Targeted nanomedicine strategies to reprogram the tumor immune microenvironment

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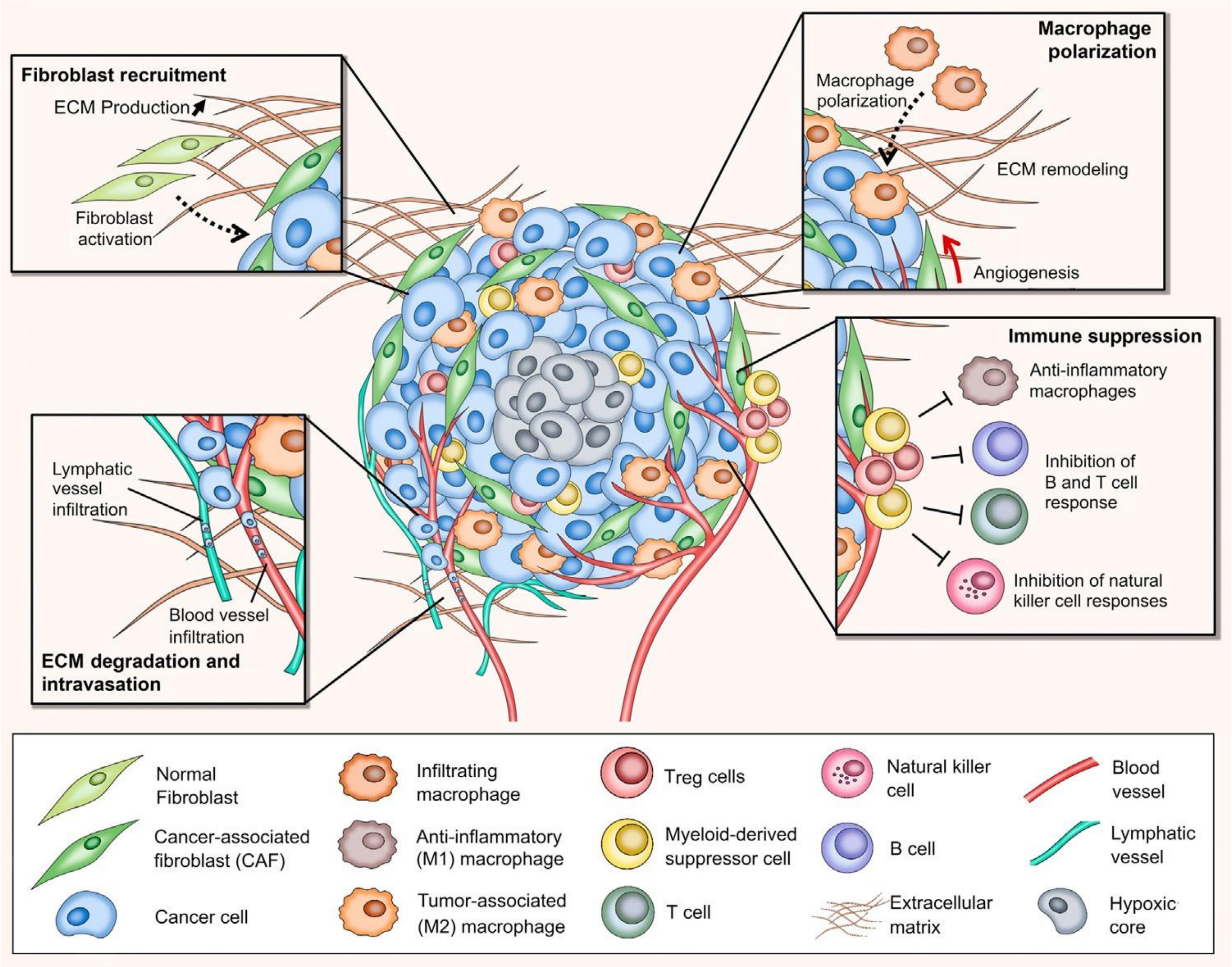
NEXT-GENERATION DELIVERY INNOVATIONS

Tumor microenvironment: A barrier to cancer therapies

Fibrotic microenvironment

- Reduced drug delivery
- Immune exclusion/ desertion
- Induce resistance in tumor cells



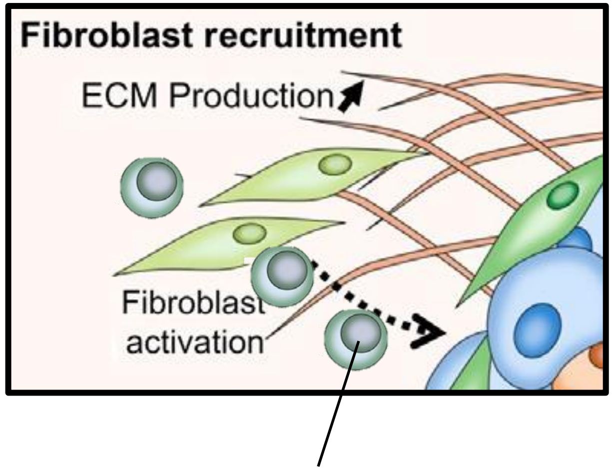
Deregulated immune microenvironment

- Immunosupressive cells
- Overexpression of immune checkpoint pathways
- Induce fibrotic stroma (e.g. TGF-β)

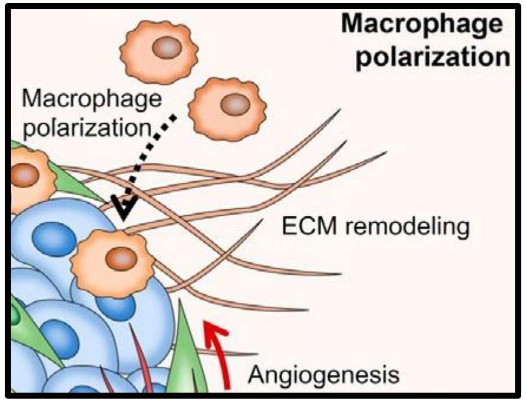
Rodrigues…. Prakash, Trends in Cancer, 2021

Strategies to reprogram the tumor immune microenvironment

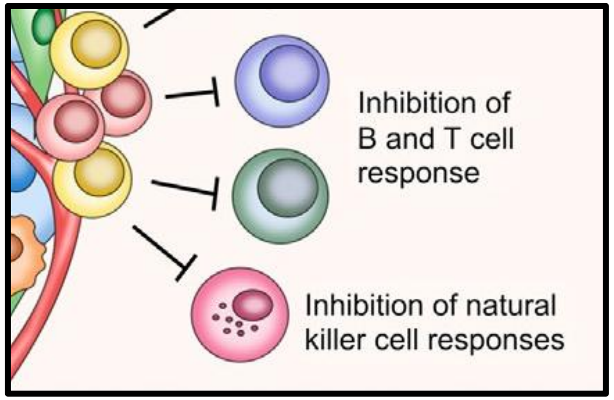
Targeting the fibrotic microenvironment



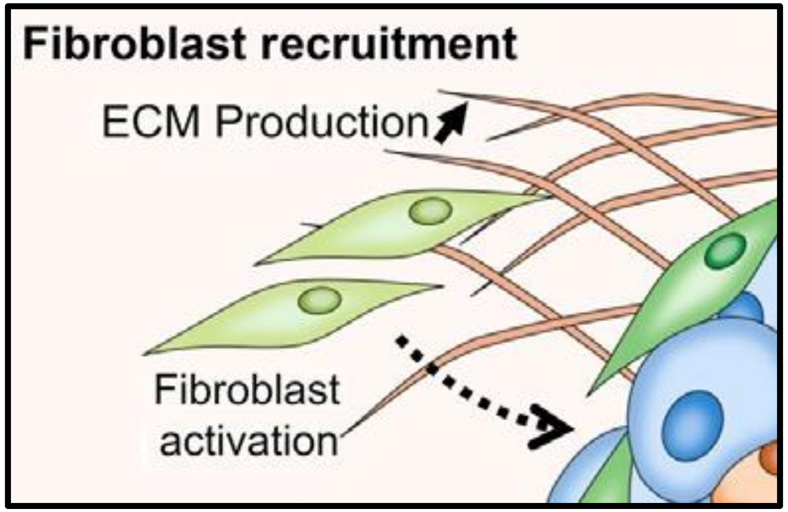
Target and repolarize tumor-associated macrophages



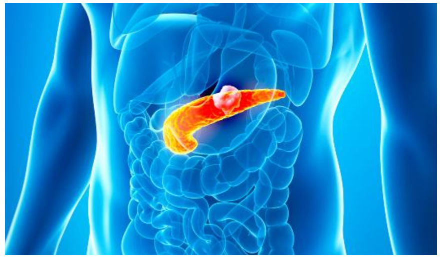
Deliver cytokines to activate immune cells



