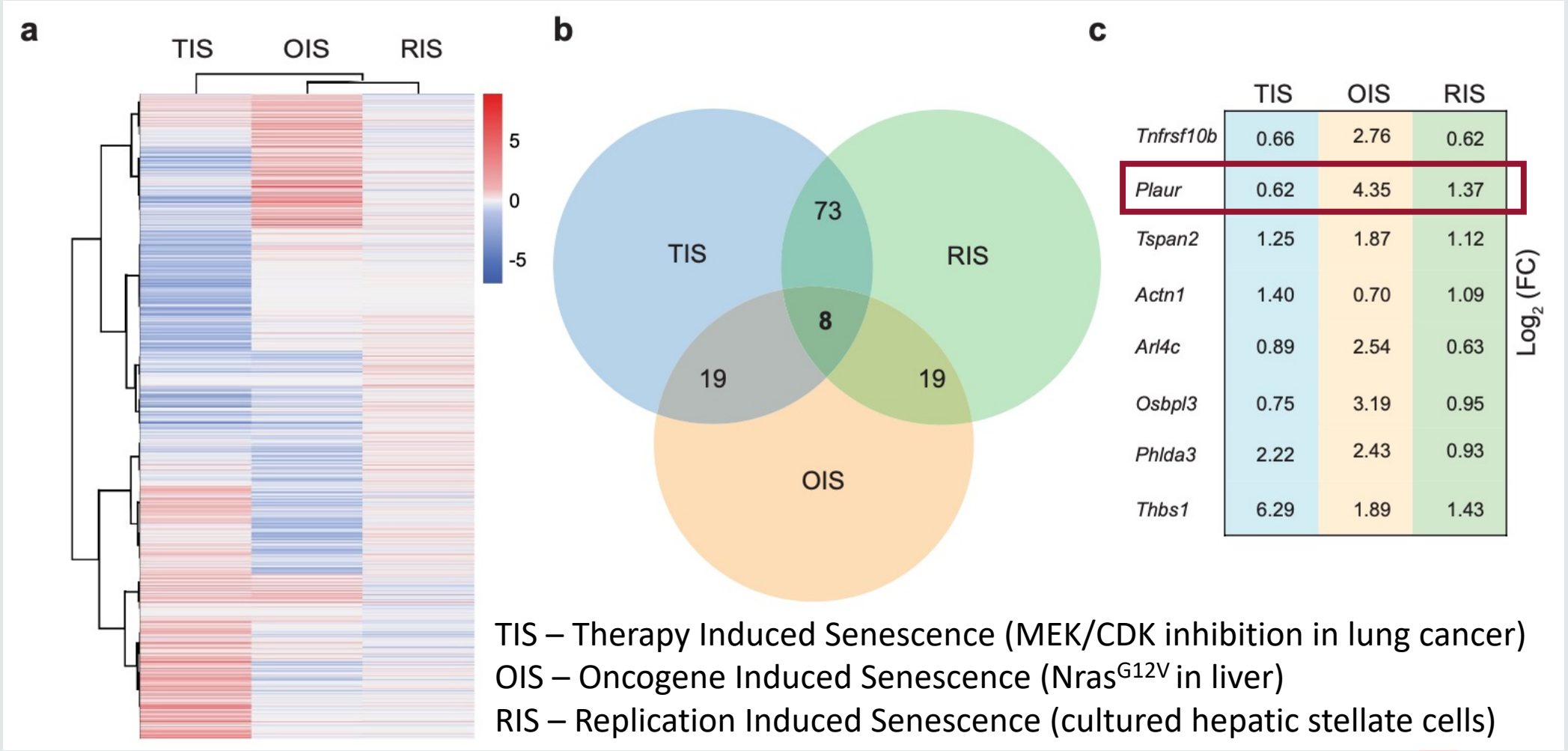
Corina Amor[1,2,12], Judith Feucht[3,4,12], Josef Leibold[2,12], Yu-Jui Ho[2], Changyu Zhu[2], Direna Alonso-Curbelo[2], Jorge Mansilla-Soto[3,4], Jacob A. Boyer[1,5], Xiang Li[2,6], Theodoros Giavridis[3,4], Amanda Kulick[5], Shauna Houlihan[2], Ellinor Peerschke[7], Scott L. Friedman[8], Vladimir Ponomarev[9], Alessandra Piersigilli[10], Michel Sadelain[3,4]✉ & Scott W. Lowe[2,11]✉

The urokinase-type plasminogen activator receptor (uPAR) is a surface molecule upregulated in senescent cells

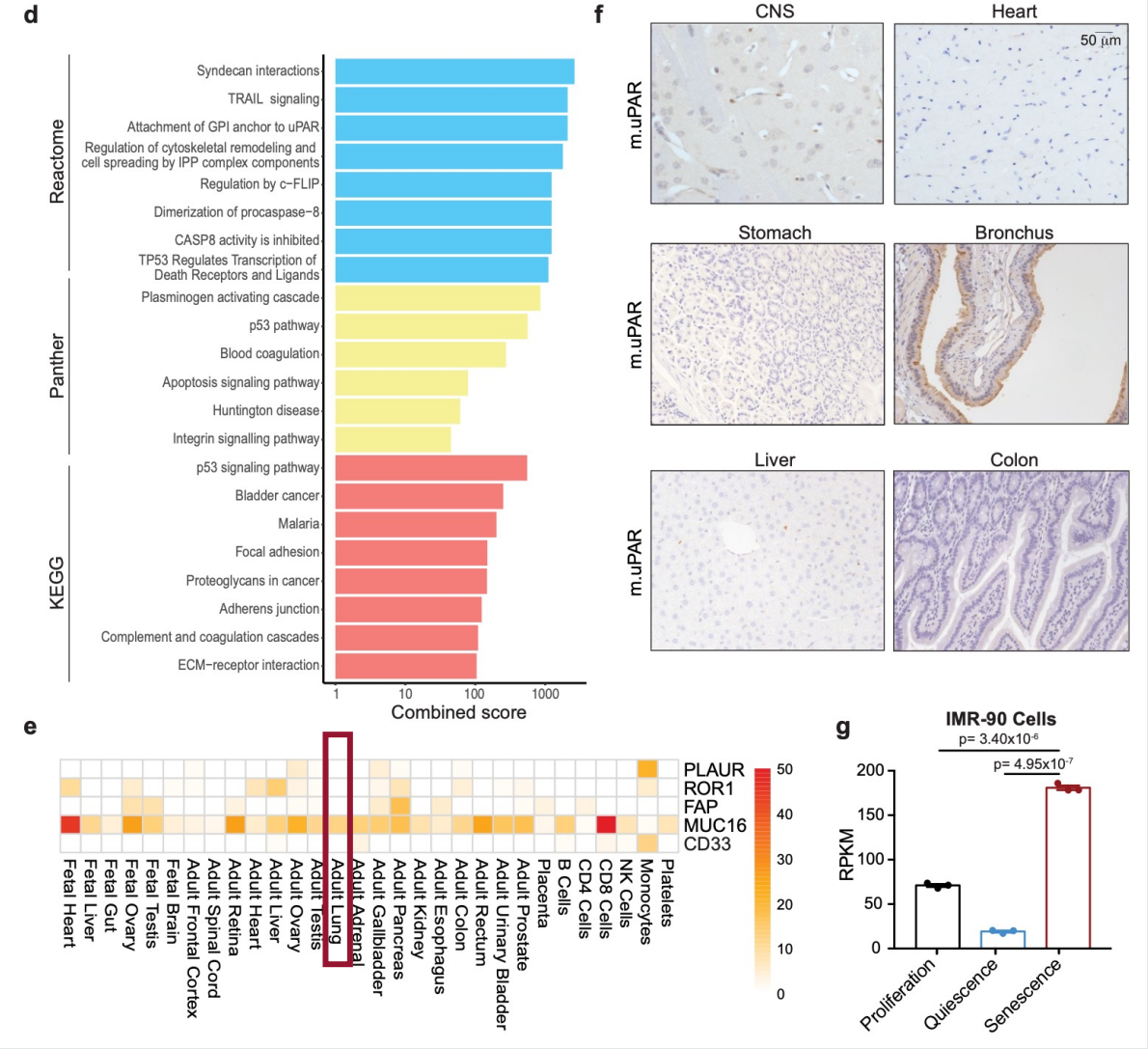


	TIS	OIS	RIS
Tnfrsf10b	0.66	2.76	0.62
Plaur	0.62	4.35	1.37
Tspan2	1.25	1.87	1.12
Actn1	1.40	0.70	1.09
Arl4c	0.89	2.54	0.63
Osbpl3	0.75	3.19	0.95
Phlda3	2.22	2.43	0.93
Thbs1	6.29	1.89	1.43

Log_2 (FC)

TIS – Therapy Induced Senescence (MEK/CDK inhibition in lung cancer)
OIS – Oncogene Induced Senescence ($Nras^{G12V}$ in liver)
RIS – Replication Induced Senescence (cultured hepatic stellate cells)

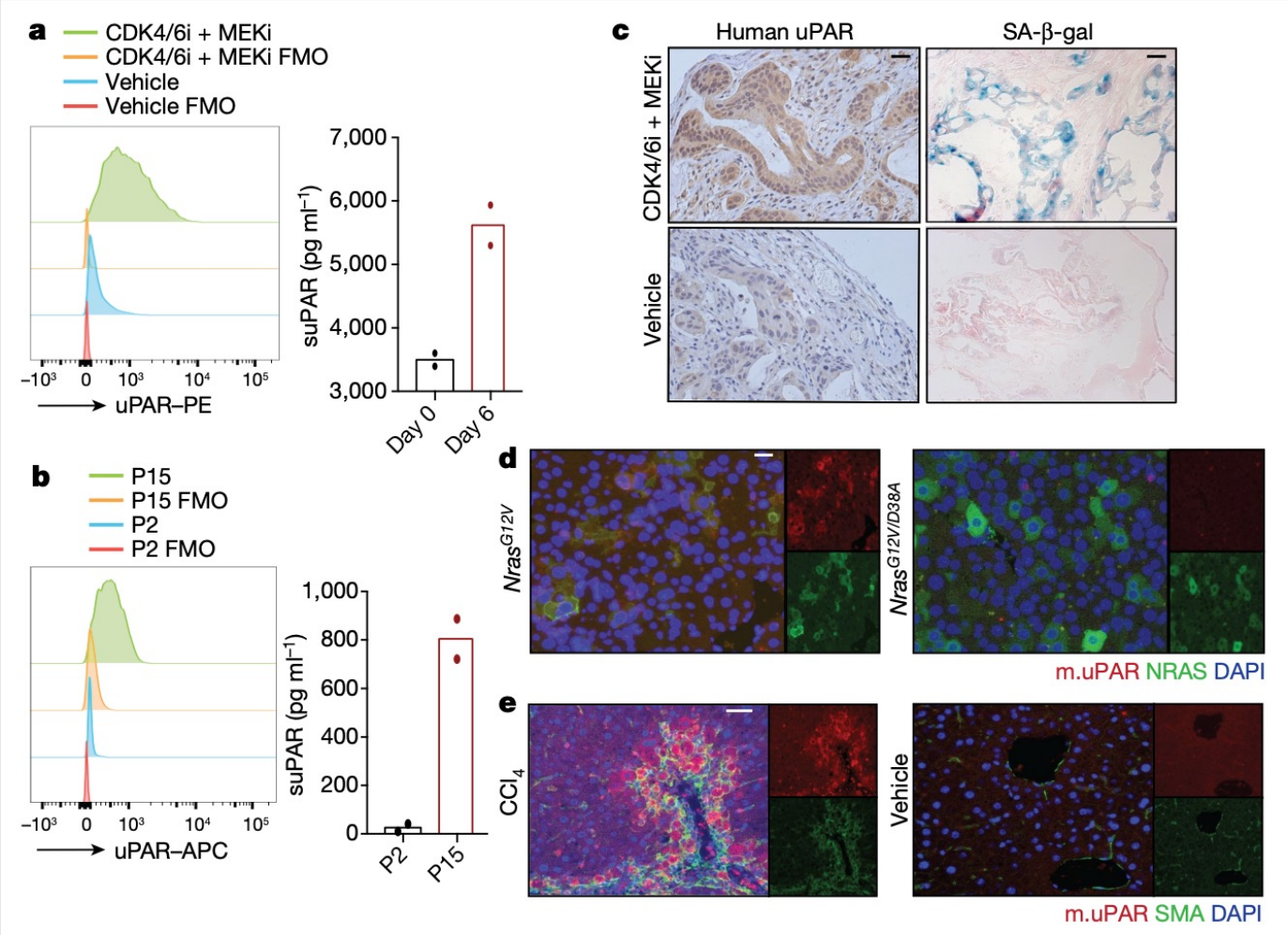
uPAR is not found in healthy tissues other than monocytes and low levels in lung



uPAR is a cell surface and secreted biomarker of senescence

Mouse Kras/Tp53 lung adenocarcinoma after MEK and CDK4/6 inhibitors

High passage human melanocytes (P15)

