

CARs in Fibrosis

Cellicon Valley '21, May 6, 2021

Jon Epstein

Senior Vice President, Executive Vice Dean
and Chief Scientific Officer

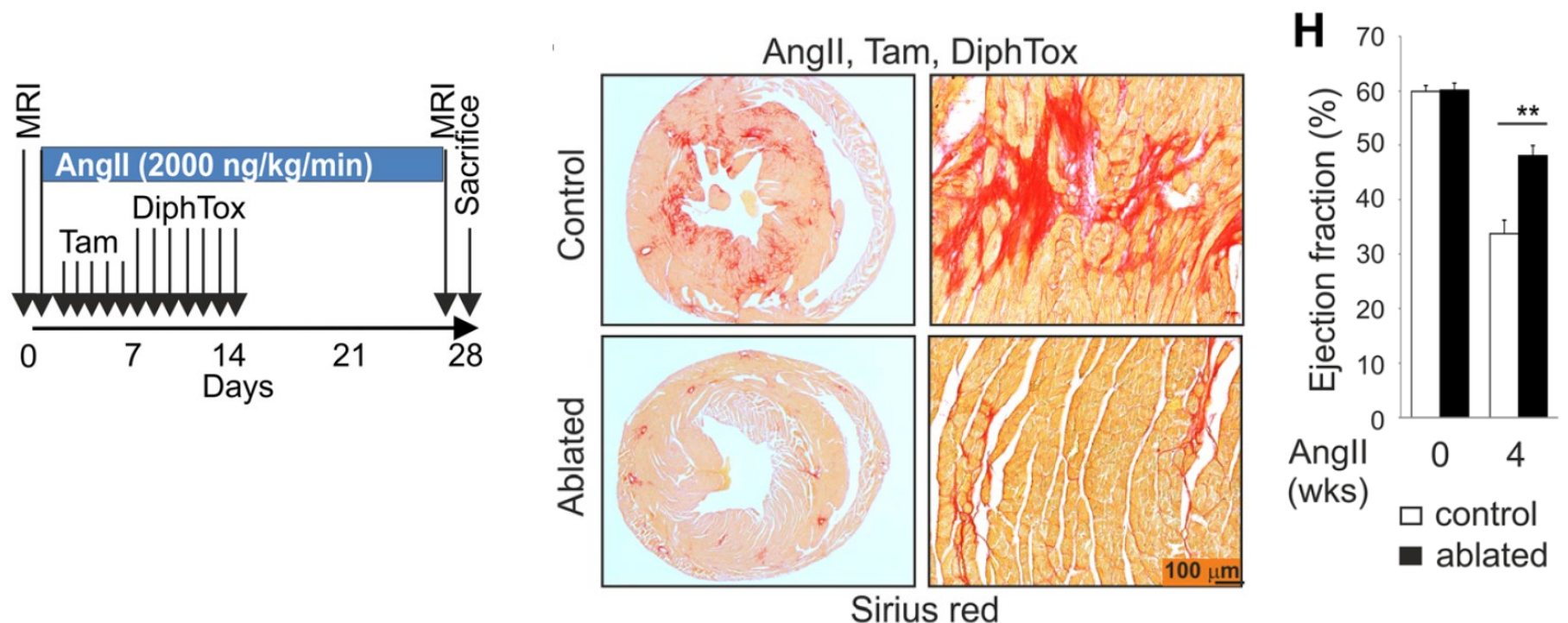
Perelman School of Medicine at the University of
Pennsylvania

Conflicts

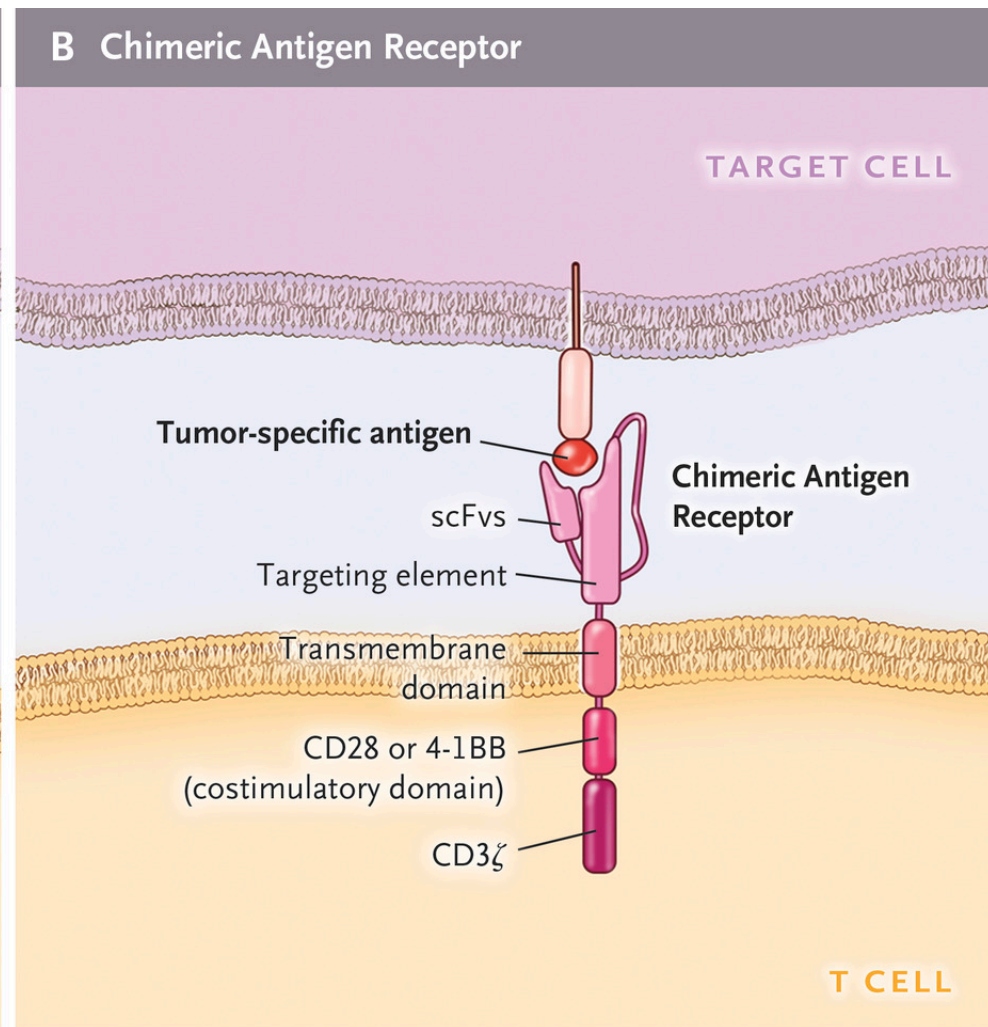
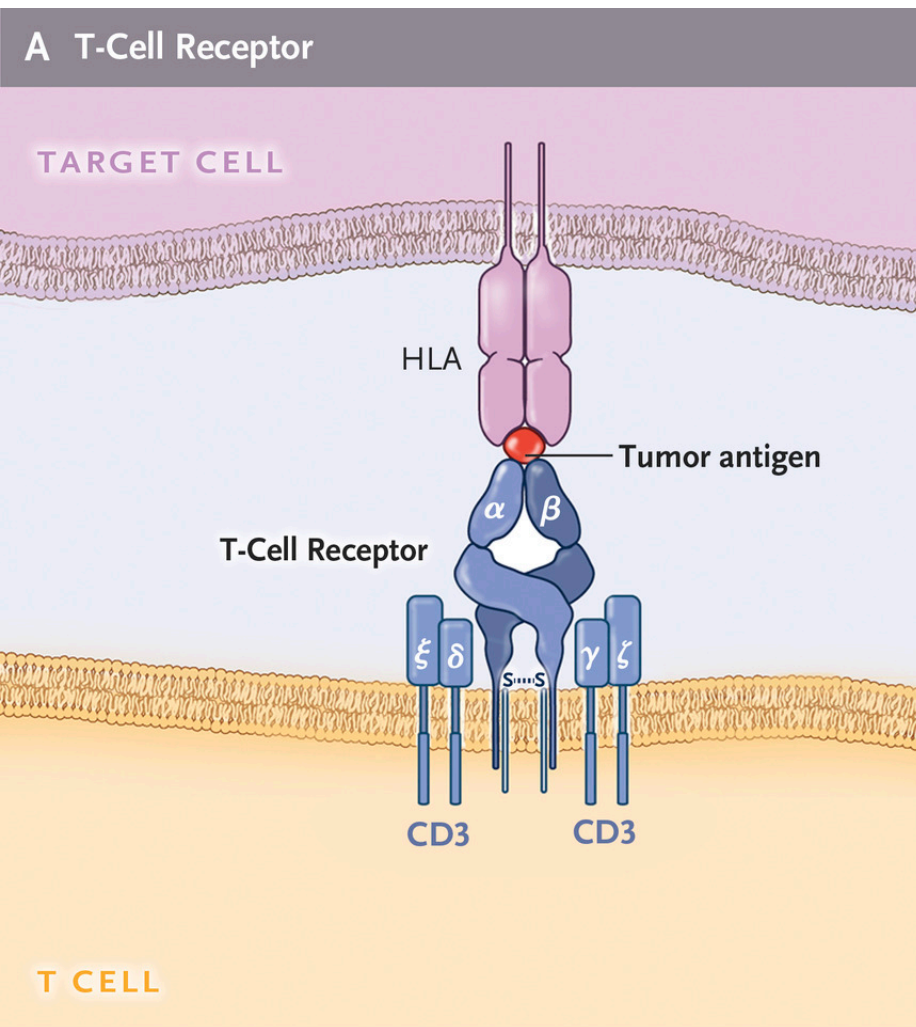
Equity in Teefib (a biotech company focused on the use of CART cells for fibrosis)