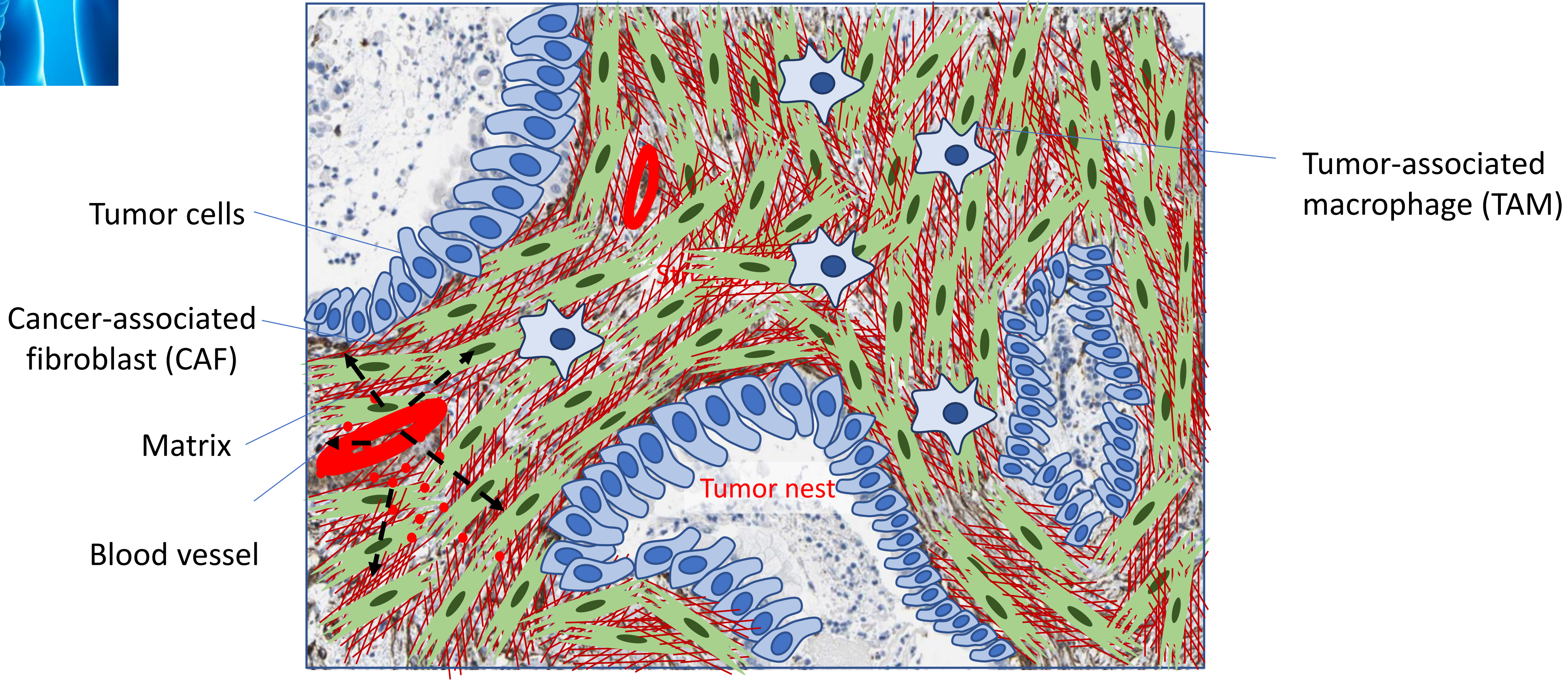
Targeting the fibrotic microenvironment



Pancreatic ductal adenocarcinoma



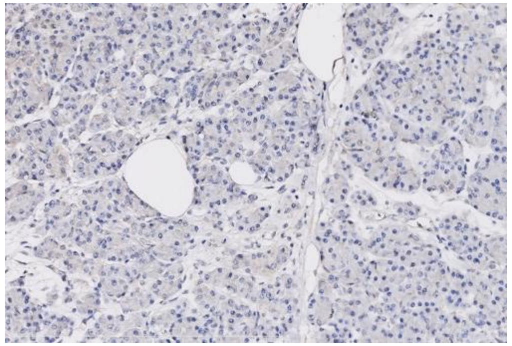
Human pancreatic tumor



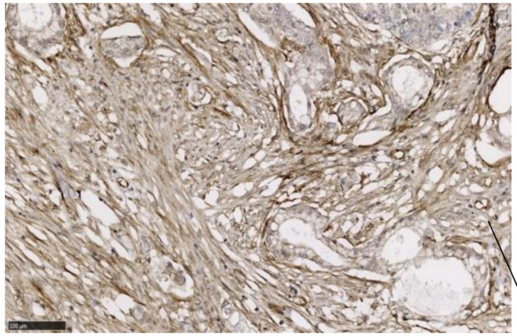
(up to 90% stroma)