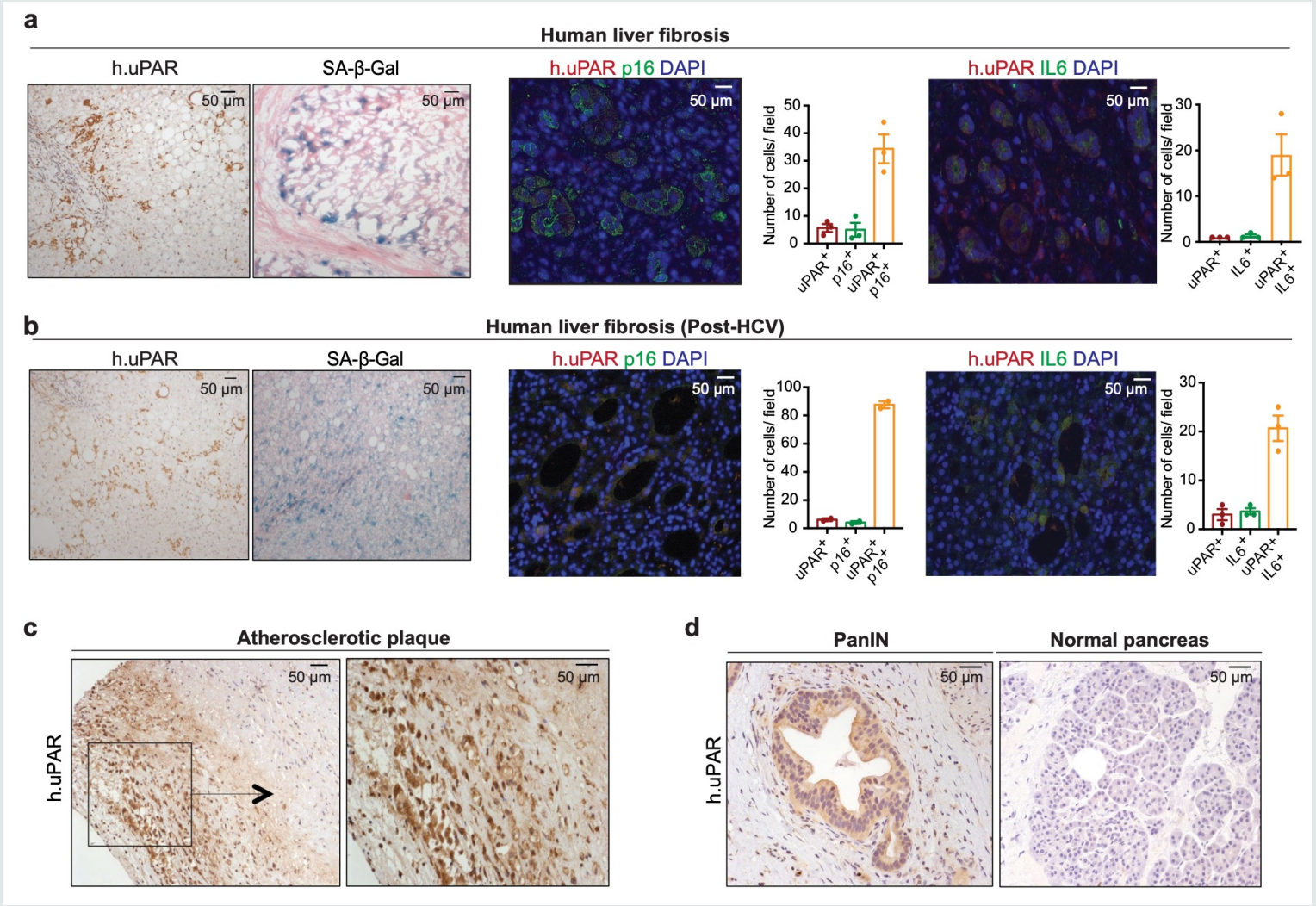


Human lung adenocarcinoma after MEK and CDK4/6 inhibitors

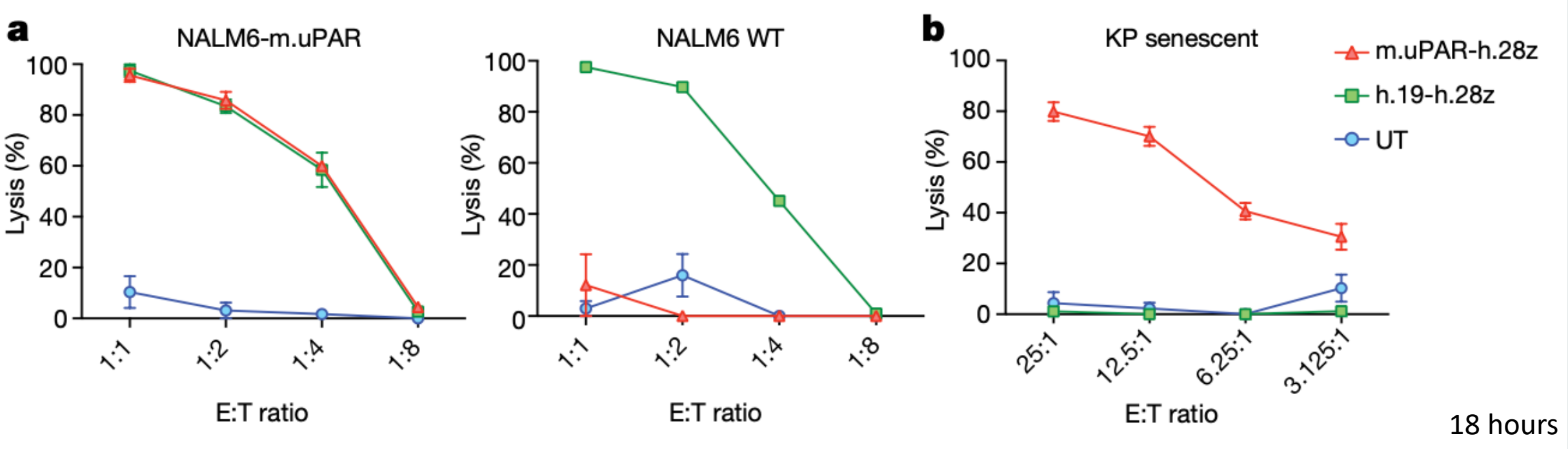
Mouse liver after Nras expression

Mouse liver after CCl4 treatment

uPAR is a senescence biomarker in humans

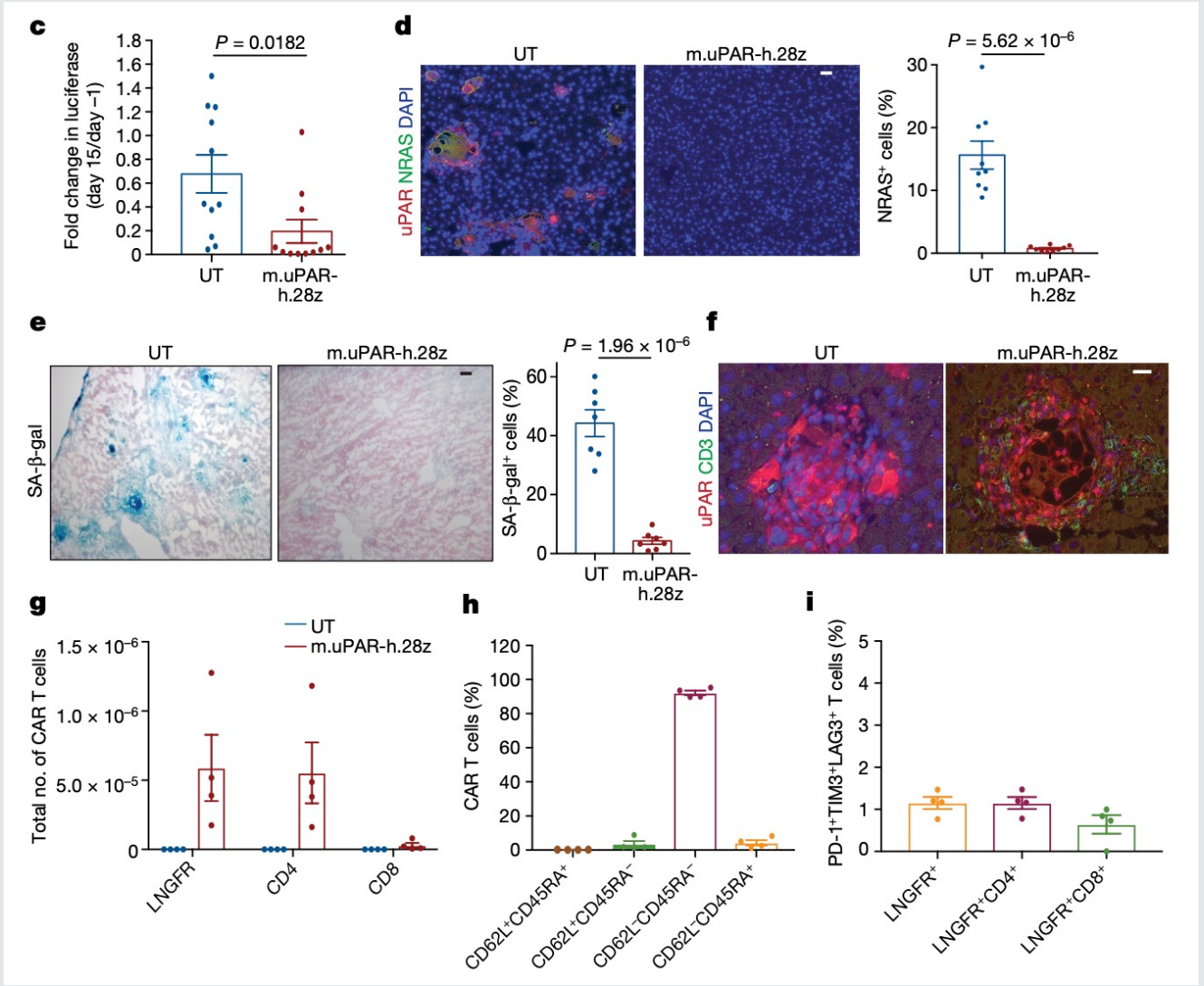


uPAR CAR T cells kill uPAR-expressing cells *in vitro*