Targeted Ablation of Periostin-Expressing Activated Fibroblasts Prevents Adverse Cardiac Remodeling in Mice

Harmandeep Kaur, Mikito Takefuji, C.Y. Ngai, Jorge Carvalho, Julia Bayer, Astrid Wietelmann, Ansgar Poetsch, Soraya Hoelper, Simon J. Conway, Helge Möllmann, Mario Looso, Christian Troidl, Stefan Offermanns, Nina Wettschureck



Engineered T cells



Human cardiac fibroblast gene expression

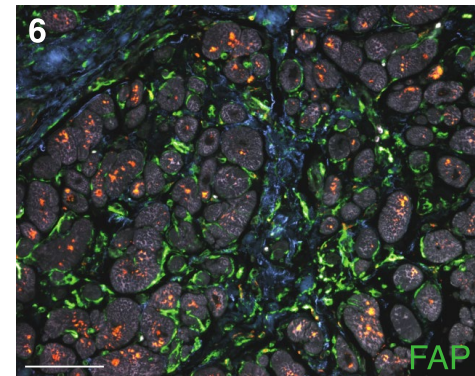
	HCM		DCM	
SYMBOL	Fold Change	P Value	Fold Change	P Value
FAP	3.92	6.97E-28	3.11	3.12E-36
THY1	3.92	6.40E-20	3.12	5.07E-27
POSTN	2.64	1.40E-11	2.02	3.73E-13
COL1A1	2.22	1.83E-15	2.71	1.04E-41
WT1	1.74	6.29E-12	1.57	4.17E-16
COL3A1	1.53	1.28E-05	1.77	8.72E-18
TCF21	1.39	1.01E-05	1.59	5.26E-19
VIM	1.26	1.43E-12	1.20	1.60E-16
ACTA2	1.26	2.64E-03	1.22	7.16E-05
DDR2	1.05	0.21	1.02	0.47
S100A4	-1.00	0.96	-1.03	0.33
FN1	-1.01	0.90	1.11	0.06
P4HA1	-1.18	4.11E-04	-1.11	1.10E-03
PDGFRA	-1.25	1.40E-05	-1.17	9.98E-06



FAP is expressed by fibroblasts of HCM and DCM LV myocardium

FAP

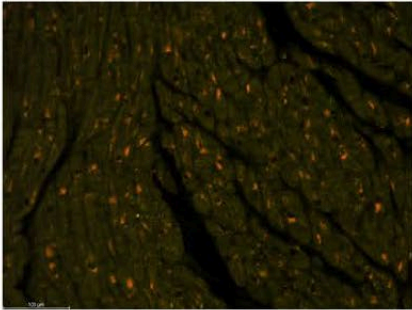
FAP



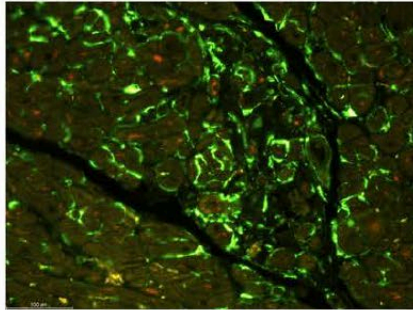
FAP is expressed in numerous forms of heart disease