Integrin alpha5 (ITGA5) expression in PDAC patients

Healthy Pancreas

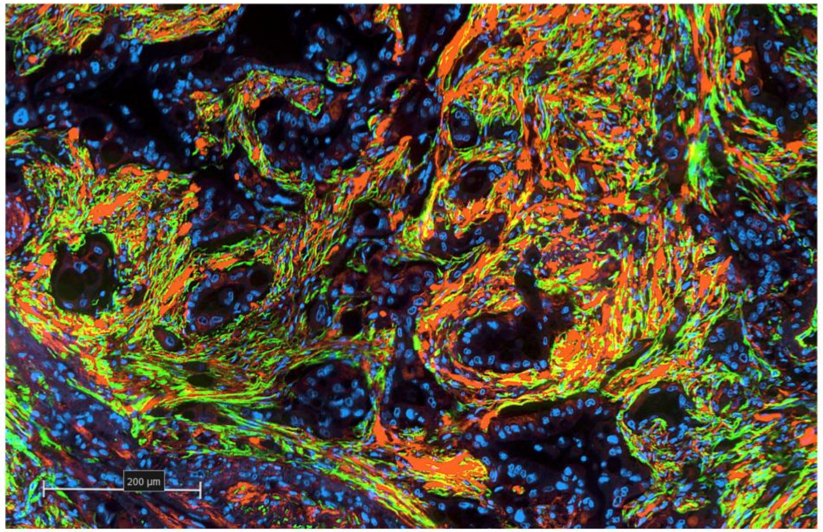


Pancreatic cancer

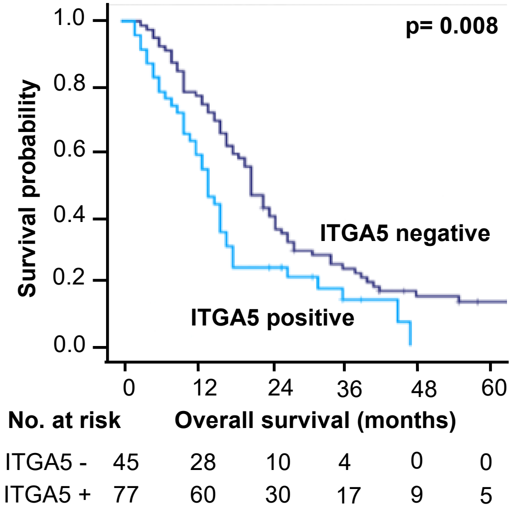


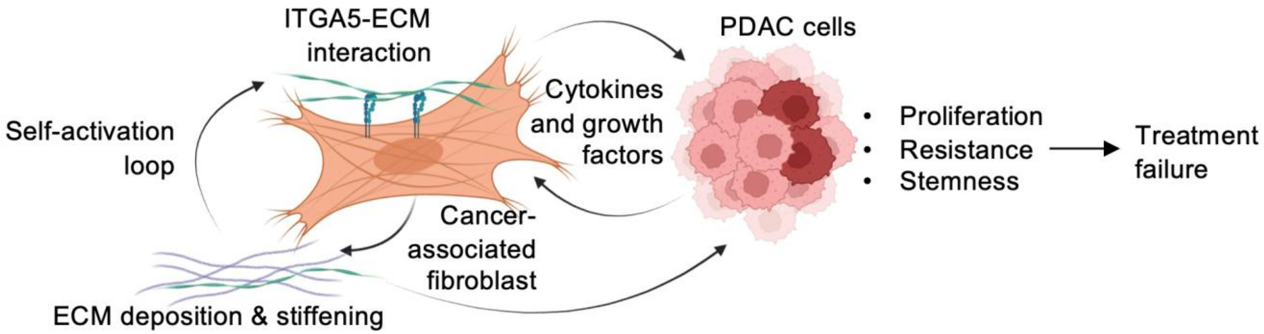
Tumor
Stroma

Human PDAC sample



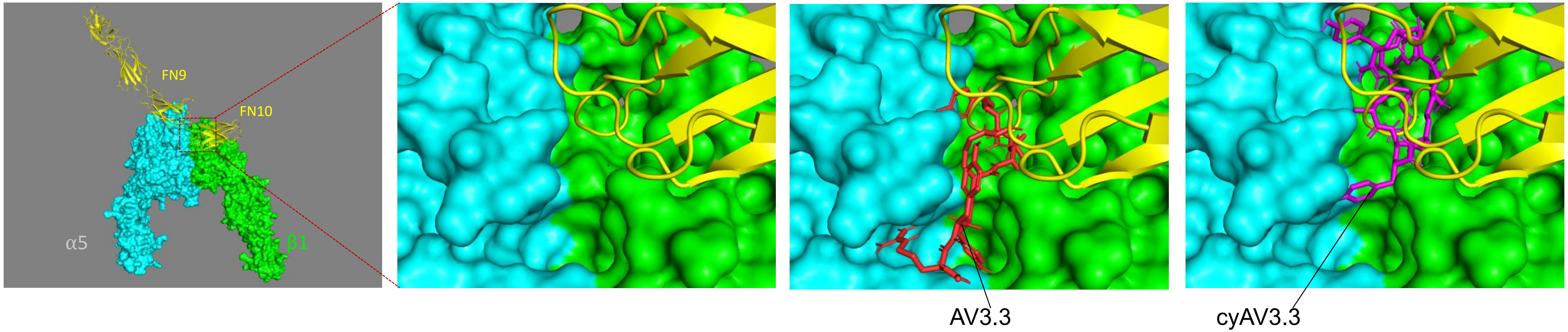
ITGA5
αSMA
DAPI

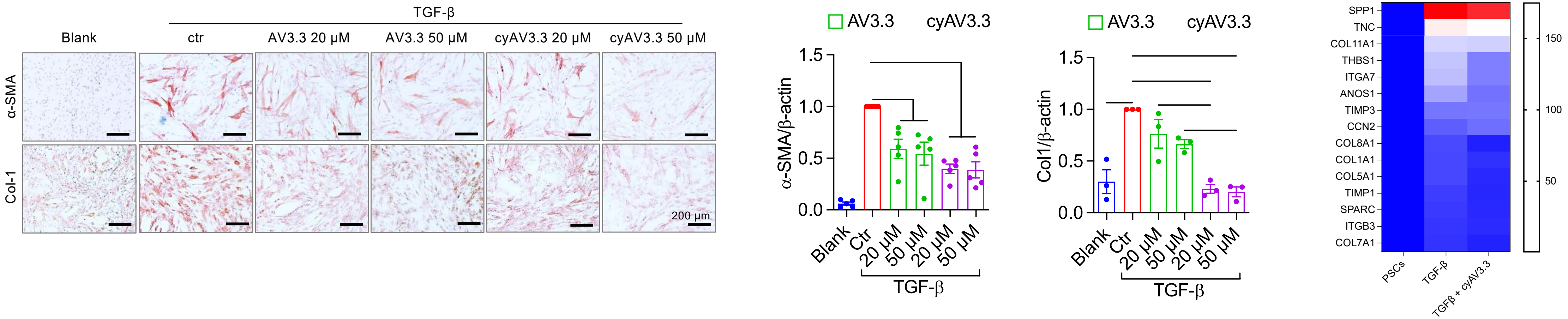




Kuninty…….Prakash, Science Advances 2019

ITGA5 targeting peptides

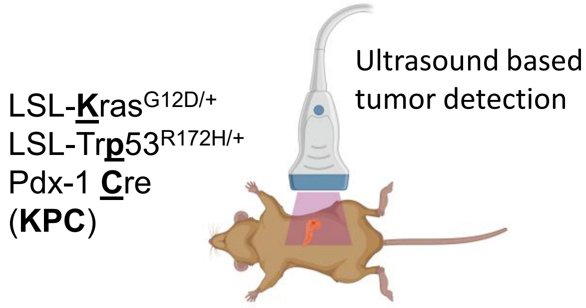


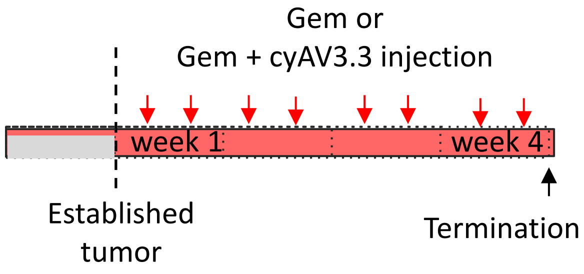


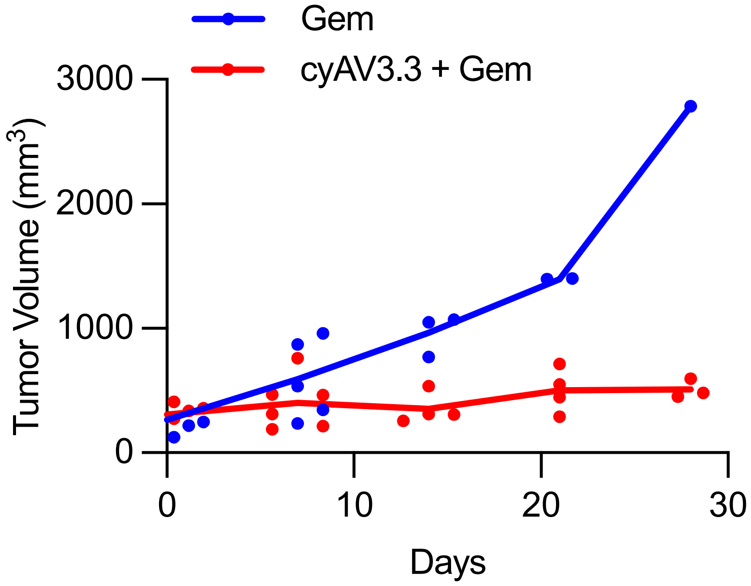
Mardhian et al. in revision

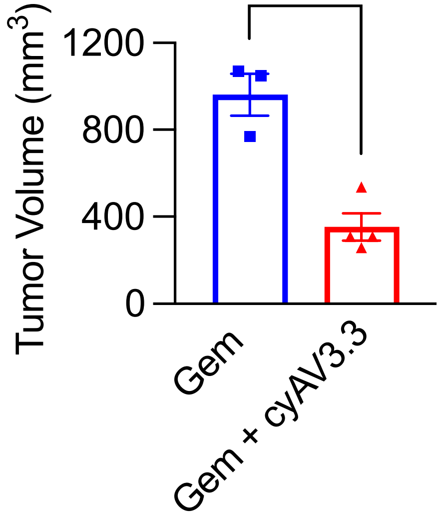
cyAV3.3 induces the efficacy of gemcitabine in spontaneous KPC model