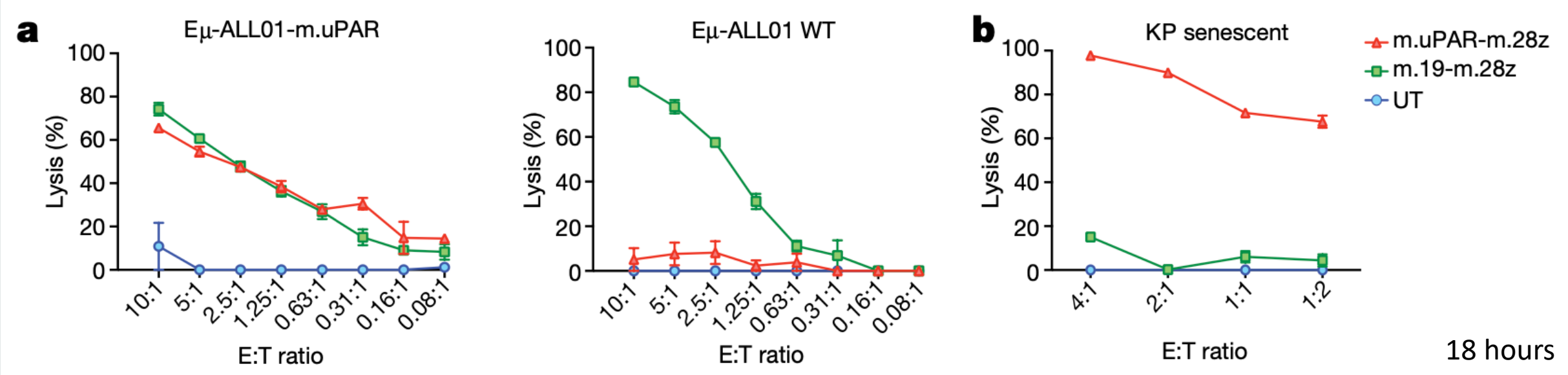
18 hours

uPAR CAR T cells kill senescent cells *in vivo*

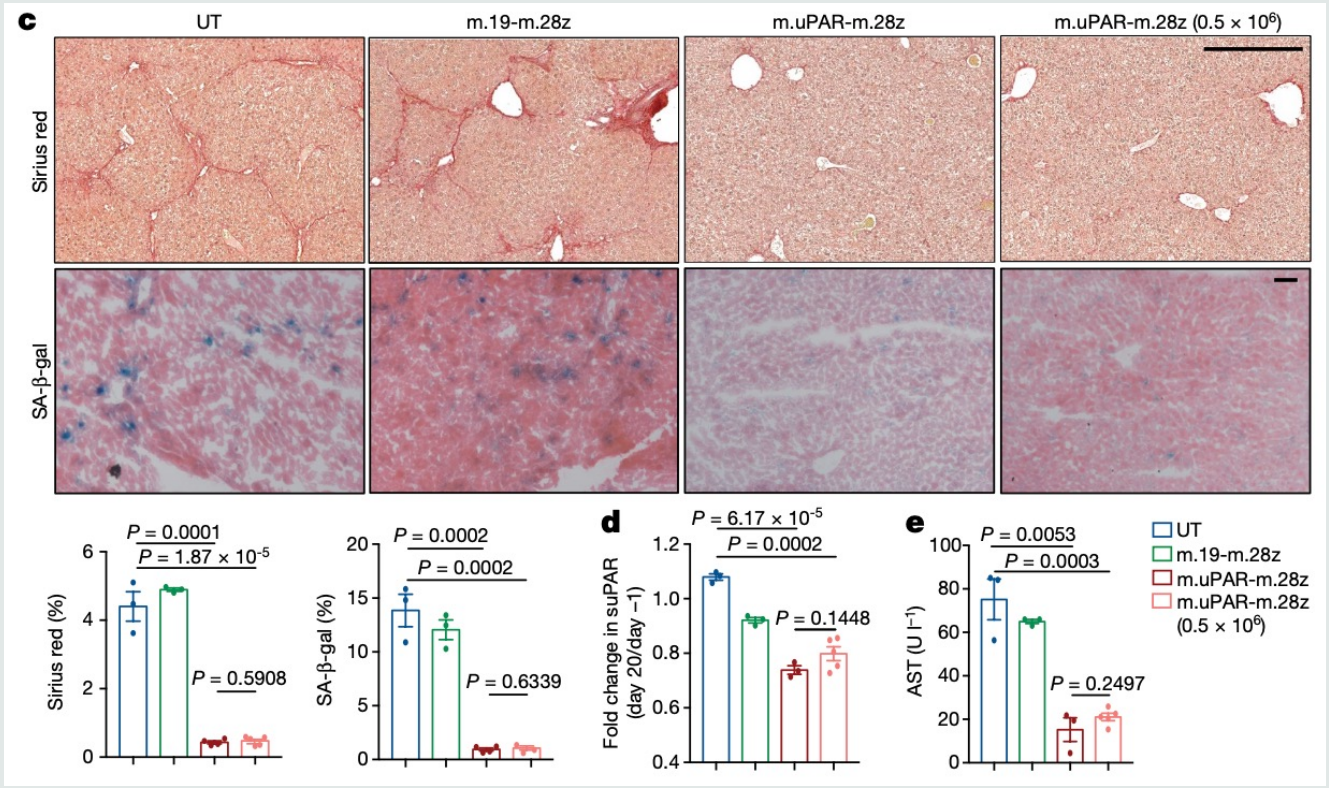


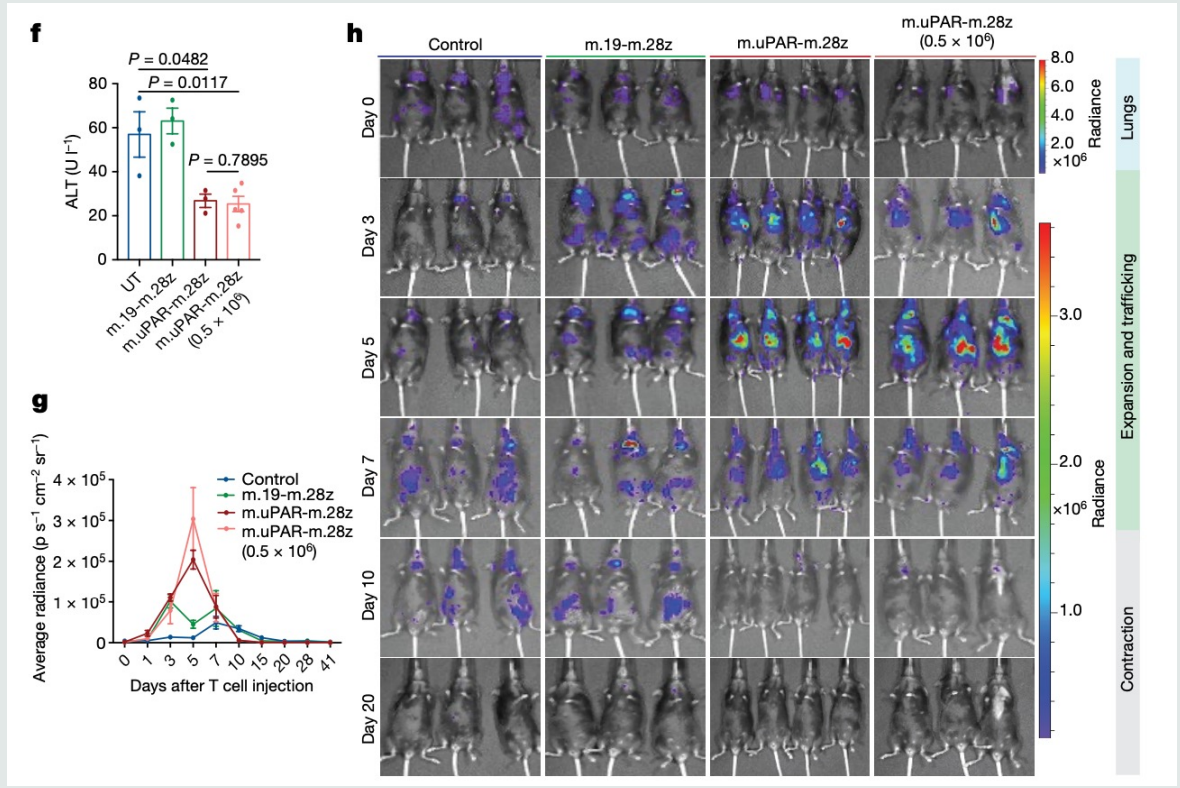
NSG mice injected with $Nras^{G12V}$-luciferase (OIS) and 10 days later injected i.v. with 0.5 x 10^6 uPAR CAR T cells