A

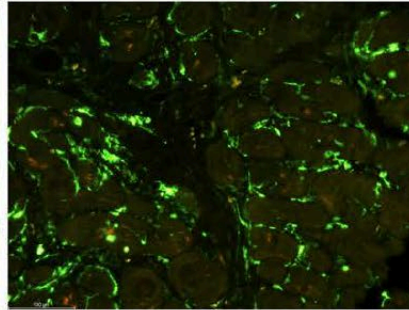
Non-failing heart



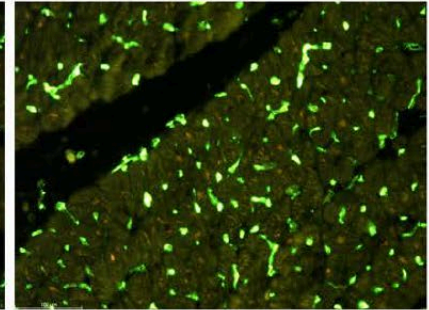
DCM



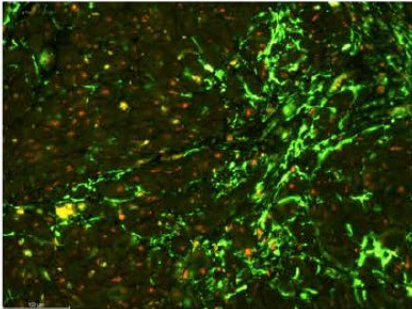
Sarcoidosis



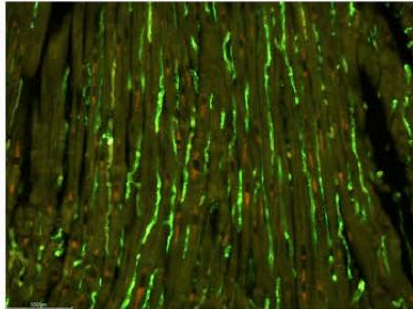
Scleroderma



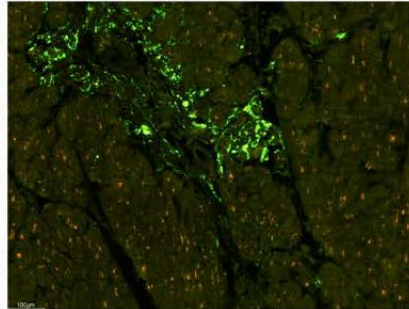
Giant Cell Myocarditis



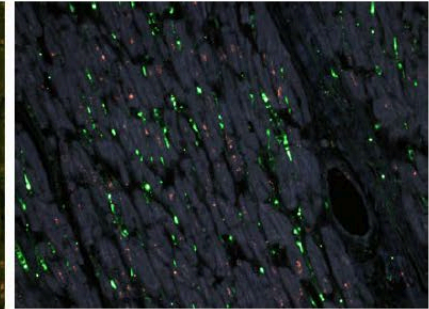
NICM



COVID-19



DMD



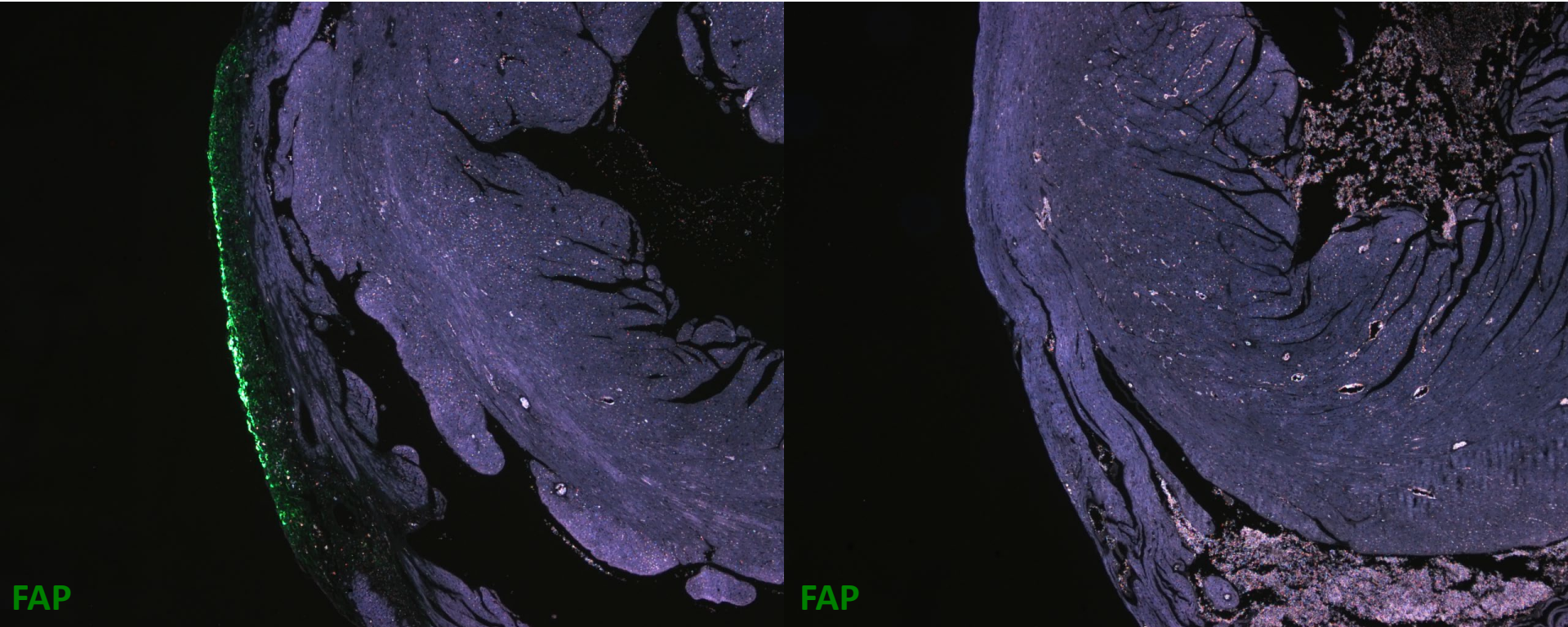
Fibroblast Activation Protein (FAP)

- Cell surface glycoprotein
- Gelatinase in the serum protease family
- Expressed during embryogenesis but not in adult tissues unless injured or cancer
 - Activated (proliferating) fibroblasts
 - 90% of tumor stromal fibroblasts
 - Apparent in human myocardium after acute MI

Fibroblast Activation Protein (FAP)