Genetically engineered KPC mouse model





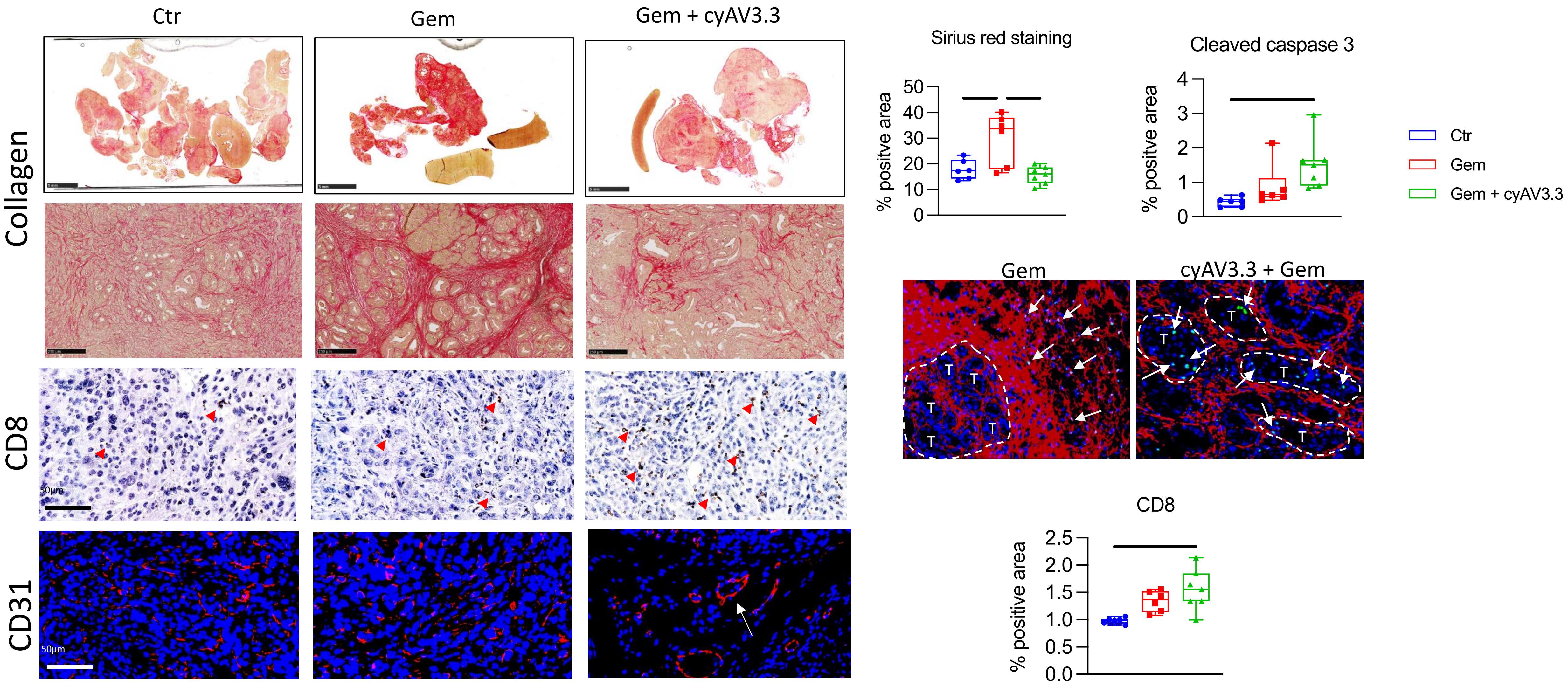




Collaborator: Jennifer Morton, Cancer Research UK

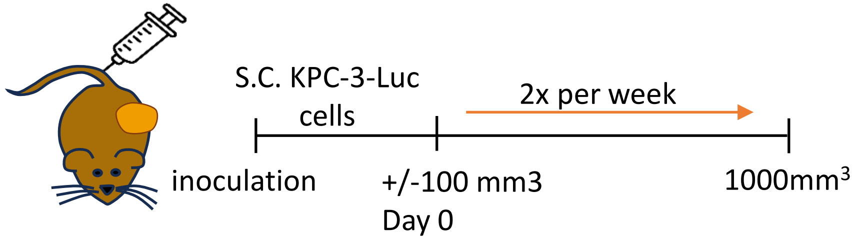
Mardhian et al, in revision

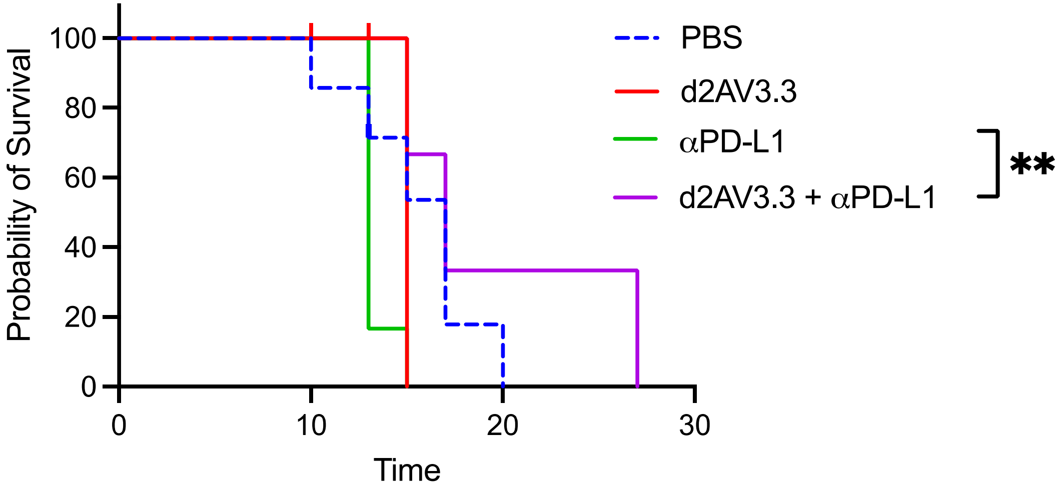
cyAV3.3 reduces tumor fibrosis and induces T cell infiltration