Mouse uPAR CAR T cells kill mouse uPAR-expressing cells *in vitro*



Mouse uPAR CAR T cells reduce CCl_4-induced liver fibrosis

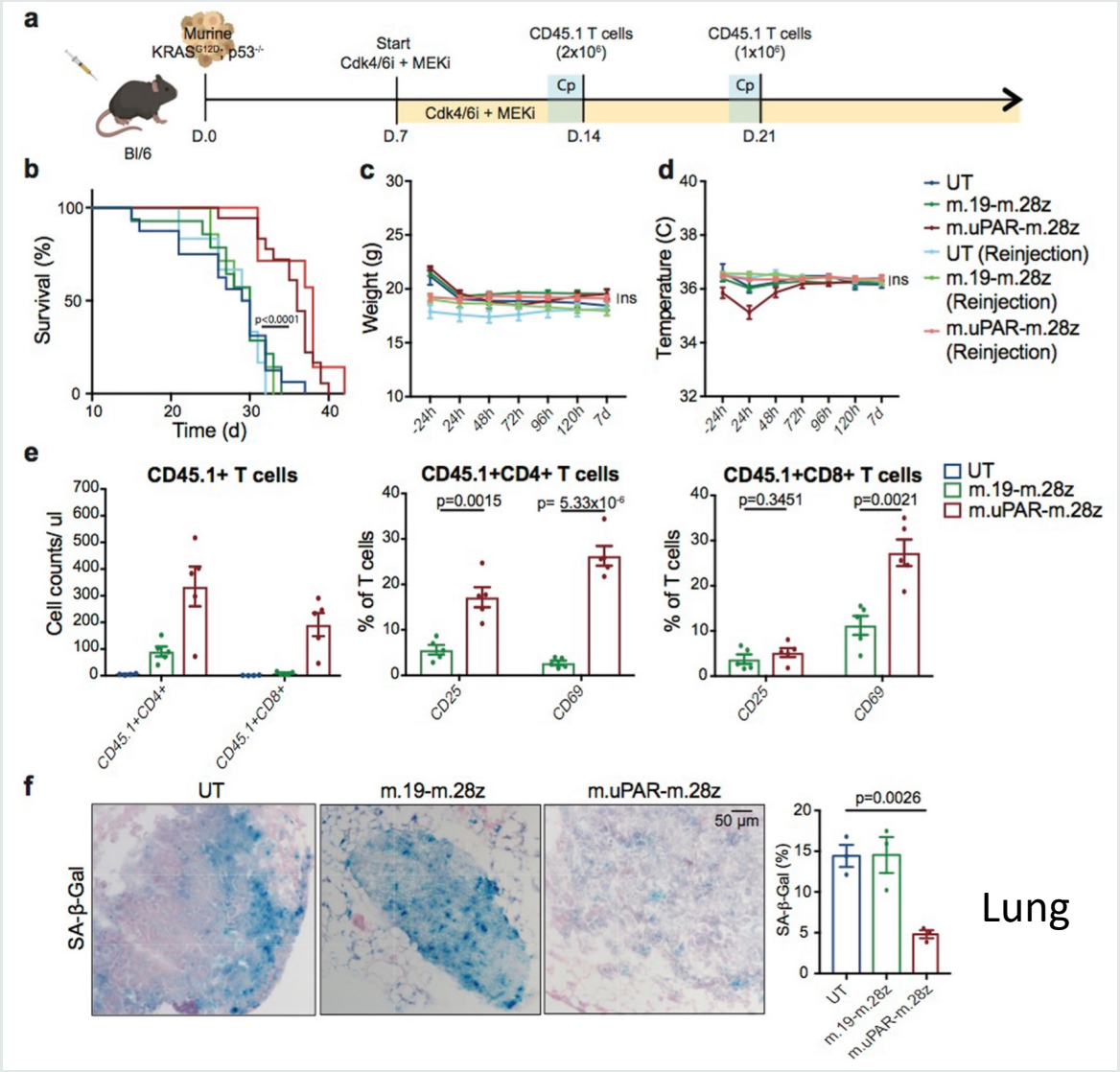




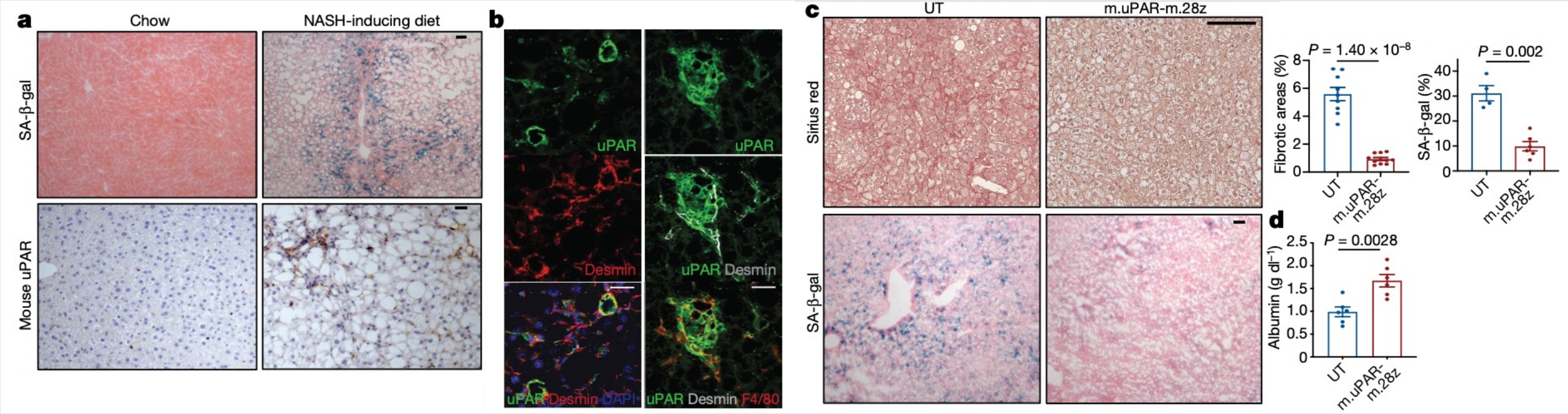
B6 mice were treated twice a week with 12 i.p. injections of CCl_4. Mice then received mouse CAR T cells and CCl_4 continued to be administered at the same dose and interval until day 20 post CAR T cell injection

AST – aspartate aminotransferase; ALT – alanine aminotransferase

Mouse uPAR CAR T cells prolong survival of mice with lung adenocarcinoma when combined with senescence induction

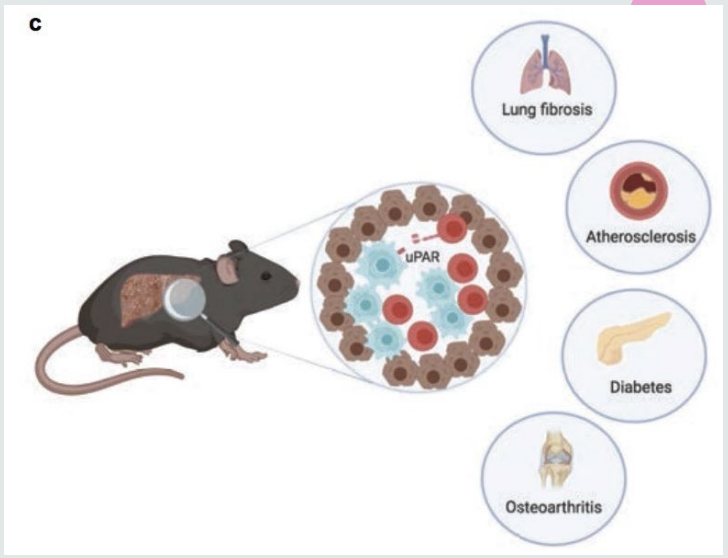


Mouse uPAR CAR T cells reduce fibrosis and improve liver function in diet-induced NASH



NASH – non-alcoholic steatohepatitis
Desmin – hepatic stellate cell marker
F4/80 – macrophage marker
Sirius red – collagen