MI

Sham

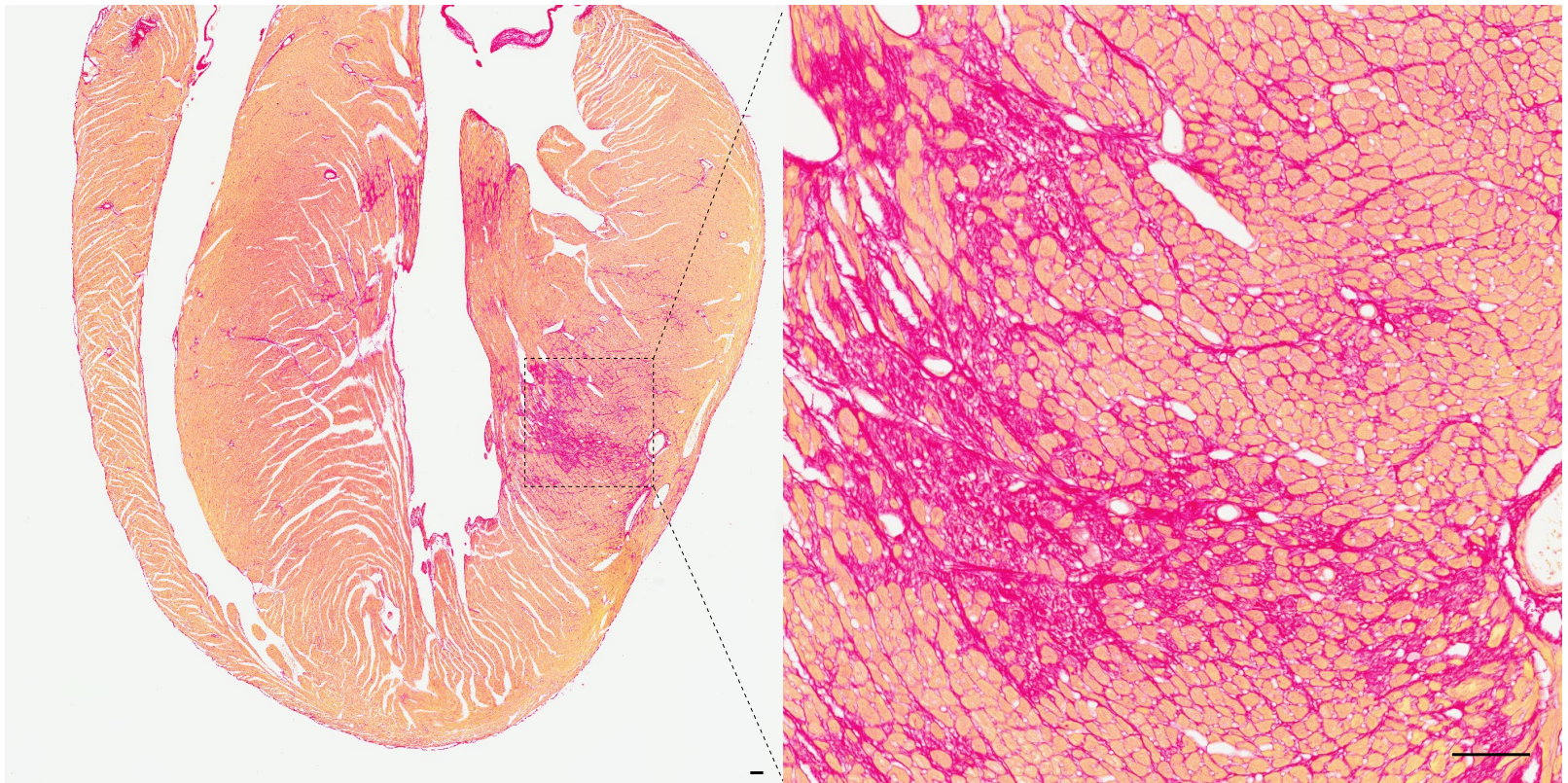


1 Week Post Myocardial Infarction

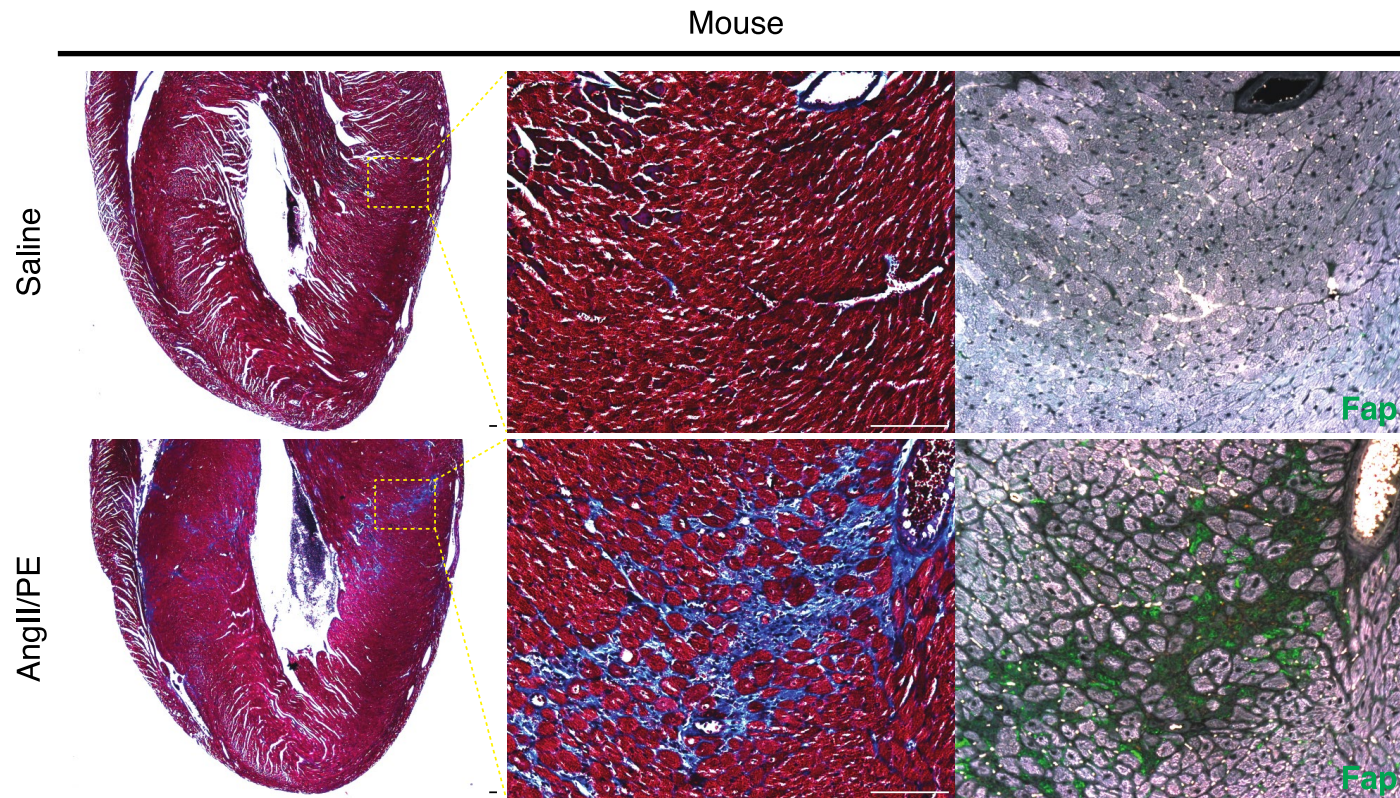
Significant fibrosis by 1 week of AngII/PE treatment