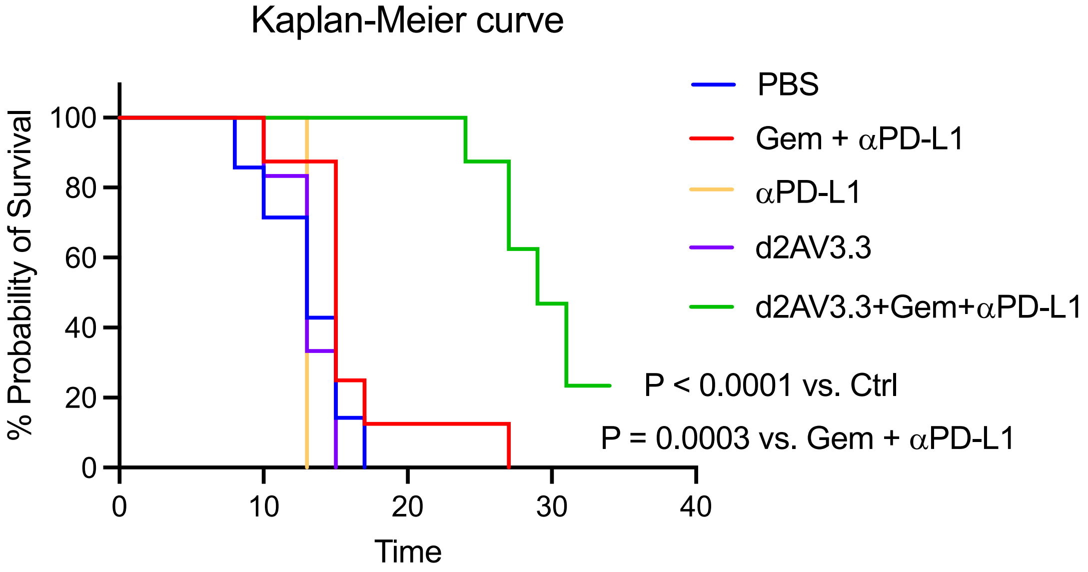


Mardhian et al, in revision

Inhibtion of ITGA5 enhances efficacy of chemoimmunotherapy

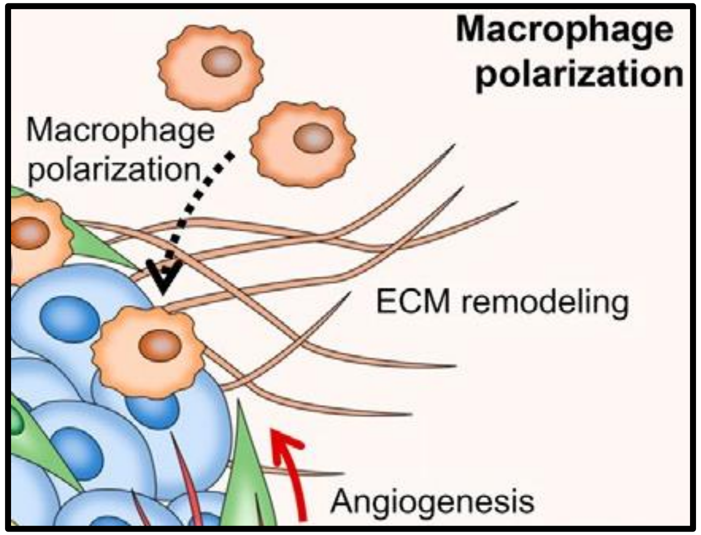




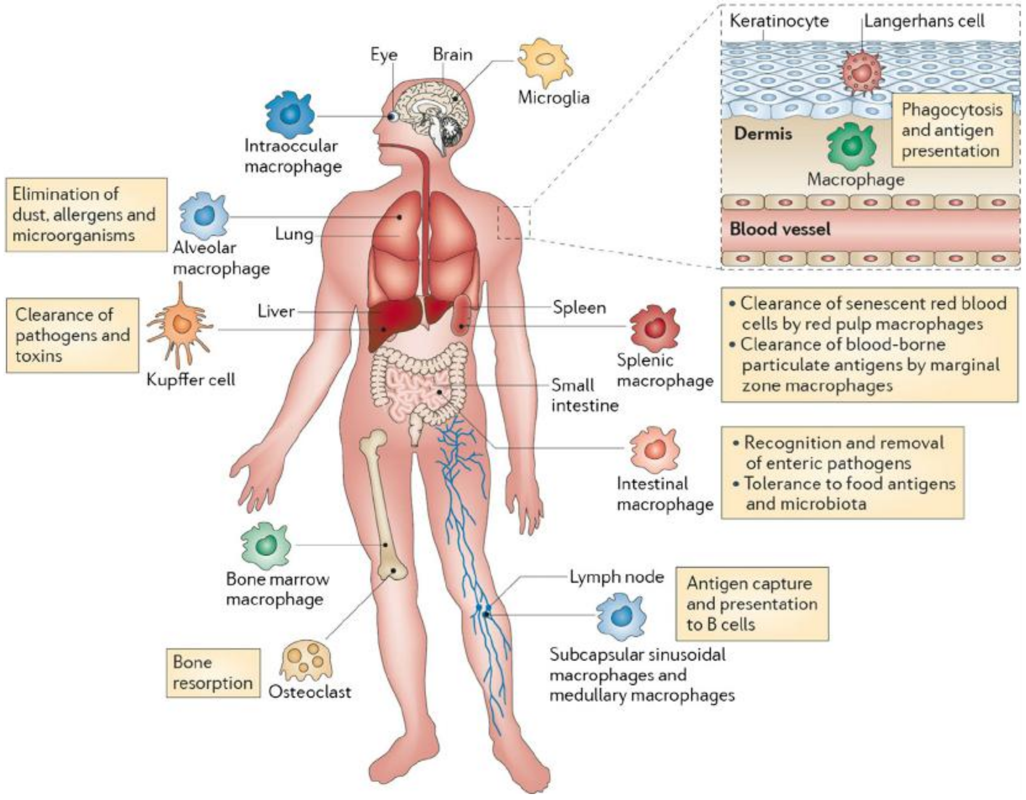


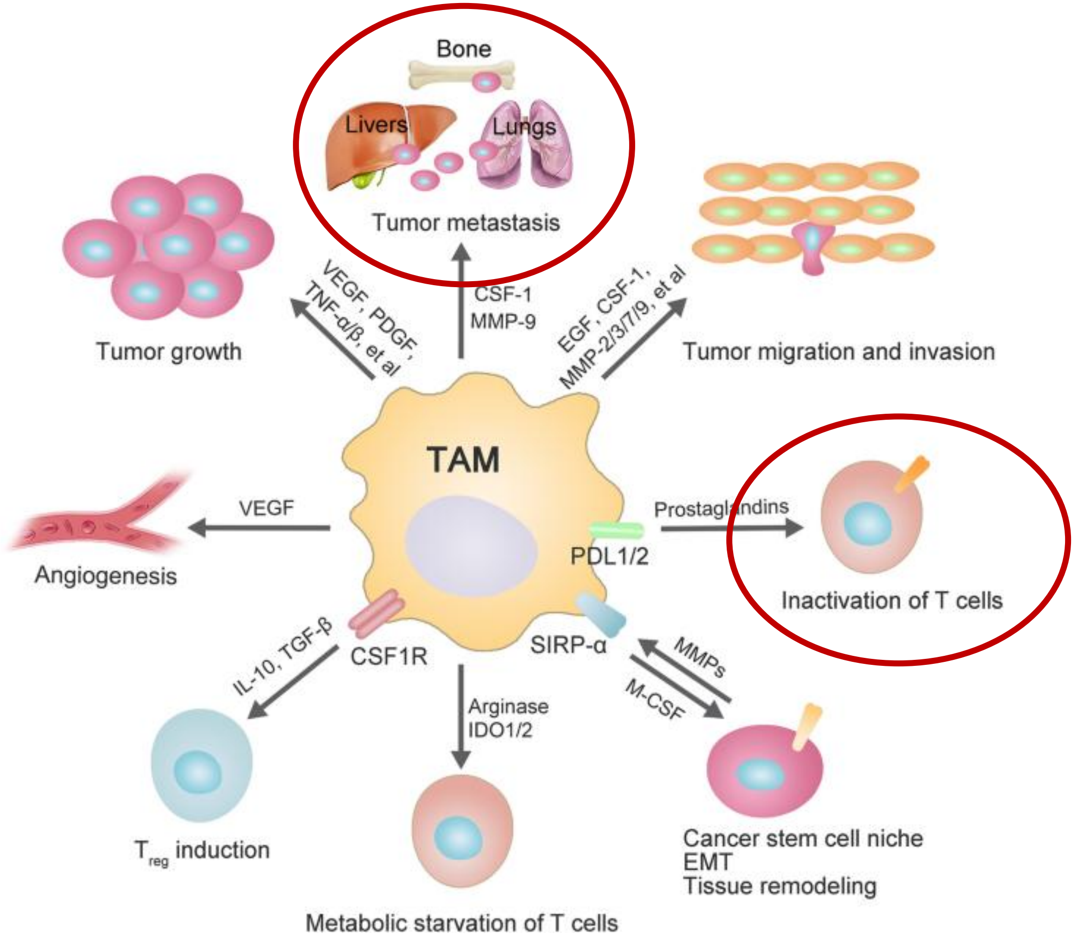
Hemden et al, unpublished - do not post

Nanosystem to target and repolarize tumor-associated macrophages



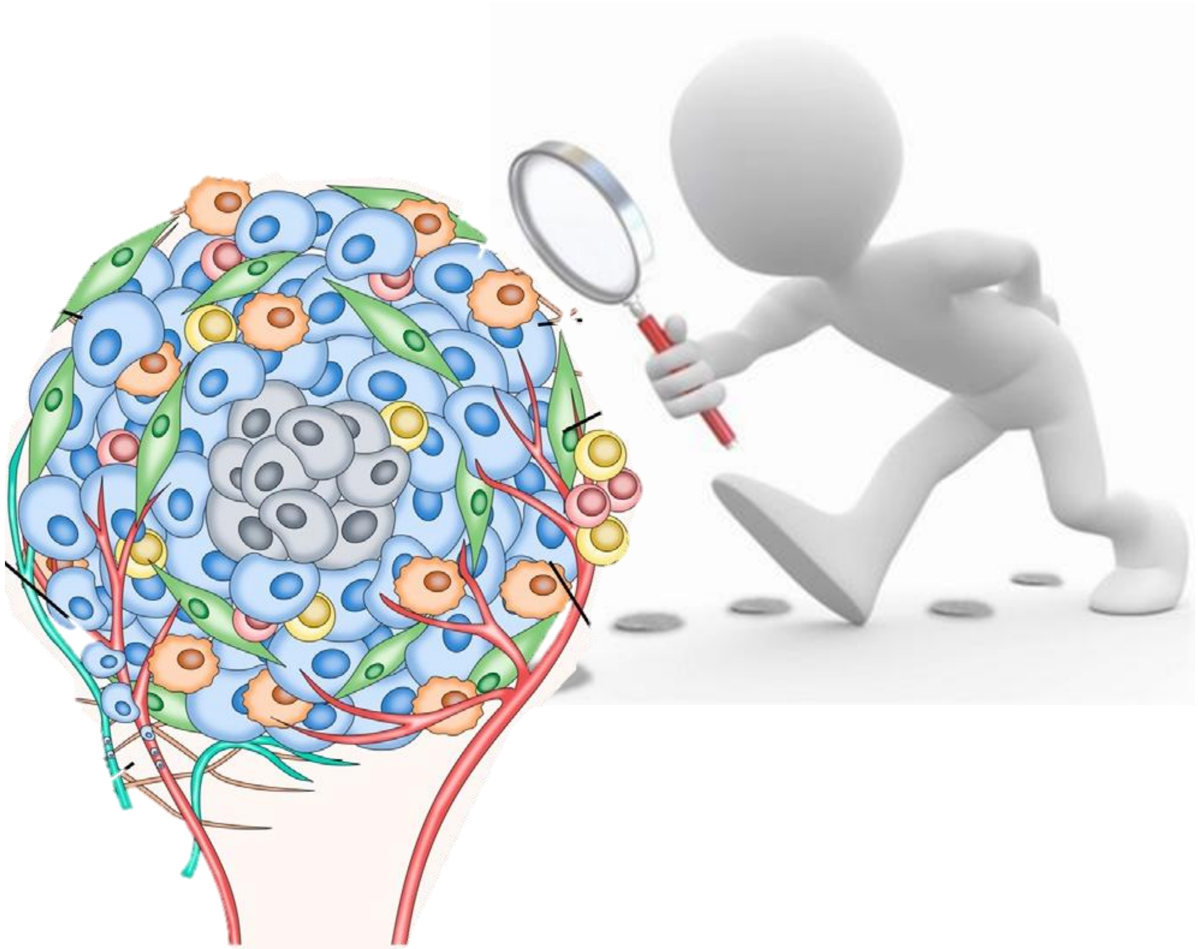
Tumor-associated macrophages (TAM)

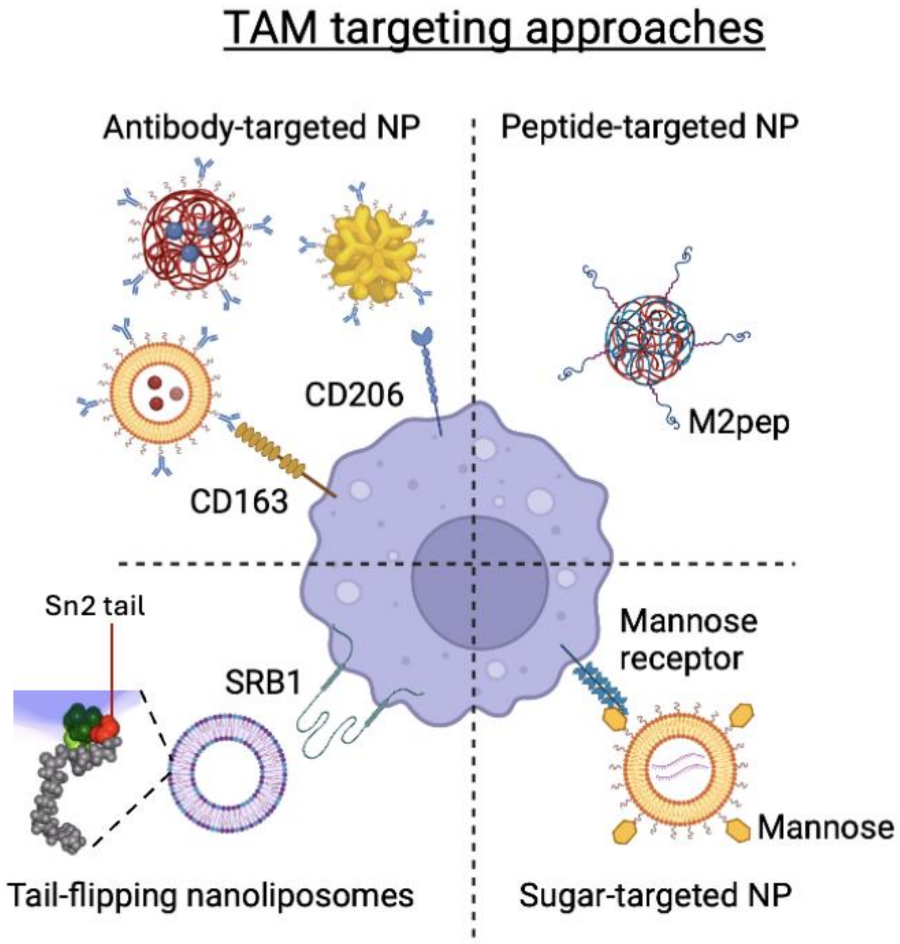




Chen et al. JBC (2019)

How to target TAMs among so many cells?