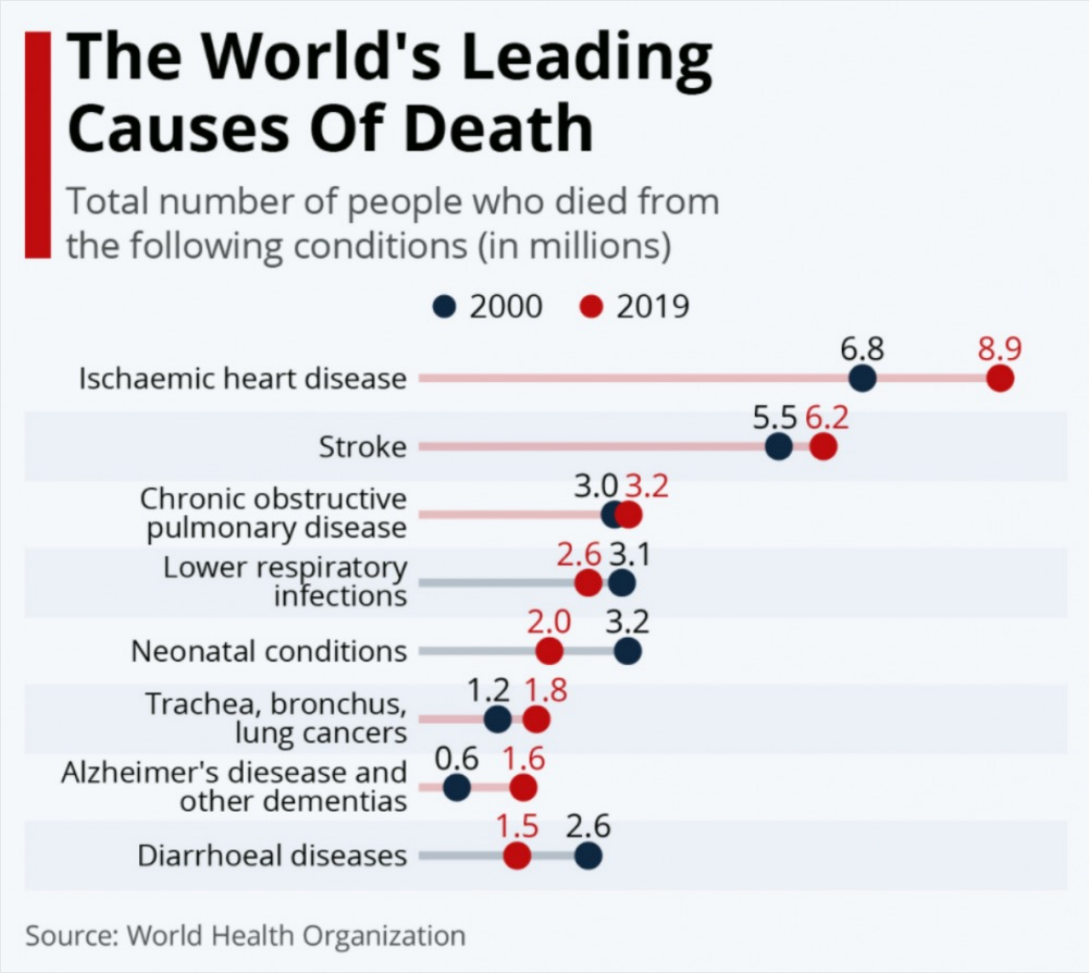
Take home messages #1

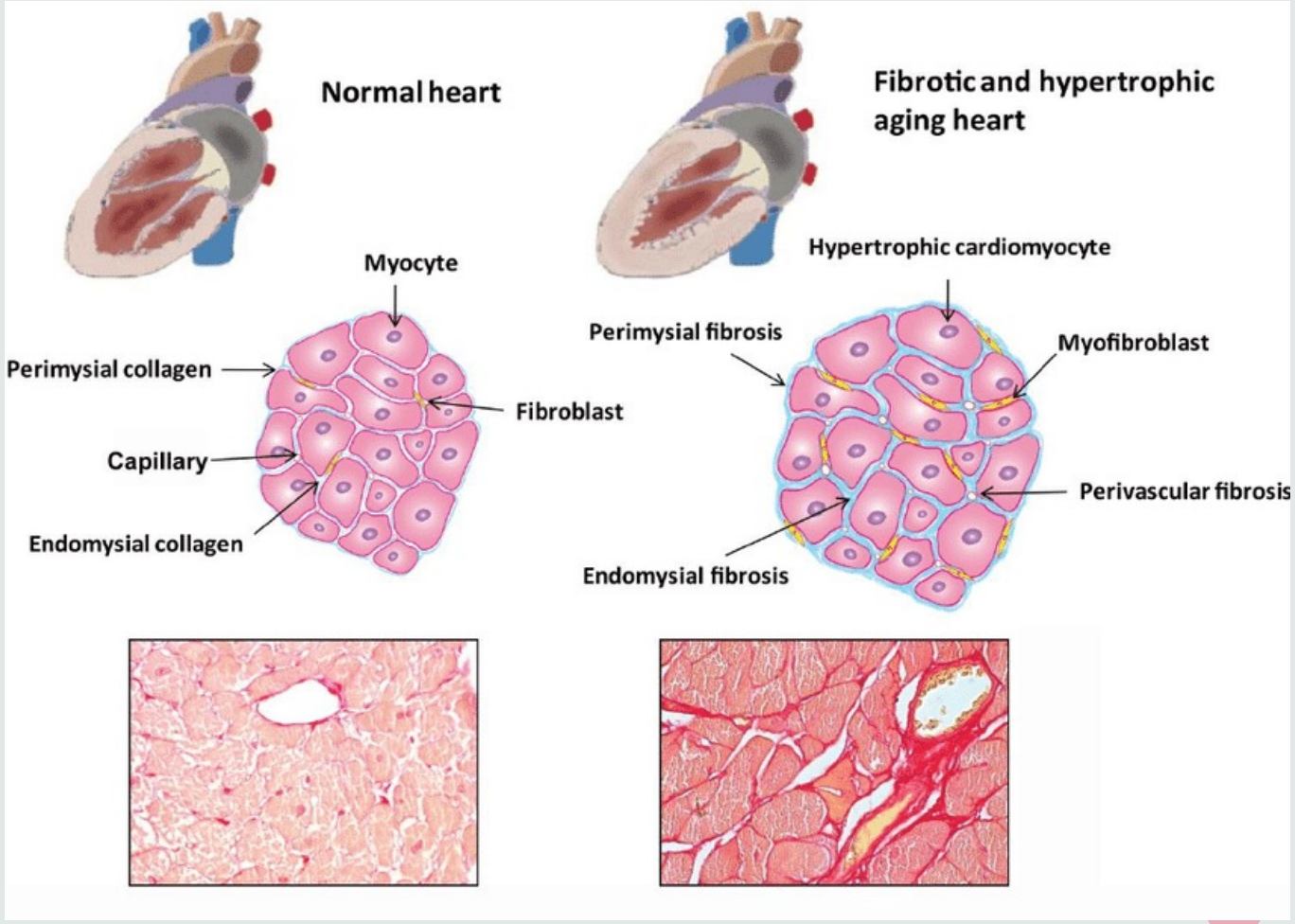


- uPAR is a protein broadly induced on the surface of senescent cells
- uPAR-targeted CAR T cells eliminate senescent cells in vitro and in vivo
- suPAR serves as a plasma biomarker to assess the senolytic activity of CAR T cells in vivo
- Appropriately dosed senolytic CAR T cells can infiltrate the areas of senescence, efficiently target senescent cells and produce a therapeutic benefit without notable toxicity in mice
- Unlike tumour cells, senescent cells do not divide or create an immunosuppressive microenvironment, presenting fewer barriers to the development of efficacious CAR T cells

Paradigm shift #2: can we use transient CAR T cells for non-cancer cells?

Heart disease and fibrosis





Masson Cardiac Fibrosis and Aging 2007

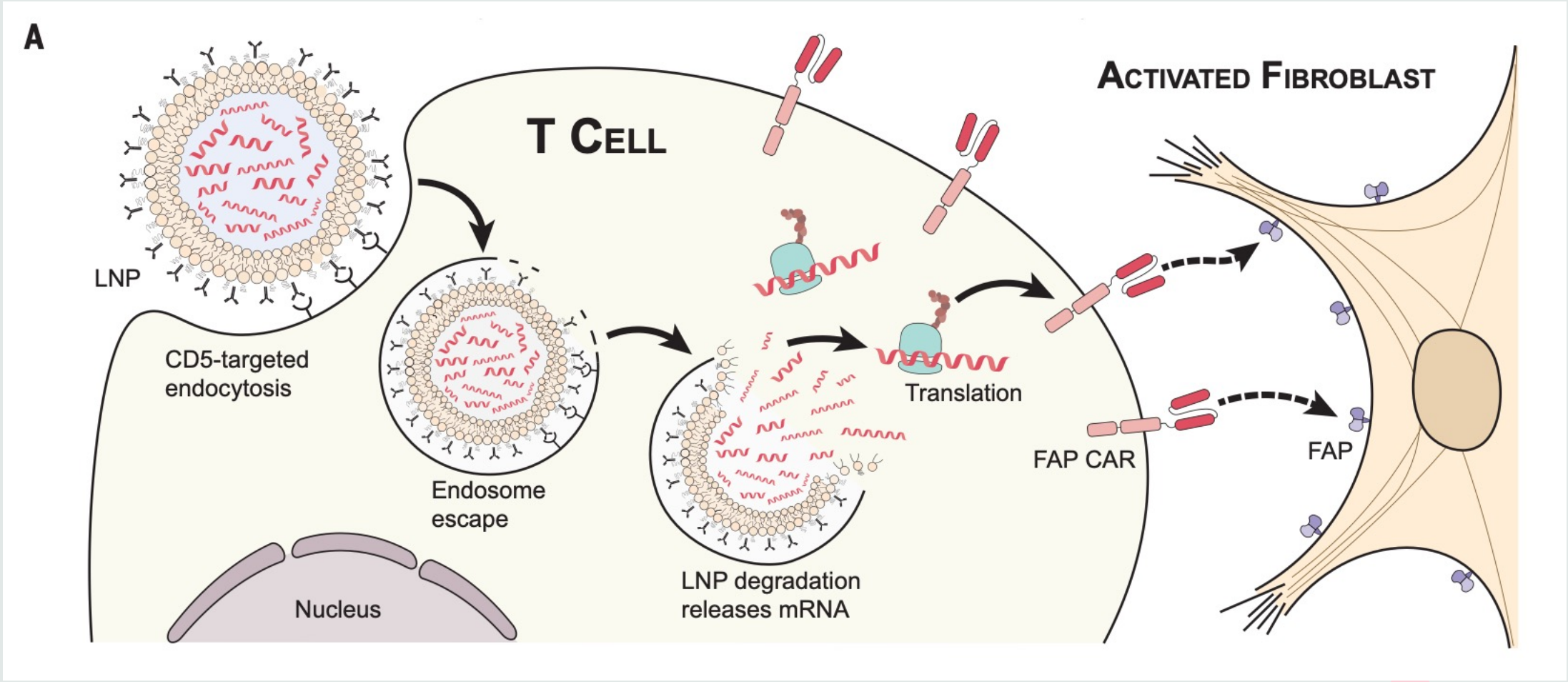
RESEARCH

CELL AND GENE THERAPY

CAR T cells produced in vivo to treat cardiac injury

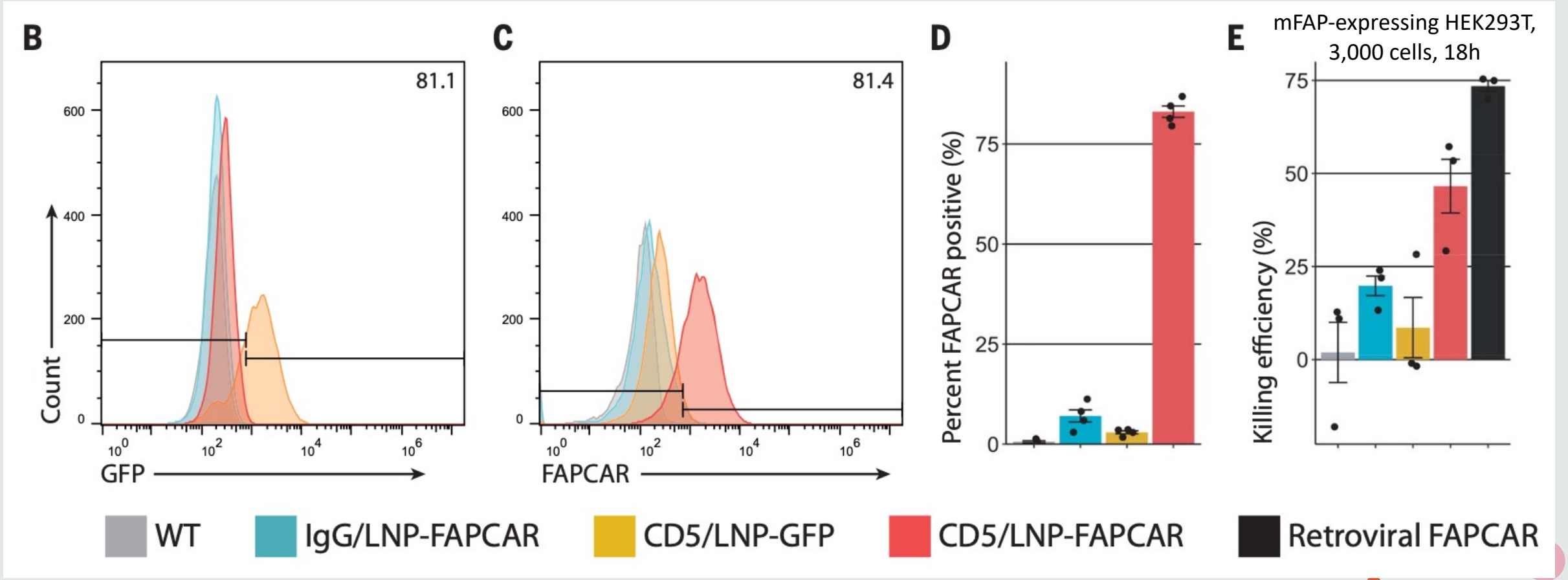
Joel G. Rurik[1,2,3], István Tombácz[4]†, Amir Yadegari[4]†, Pedro O. Méndez Fernández[1,2,3], Swapnil V. Shewale[2], Li Li[1,2], Toru Kimura[4]‡, Ousamah Younoss Soliman[4], Tyler E. Papp[4], Ying K. Tam[5], Barbara L. Mui[5], Steven M. Albelda[4,6], Ellen Puré[7], Carl H. June[6], Haig Aghajanian[1,2,3]*, Drew Weissman[4]*, Hamideh Parhiz[4]*, Jonathan A. Epstein[1,2,3,4]*

Avoiding removing T cells from the body and indefinitely persistent CAR T cells by generating transient CAR T cells using CD5-LNP-CAR



CD5 – T cell marker; FAP – fibroblast activation protein; LNP – lipid nanoparticle

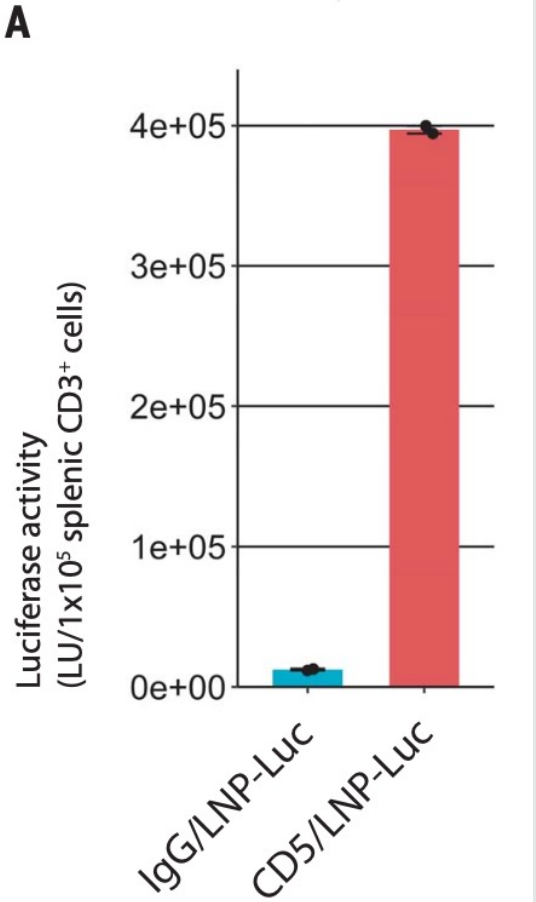
CD5-targeted LNP produce functional FAP CAR T cells *in vitro*