AngII/PE + Tam – 1 Week

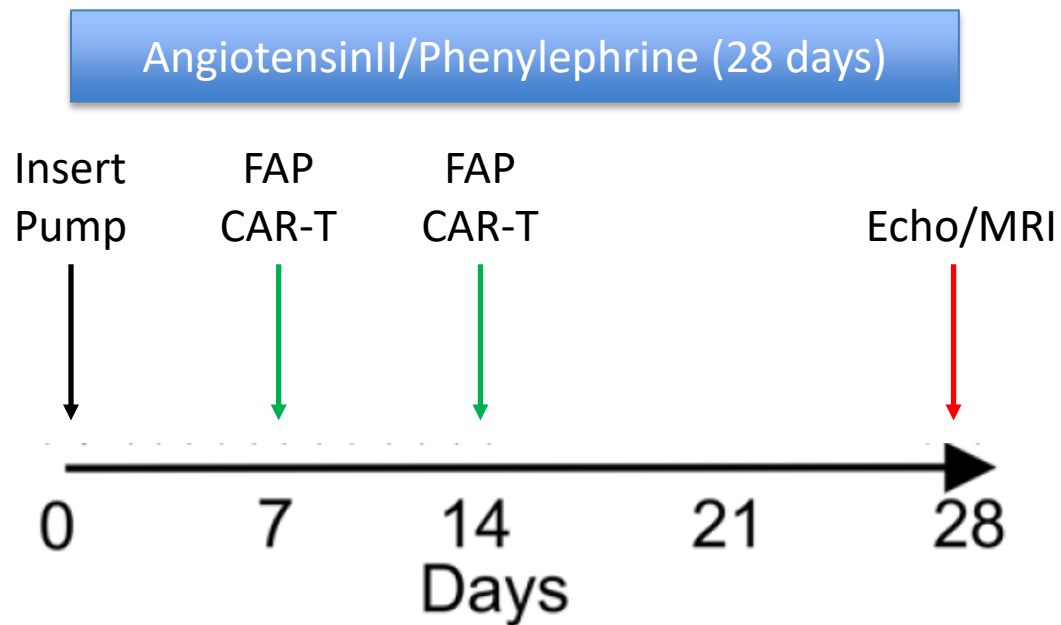
Periostin^{MCM};RosaOVA



FAP is expressed by fibroblasts of mouse hearts after 1 week of Ang/PE



CAR-T cell therapy – AngII/PE



N = 8 for AngII/PE and CAR-T treated mice

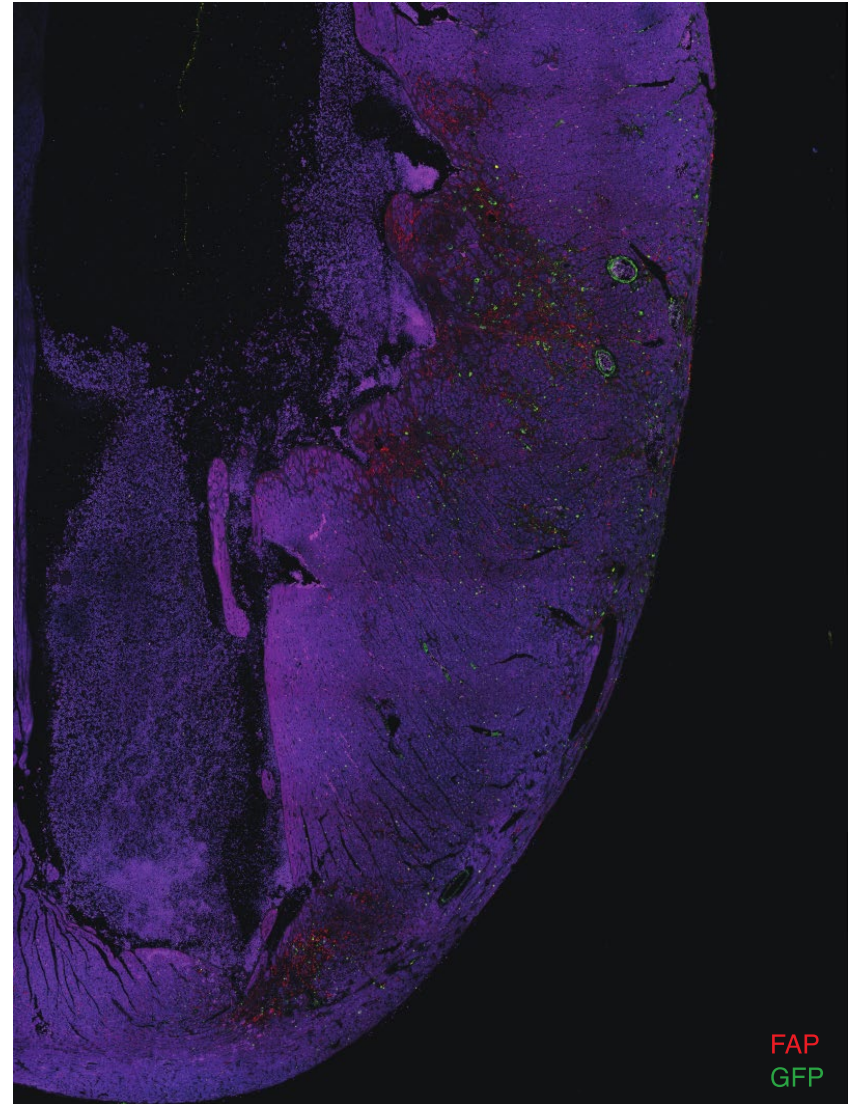
N = 8 for AngII/PE and T cell treated controls

CAR-T cells populate the scar

Control + FAP-GFP CAR T-cells

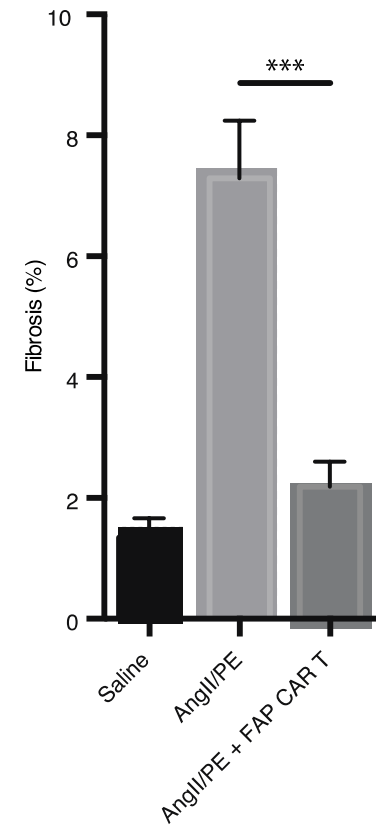
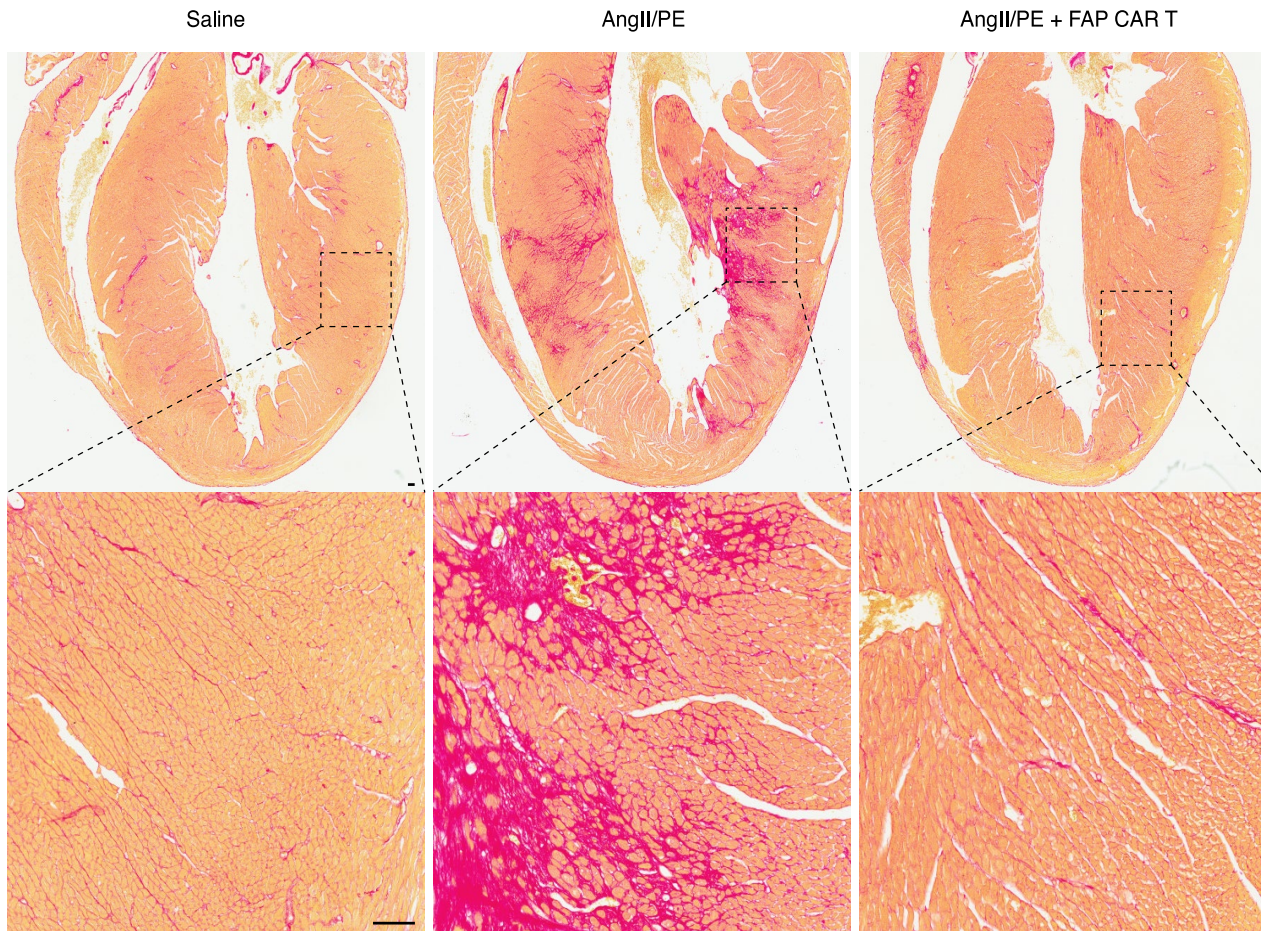