Pednekar…..Prakash. Eur J Pharm Biopharm 2024

nature communications

Article

https://doi.org/10.1038/s41467-022-32091-9

Cancer immune therapy using engineered 'tail-flipping' nanoliposomes targeting alternatively activated macrophages

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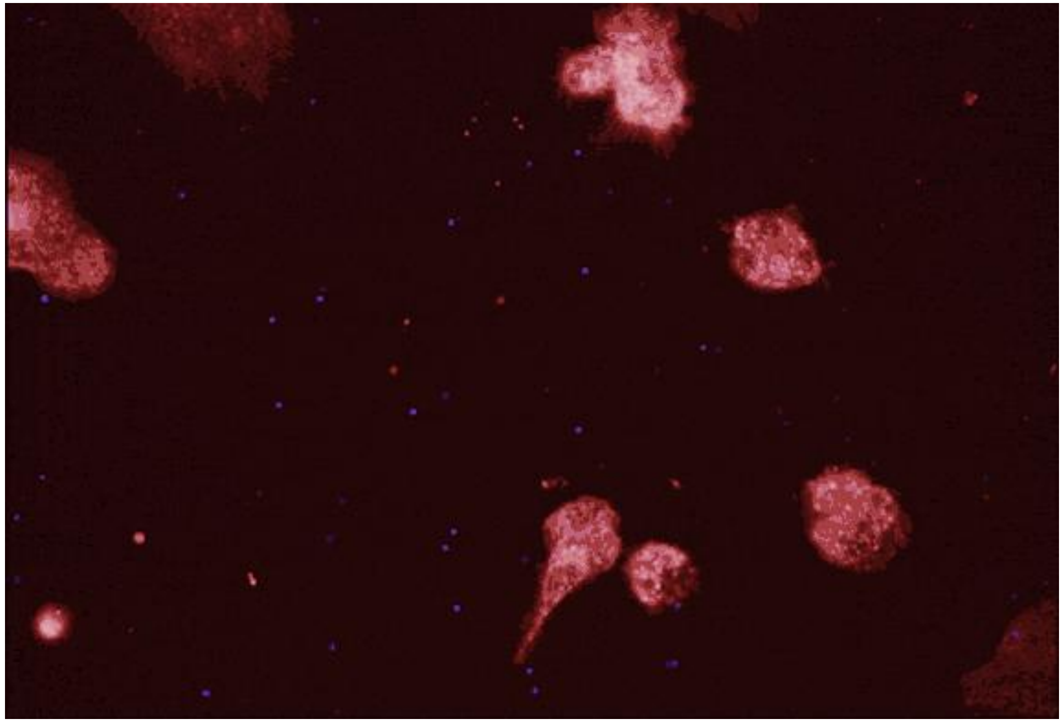
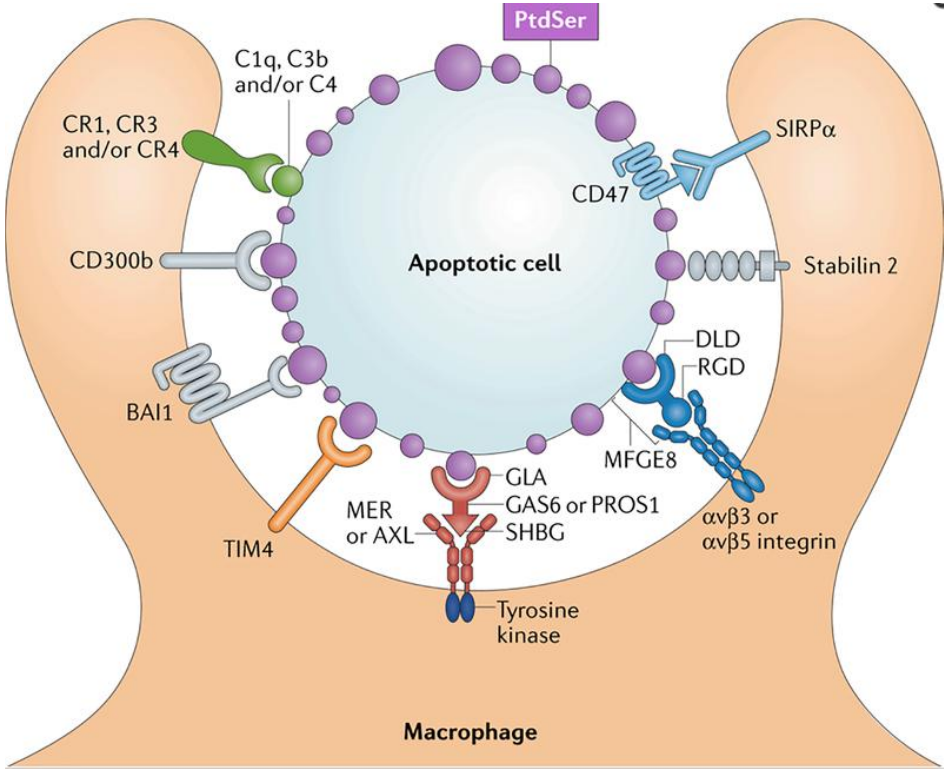
Praneeth R. Kuninty[1,7], Karin Binnemars-Postma[1,7], Ahmed Jarray[2,3], Kunal P. Pednekar[1], Marcel A. Heinrich[1], Helen J. Pijffers[1], Hetty ten Hoopen[1], Gert Storm[1,4,5], Peter van Hoogevest[6], Wouter K. den Otter[2] & Jai Prakash[1]

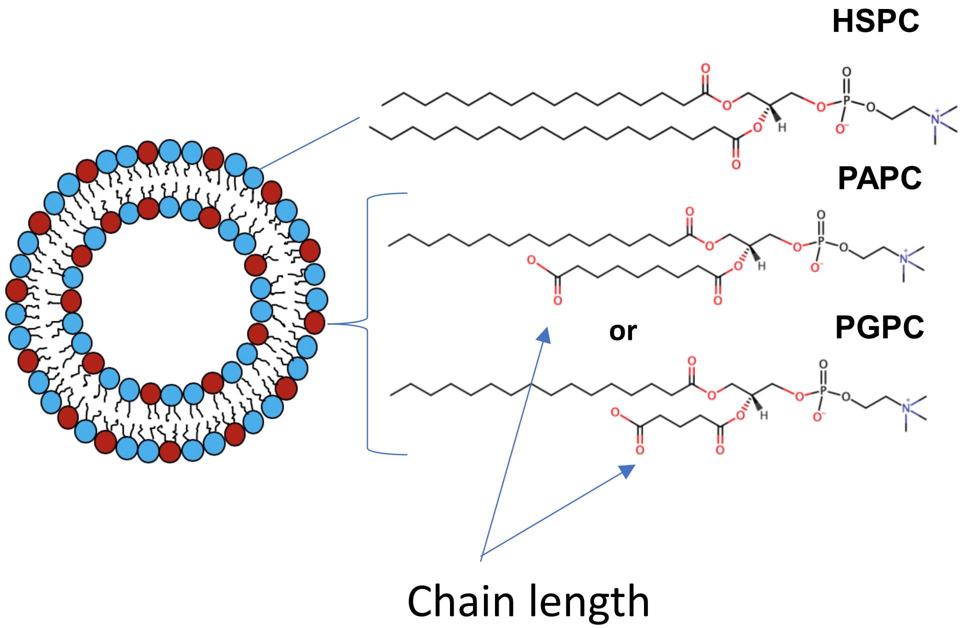
Natural habit: Macrophages love eating



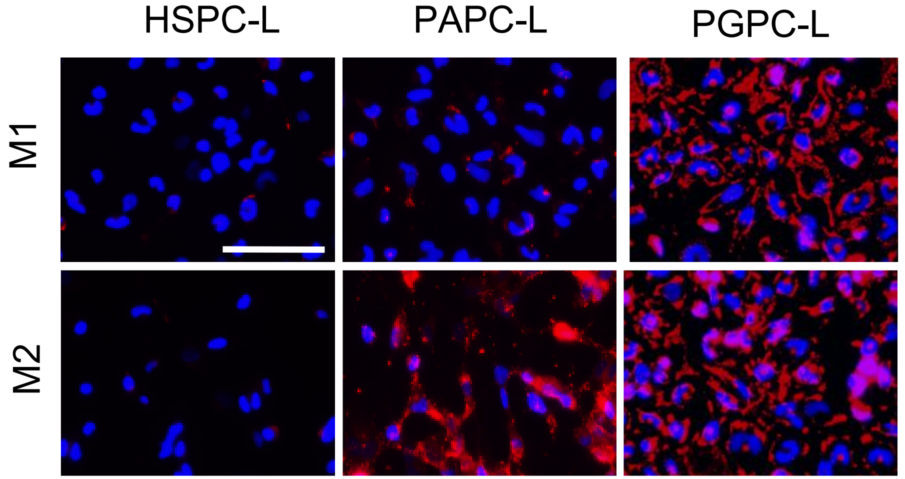


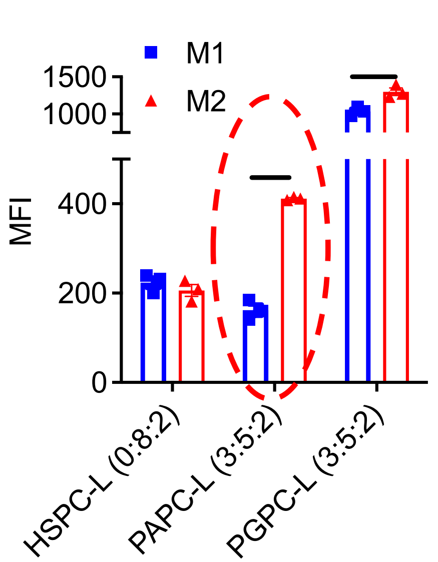
Lemke G. Nat Rev Immunol 2019

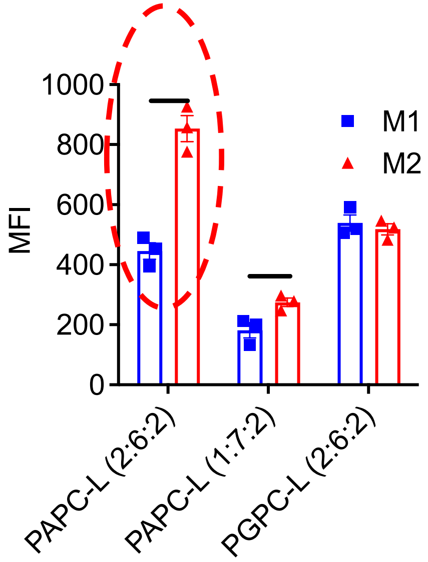
Nanoliposomes targeting M2-like macrophages