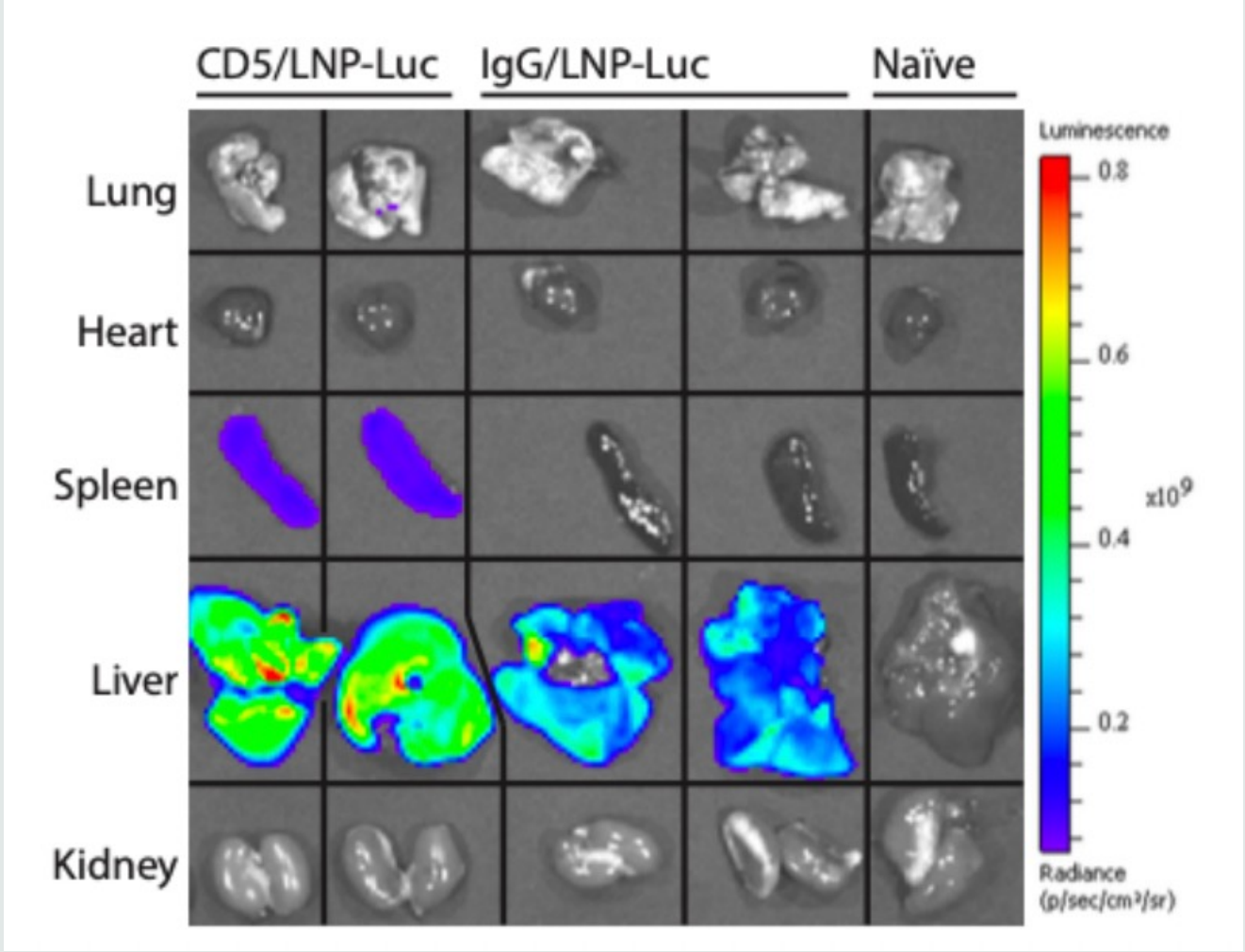


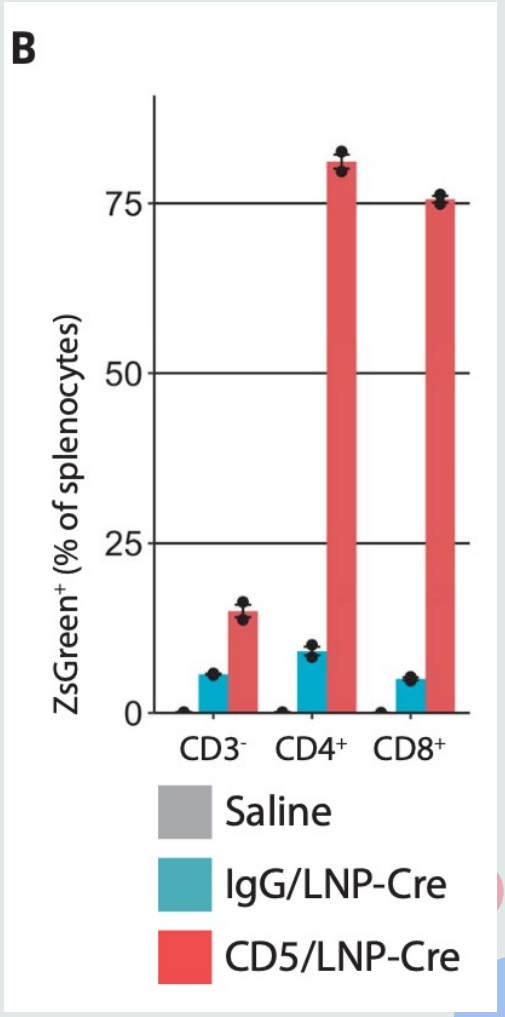
CD5-targeted LNP efficiently transfect T cells *in vivo*

CD5-LNP-Luc i.v. into mice (24h)

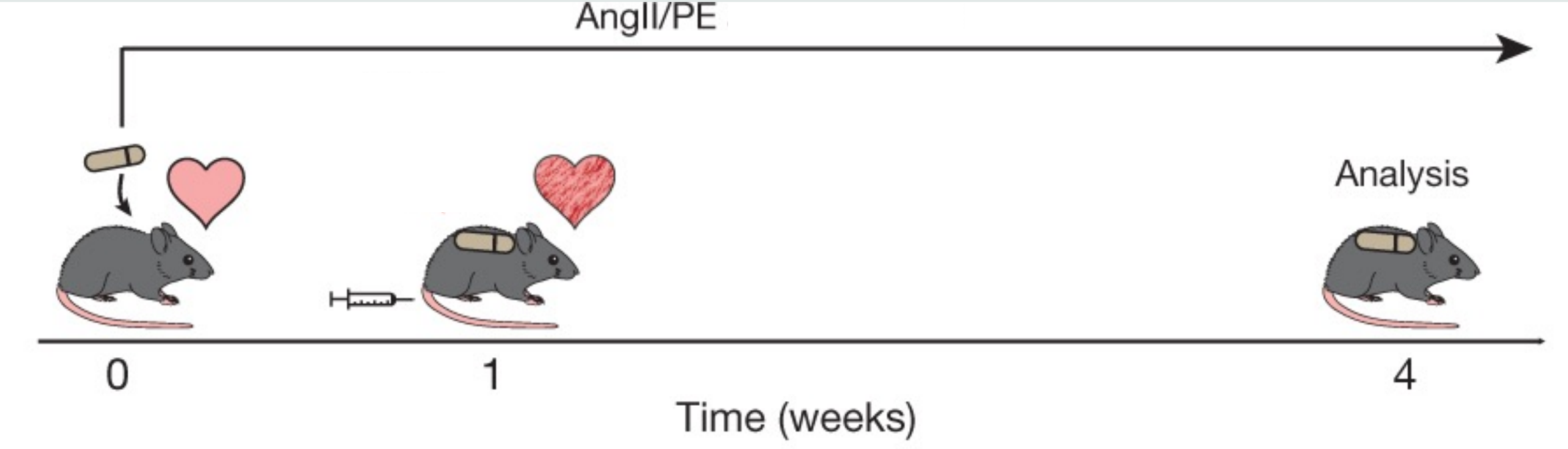
CD5-LNP-Cre i.v.
into CAG-LSL-ZsGreen mice (24h)







Murine hypertensive model of cardiac injury and fibrosis

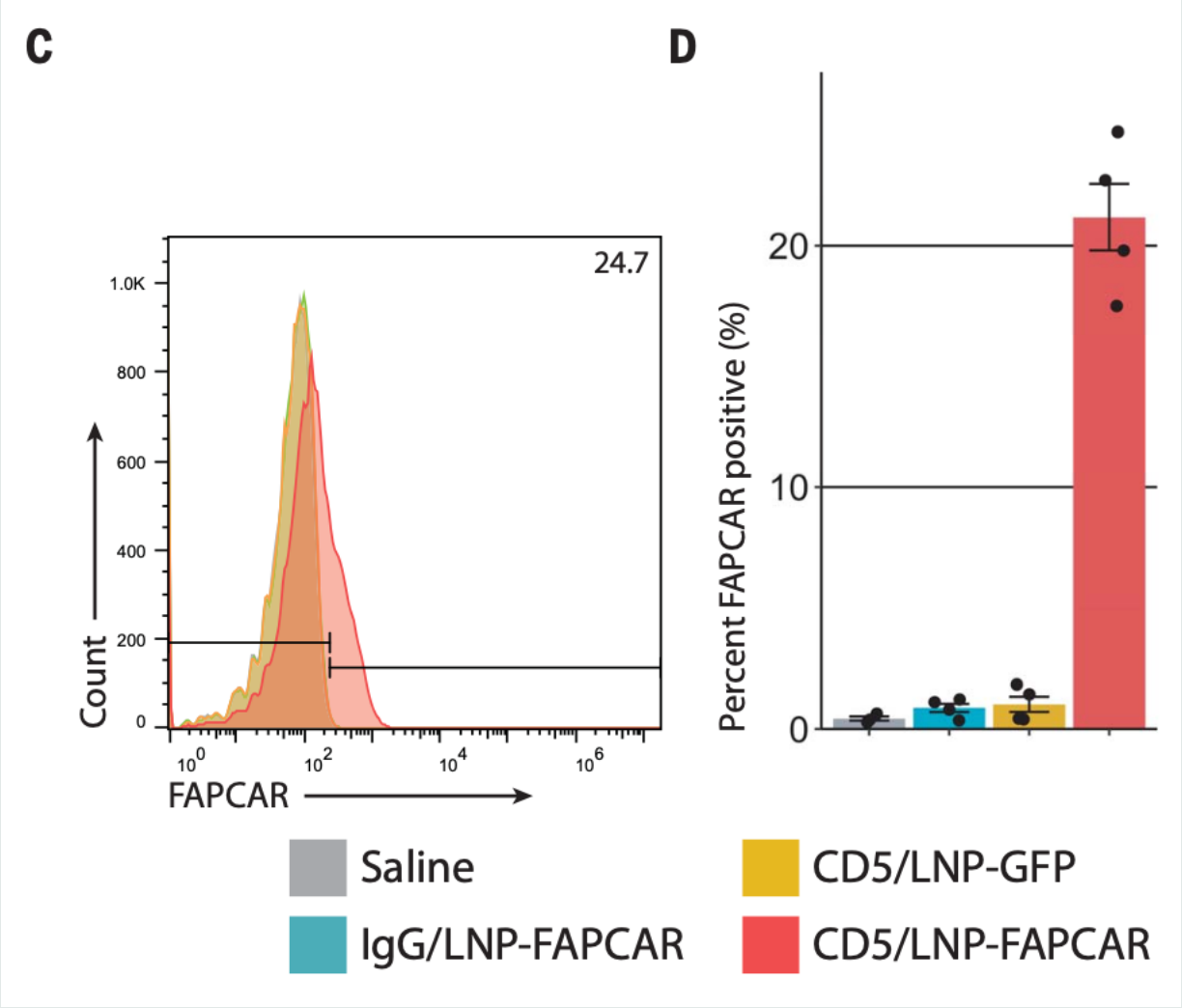


Aghajanian Nature 2019

Constant infusion of angiotensin II/phenylephrine (AngII/PE) through implanted 28-day osmotic mini-pumps