AngII/PE + FAP-GFP CAR T-cells

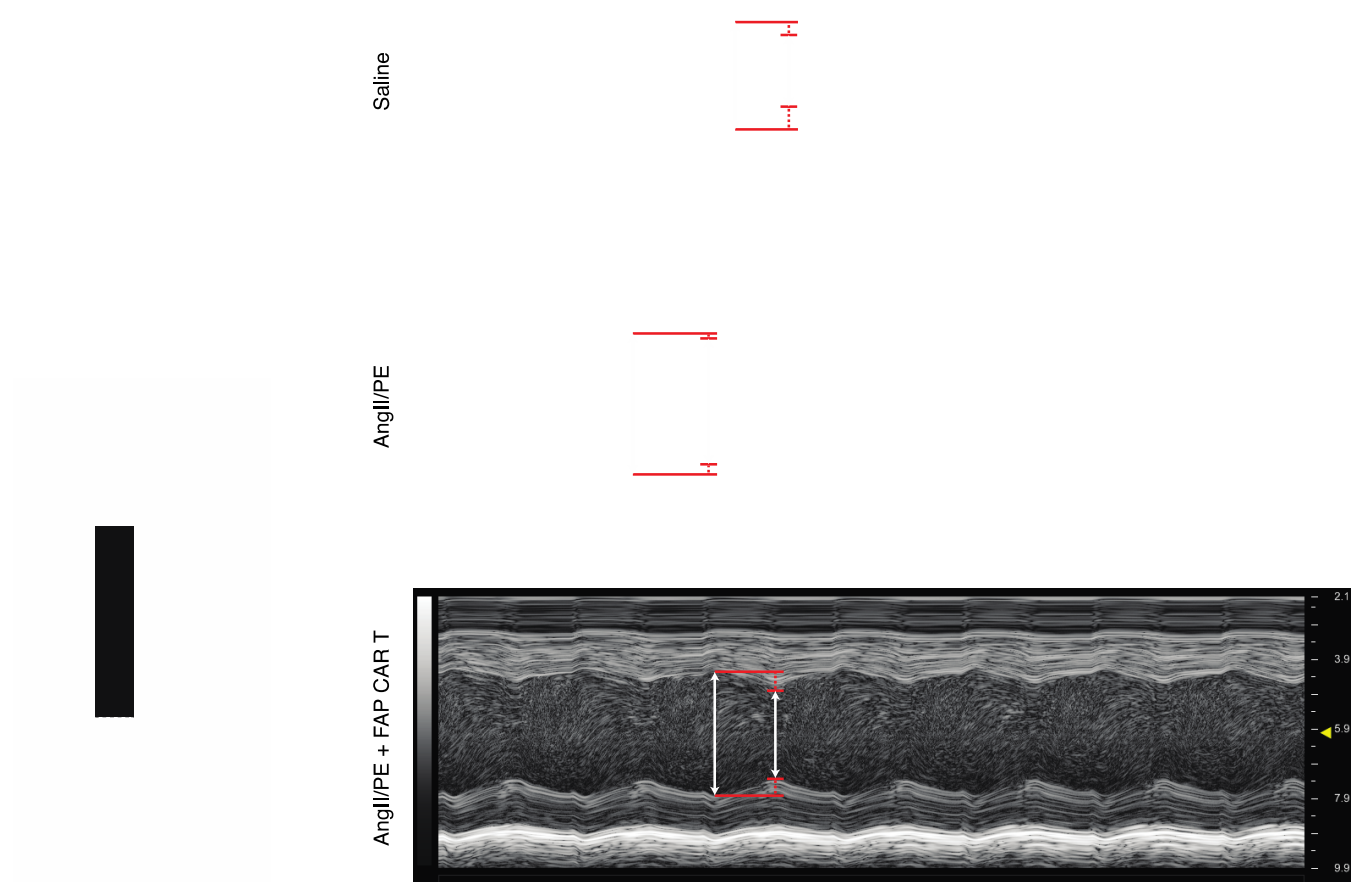


1 day post adoptive T cell transfer

FAP CAR T therapy reduces cardiac fibrosis



FAP CAR-T therapy enhances cardiac function



nature
International journal of science

Letter | Published: 11 September 2019

Targeting cardiac fibrosis with engineered T cells

Haig Aghajanian, Toru Kimura, Joel G. Rurik, Aidan S. Hancock, Michael S. Leibowitz, Li Li, John Scholler, James Monslow, Albert Lo, Wei Han, Tao Wang, Kenneth Bedi, Michael P. Morley, Ricardo A. Linares Saldana, Nikhita A. Bolar, Kendra McDaid, Charles-Antoine Assenmacher, Cheryl L. Smith, Dagmar Wirth, Carl H. June, Kenneth B. Margulies, Rajan Jain, Ellen Puré, Steven M. Albelda & Jonathan A. Epstein ✉

The New York Times
This Treatment Can Cure Cancer. Can It Mend the Heart?

SCIENTIFIC AMERICAN
Could Immunotherapy Treat Diseases Besides Cancer?