PAPC-containing liposomes: PAPC-L
PGPC-containing liposomes: PGPC-L







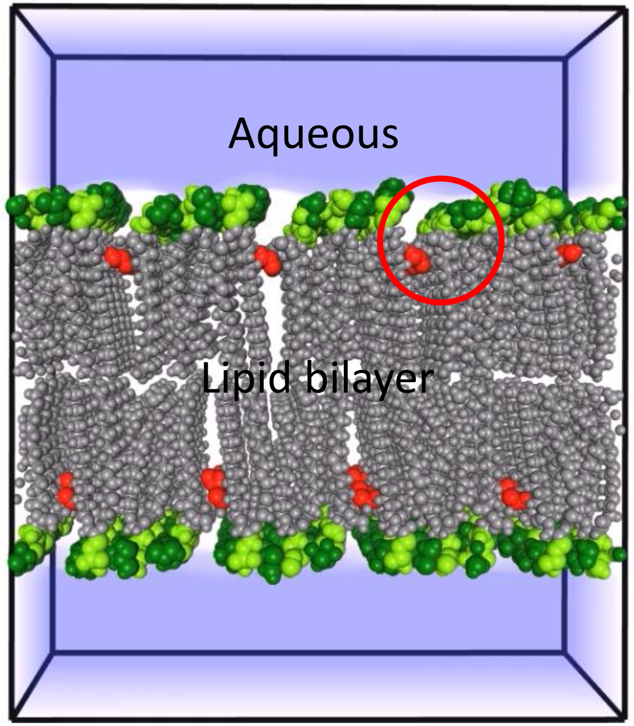
Patent granted: US12156938B2

Kuninty…Prakash. Nat. Commun. 2022

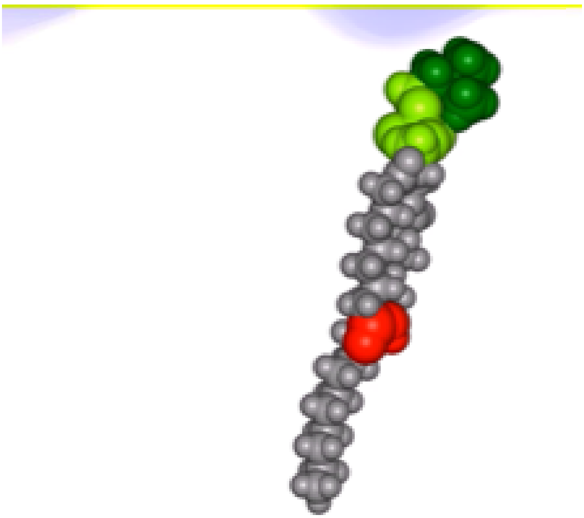
“Tail-flipping” mechanism of PAPC in lipid bilayer

Molecular dynamic simulation

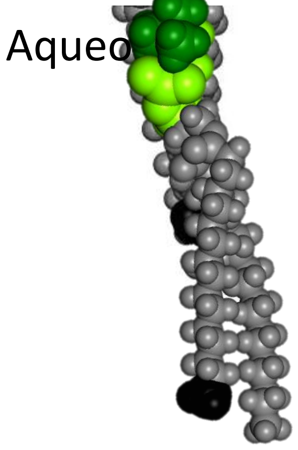
Bilayer of PAPC:HSPC



PAPC in lipid bilayer

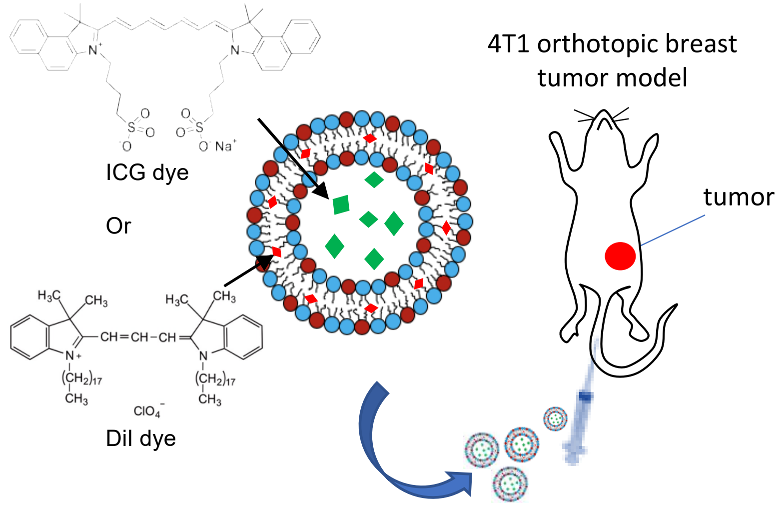


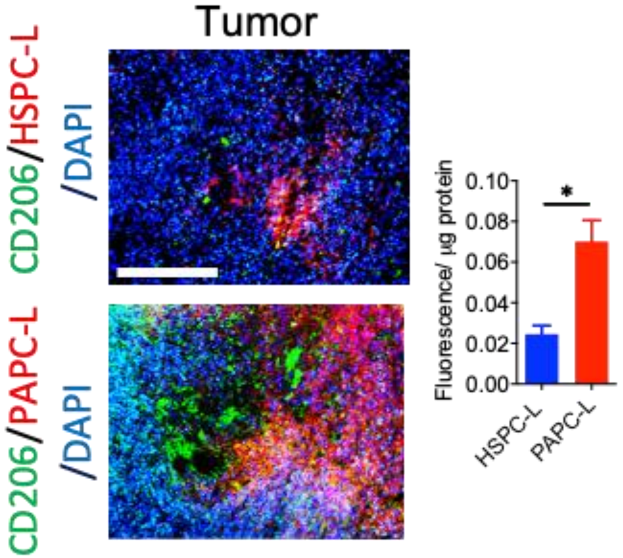
HSPC in lipid bilayer

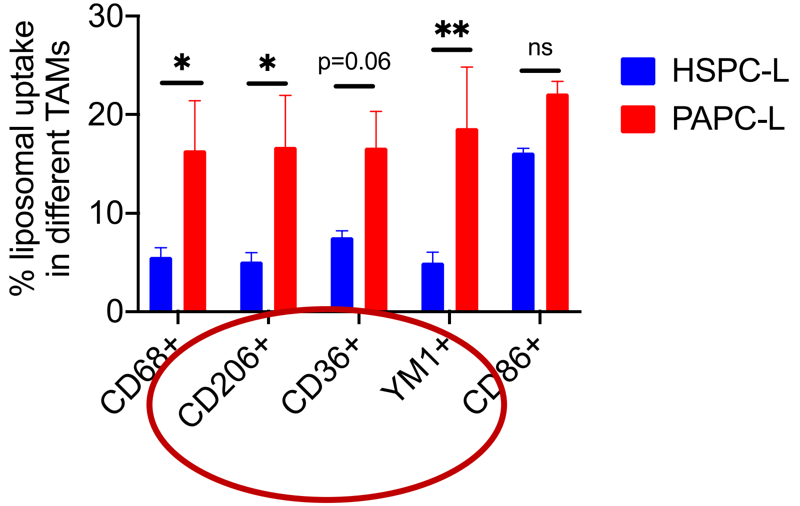


Collaboration: Dr. Otter & Dr. Jarray (UT)

Biodistribution of PAPC-L in breast tumor model







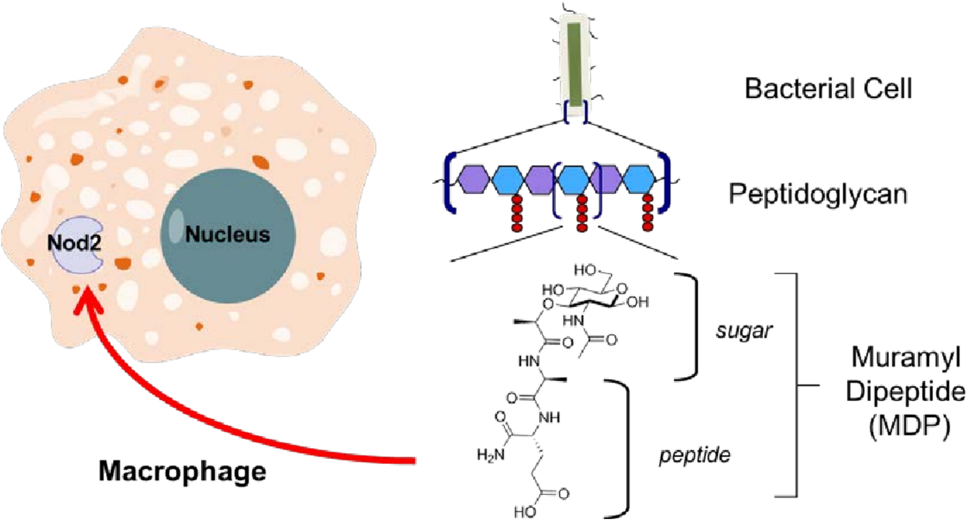
Kuninty…Prakash. Nat. Commun. 2022

“Learning from old”: Targeting microbiome

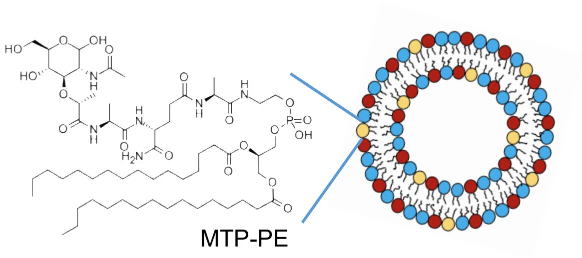
William Coley
(1862 – 1936)