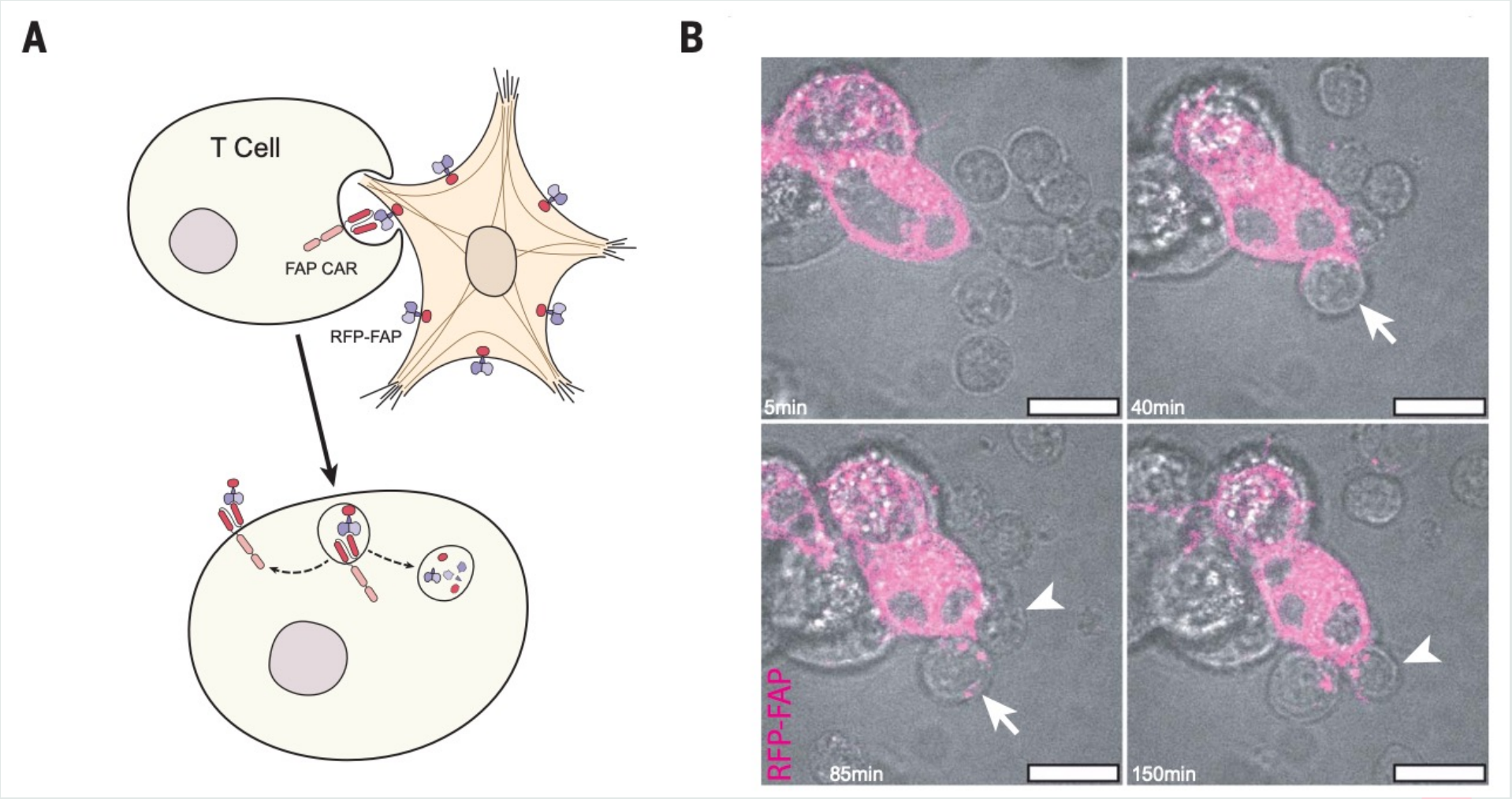
CD5-targeted LNP generate FAP CAR T cells in AngII/PE-injured mice

T cells isolated from spleen 48h after LNP injection



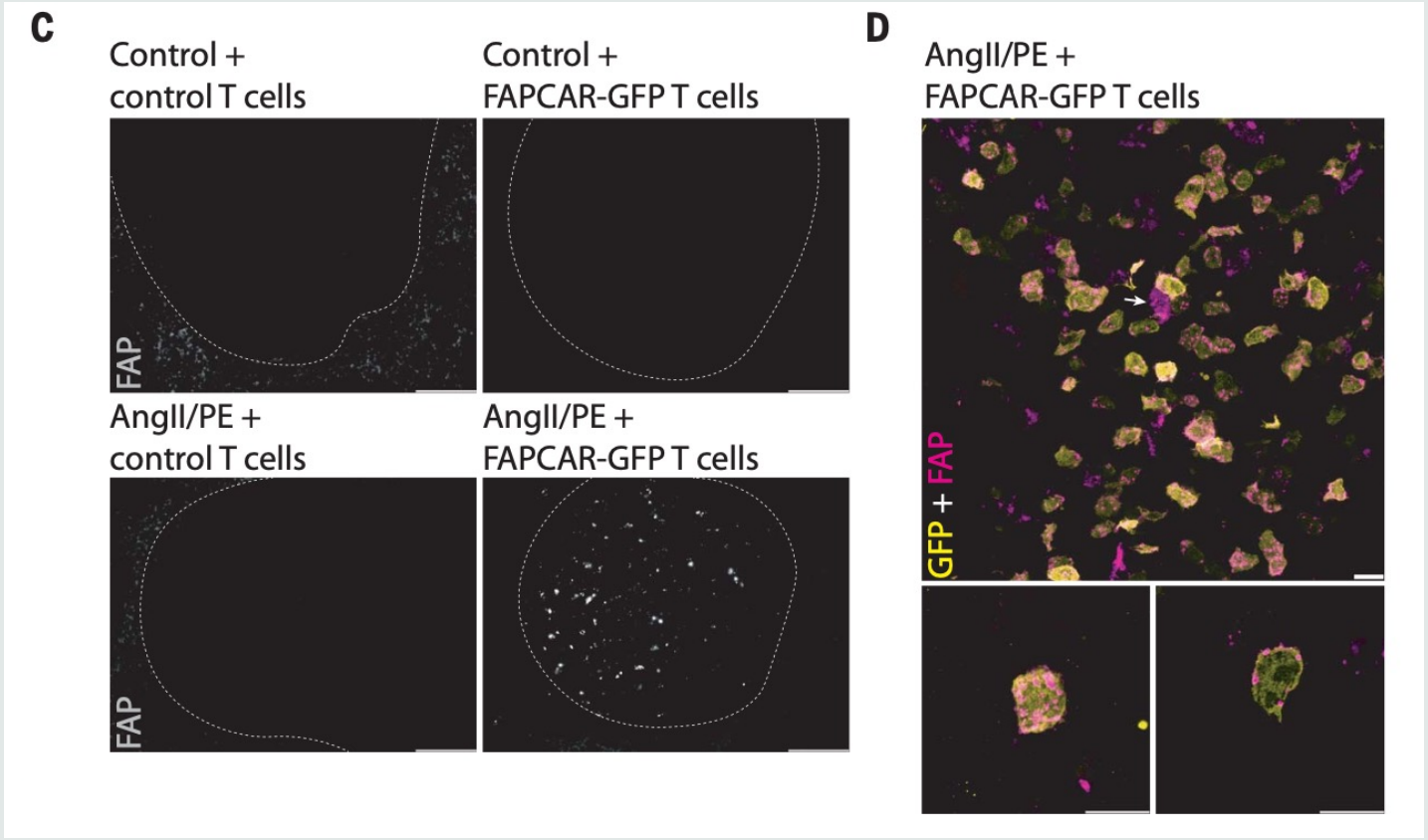
No FAPCAR ex- pression was found in splenic T cells 1 week after injection

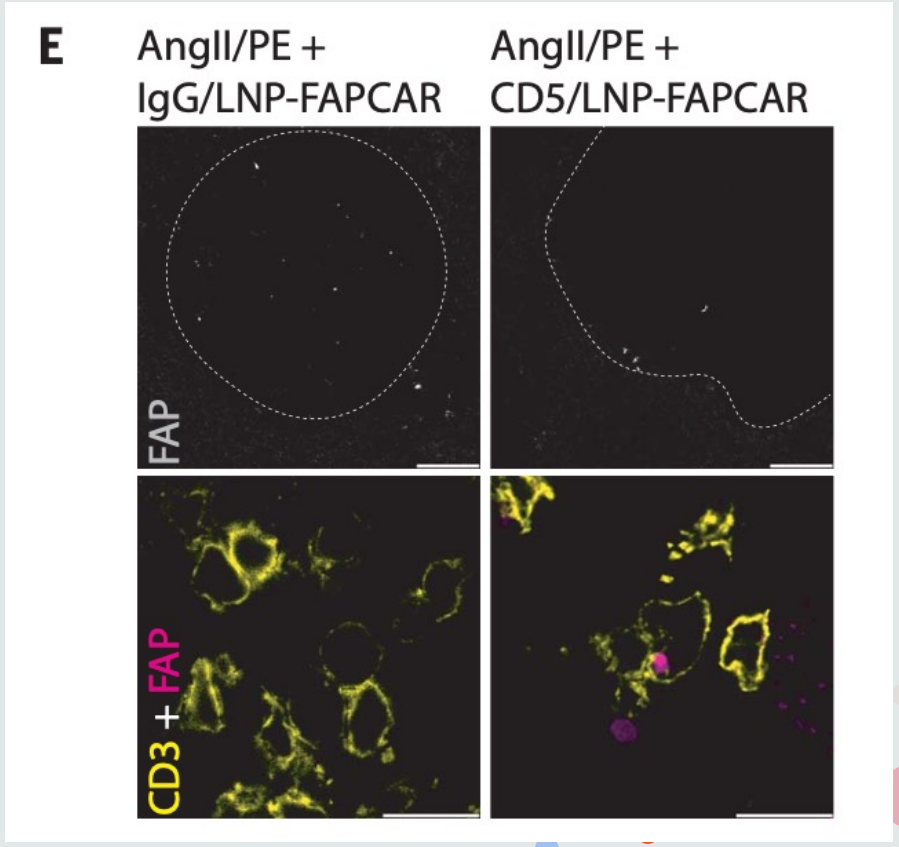
FAP CAR T cells perform trogocytosis *in vitro*