PHARMACEUTICAL
TECHNOLOGY

Penn researchers study cancer therapy in heart disease treatment

The NEW ENGLAND JOURNAL of MEDICINE

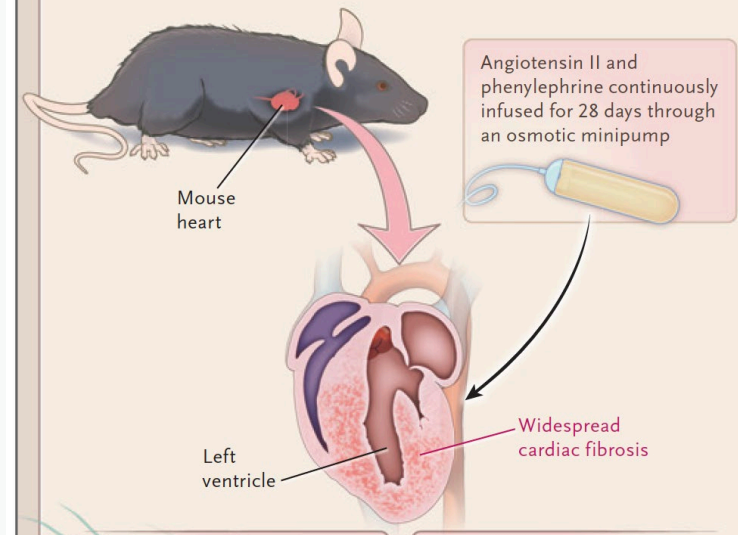
CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., Editor

When the CAR Targets Scar

Joseph A. Hill, M.D., Ph.D.

Mouse Model of Cardiac Fibrosis

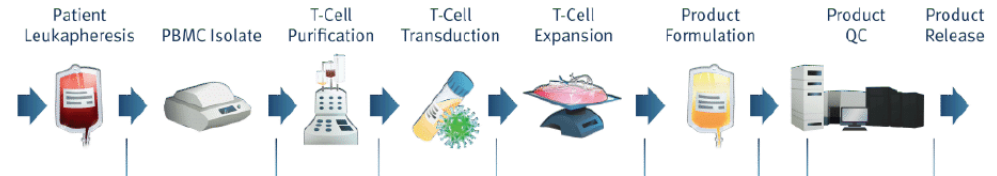


What is the safest and “best” way to make a FAP CART cell?

- Lentivirus ex vivo → autologous, manufactured, long lived
- mRNA ex vivo → autologous, manufactured, short lived
- LNP/mRNA ex vivo
- LNP/mRNA in vivo

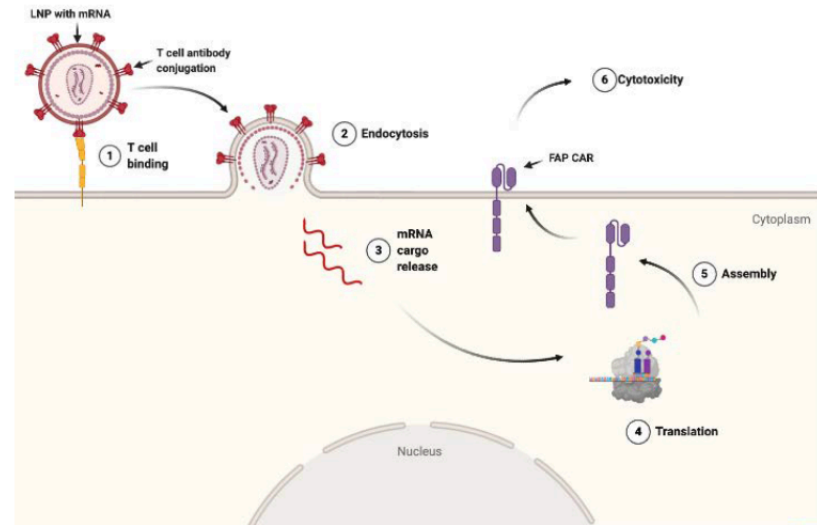
From lab manufactured CAR T to *in vivo* transduction

In vivo transduction of T cells using CD 5 targeted Lipid Nanoparticles (tLNP)

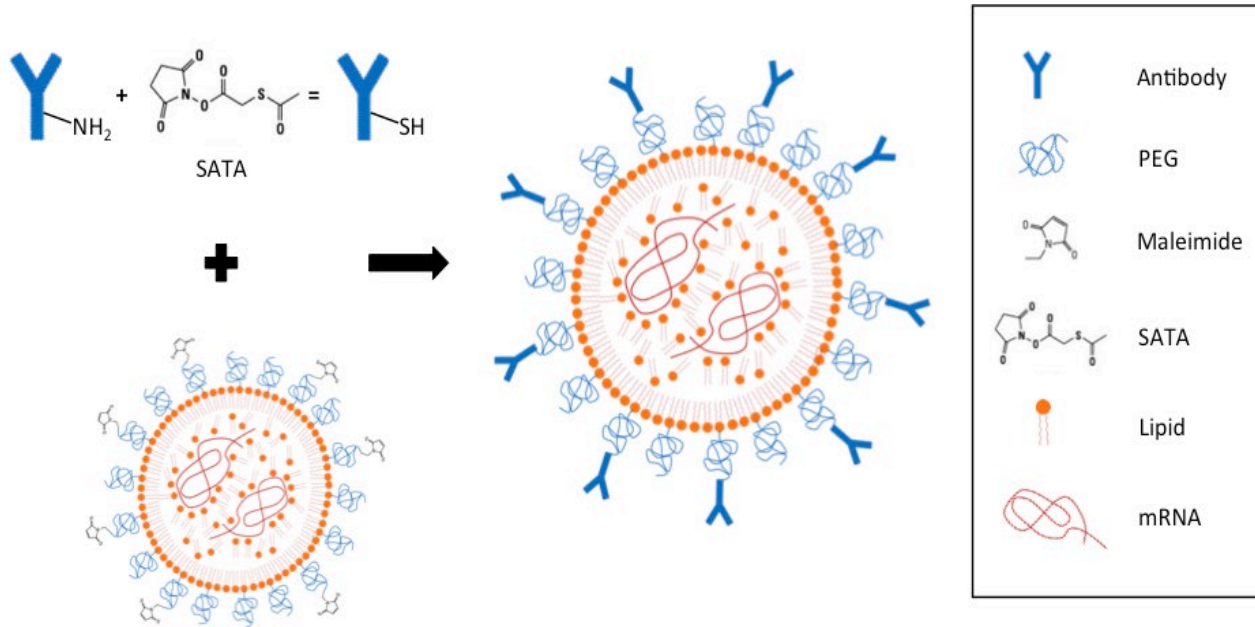


- Would greatly facilitate the delivery of antifibrotic treatments allowing targeting indications with large prevalence and lower medical need such as:

- NASH
- COVID 19 lung or cardiac fibrosis
- Rheumatoid Arthritis
- Crohn's disease
- ...

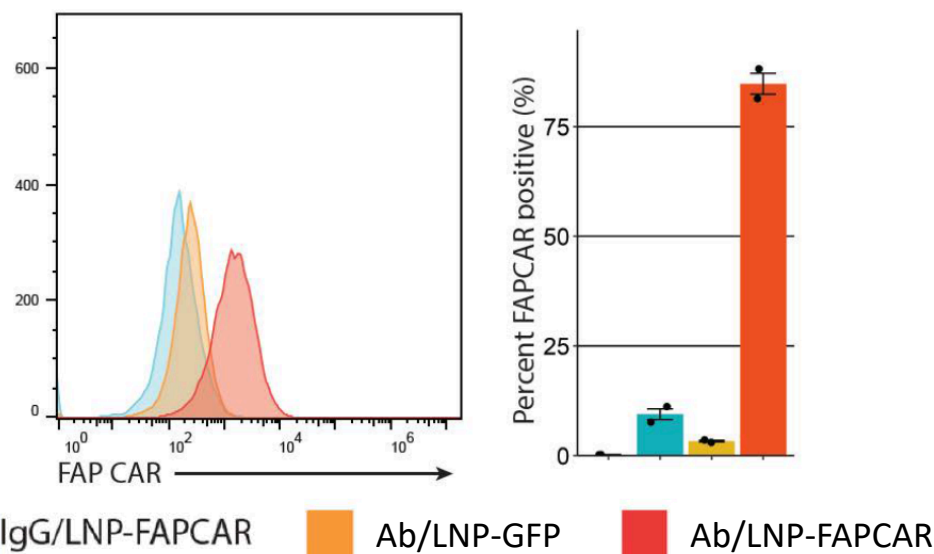


Addition of targeting molecules to the surface of LNPs

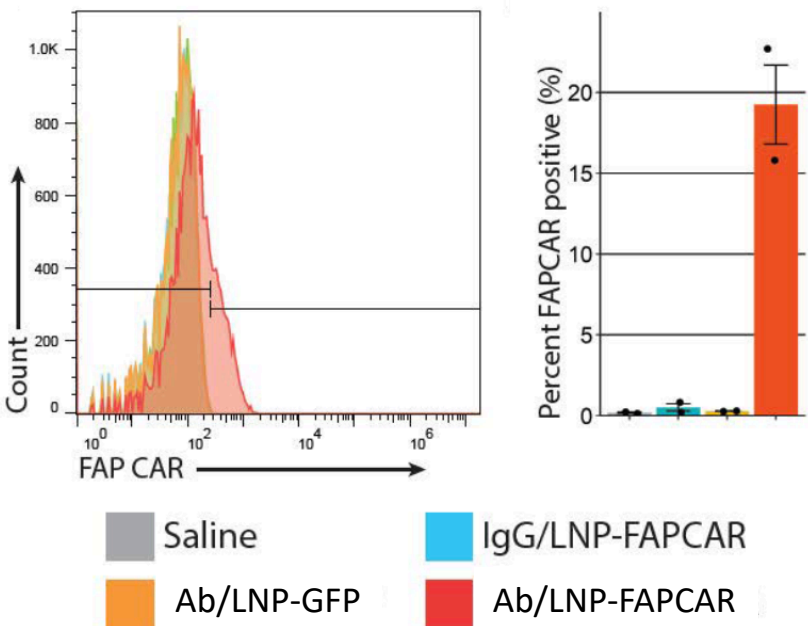


FAP CAR is expressed via *in vitro* and *in vivo* LNP gene transfer

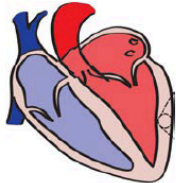
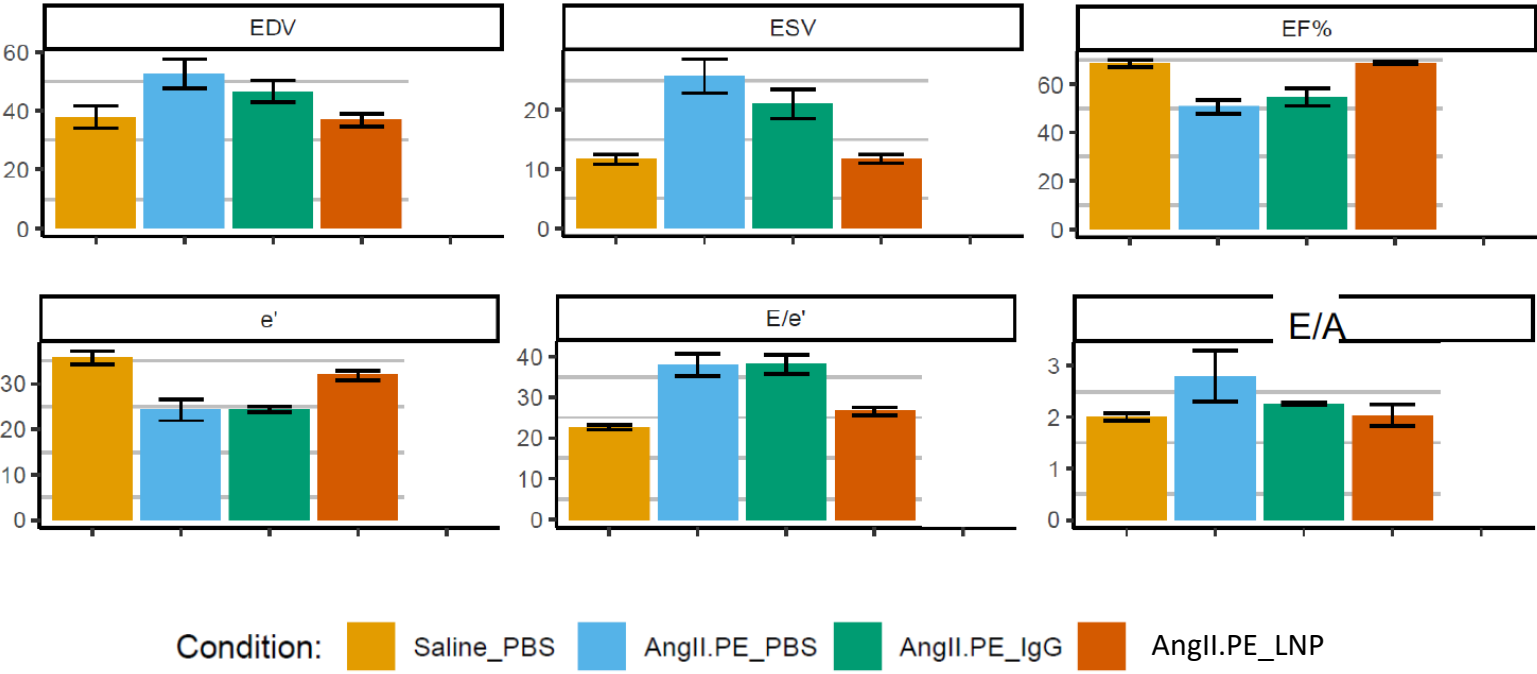
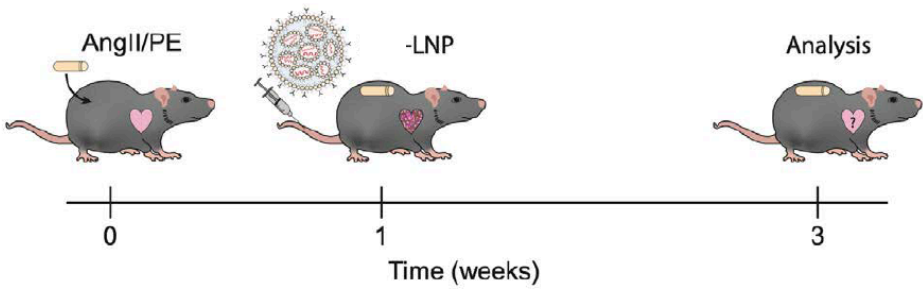
In vitro



In vivo



In vivo LNP FAP CAR T rescues cardiac function





Ellen Pure
Steve Albelda
Carl June
Ken Margulies
Raj Jain
Drew Weissman

Karen

Joel

Haig

Cheryl

Diana

Anna

Kurt
Jun Li
Feiyan

Where's
Andrey Poleshko?

Kelvin

Pedro Mendez
Ricardo Linares