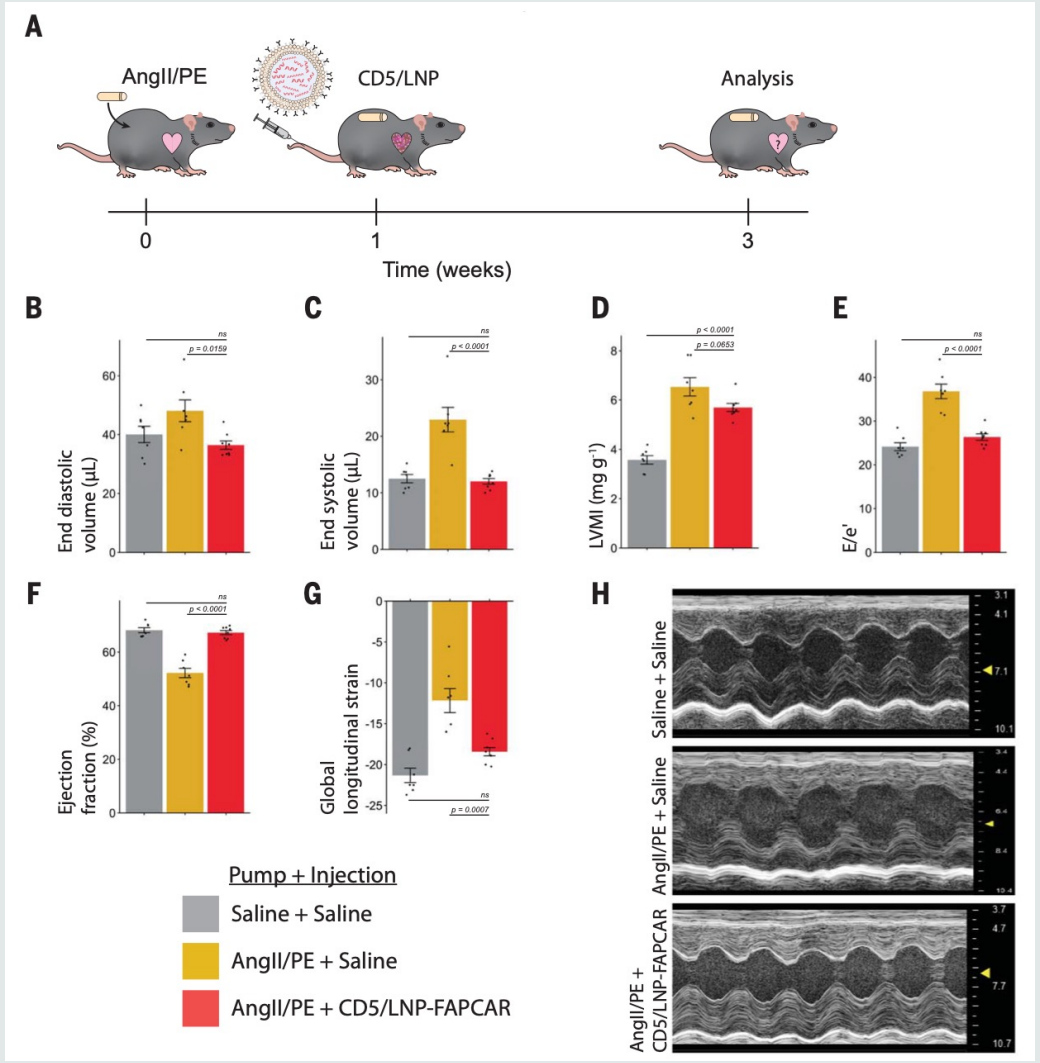
FAP CAR T cells perform trogocytosis *in vivo*

Spleens from AngII/PE–injured animals treated with adoptively transferred, virally transduced GFP-tagged FAPCAR T cells

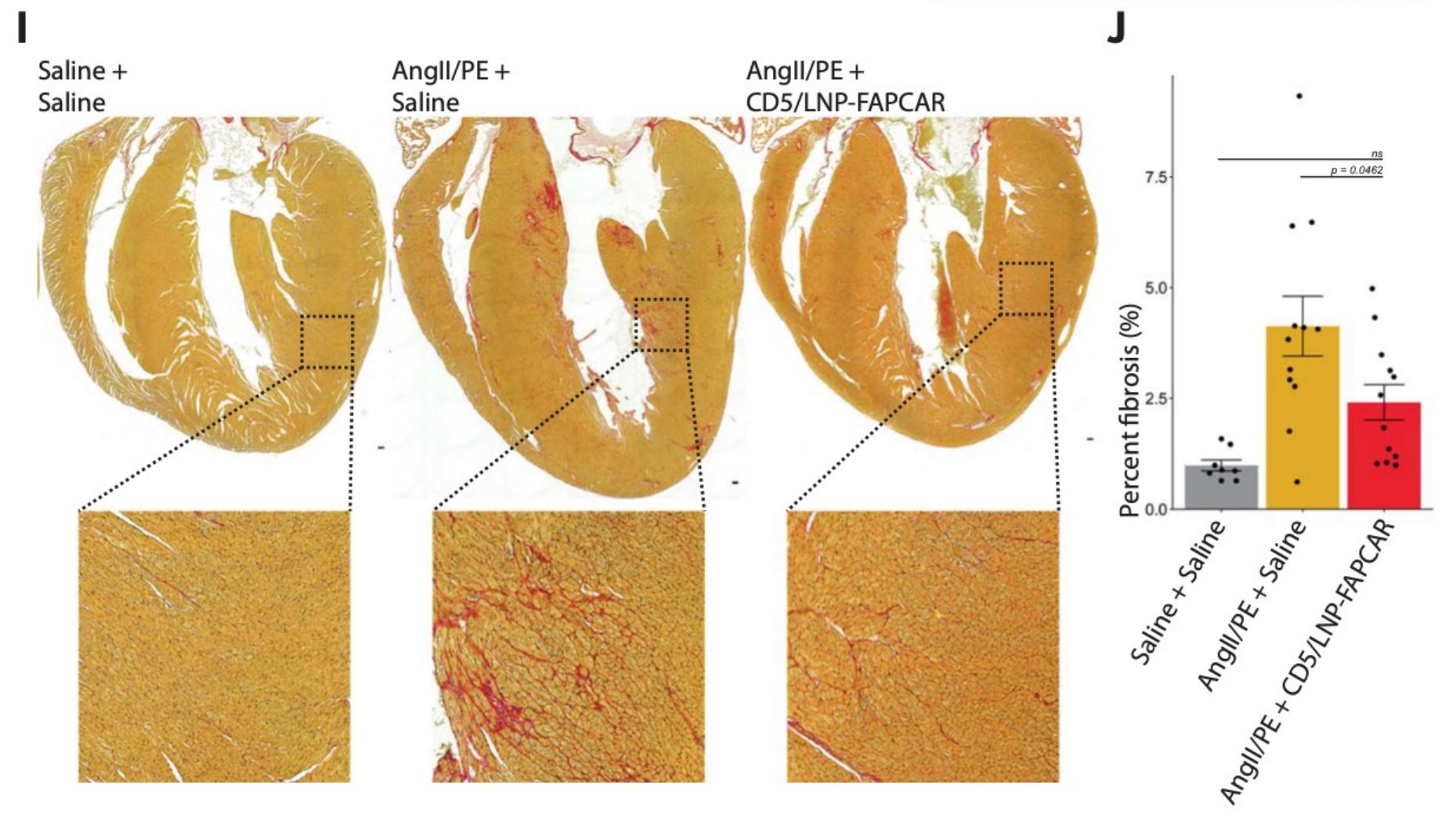




Transient FAP CAR T cells improve cardiac function after injury



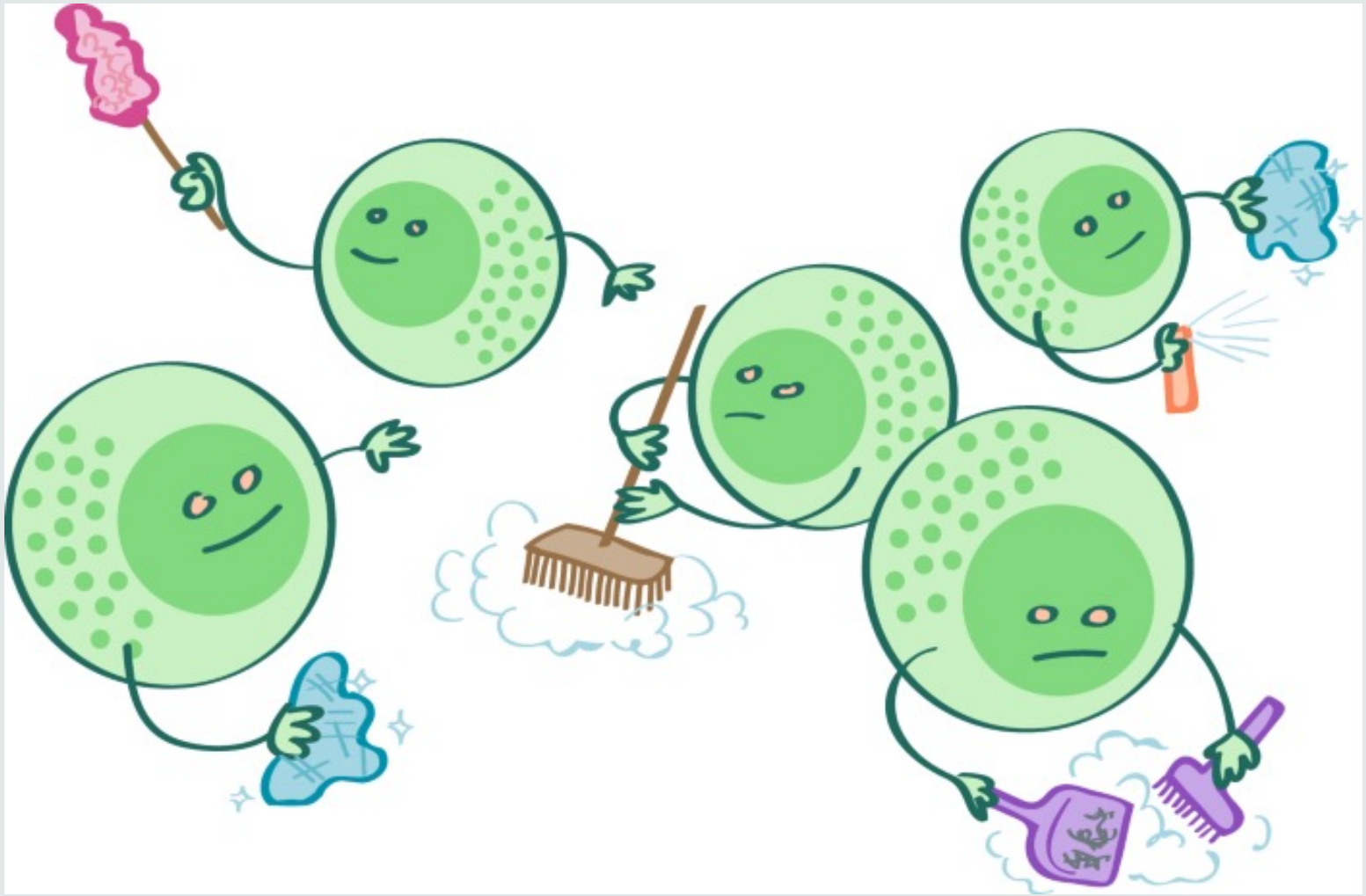
Transient FAP CAR T cells reduce fibrosis following cardiac injury



Take home messages #2

- Modified mRNA encapsulated in targeted LNPs can be delivered intravenously to produce functional engineered T cells in vivo
- The generation of engineered T cells in vivo using mRNA is attractive for certain disorders because the transient nature of the produced CAR T cells is likely to limit toxicities, including risks incurred by lymphodepletion before injection
- Targeted LNP/mRNA technology allows to titrate dosing and to re-dose as needed
- “Off-the-shelf” universal therapeutic capable of engineering specific immune functions?

CAR T cells as programmable living nanobots to keep every disease at bay



Lara Crow/Springer Nature Limited