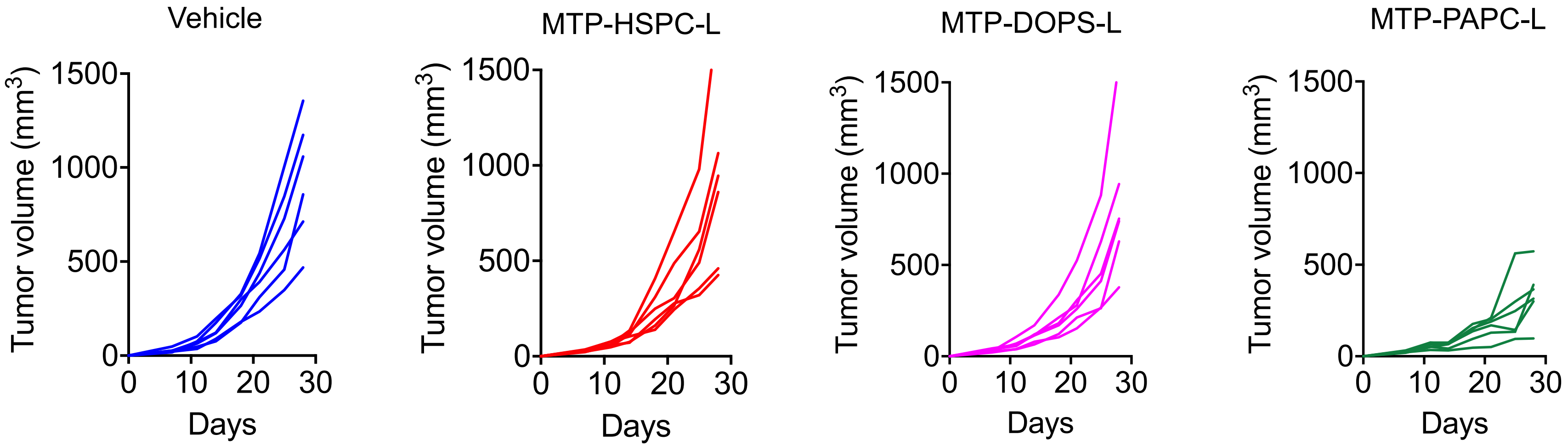
Infected his patients with
Streptococcus pyogenes

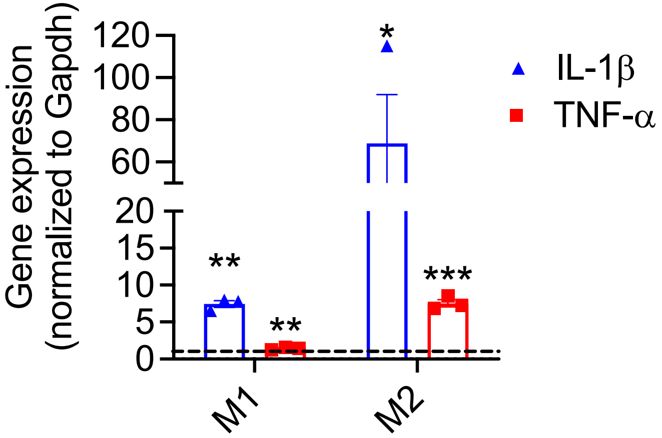
Peptidoglycan in bacterial cell walls is sensed by multiple pattern-recognition receptors

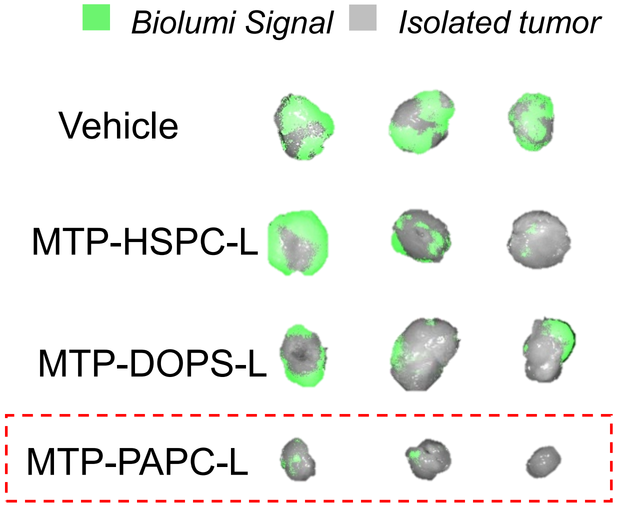


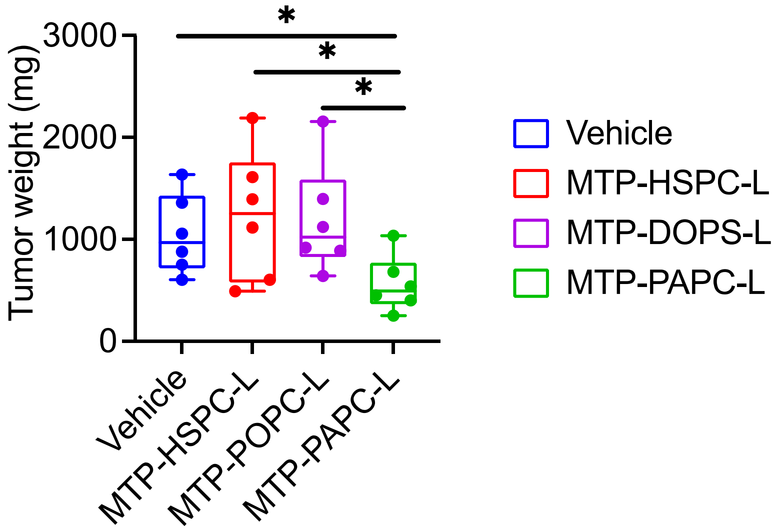
Delivery of muramyl tripeptide reduces the tumor growth







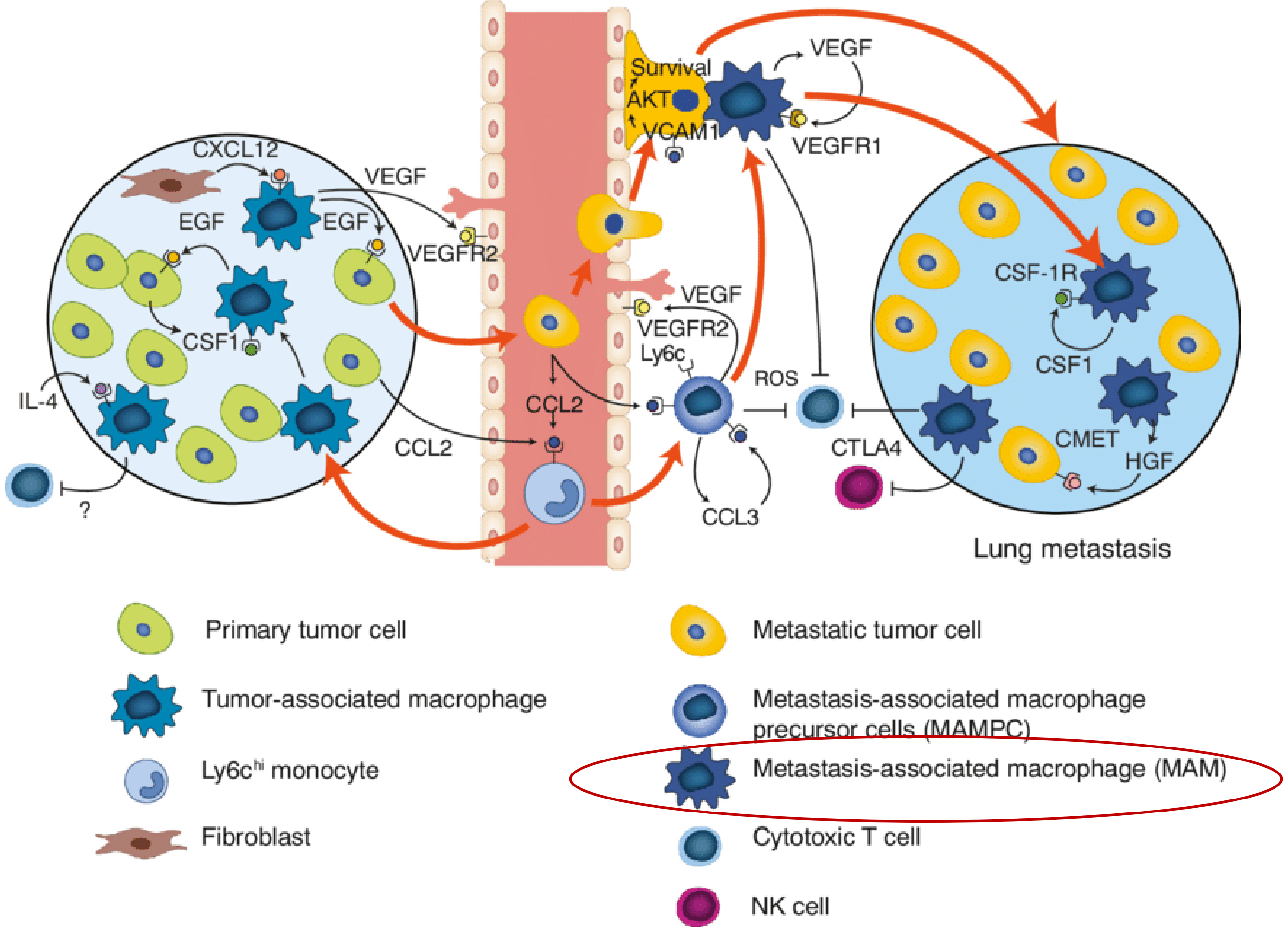




4T1 orthotopic TNBC tumor model, i.v. twice a week, 1 mg/kg

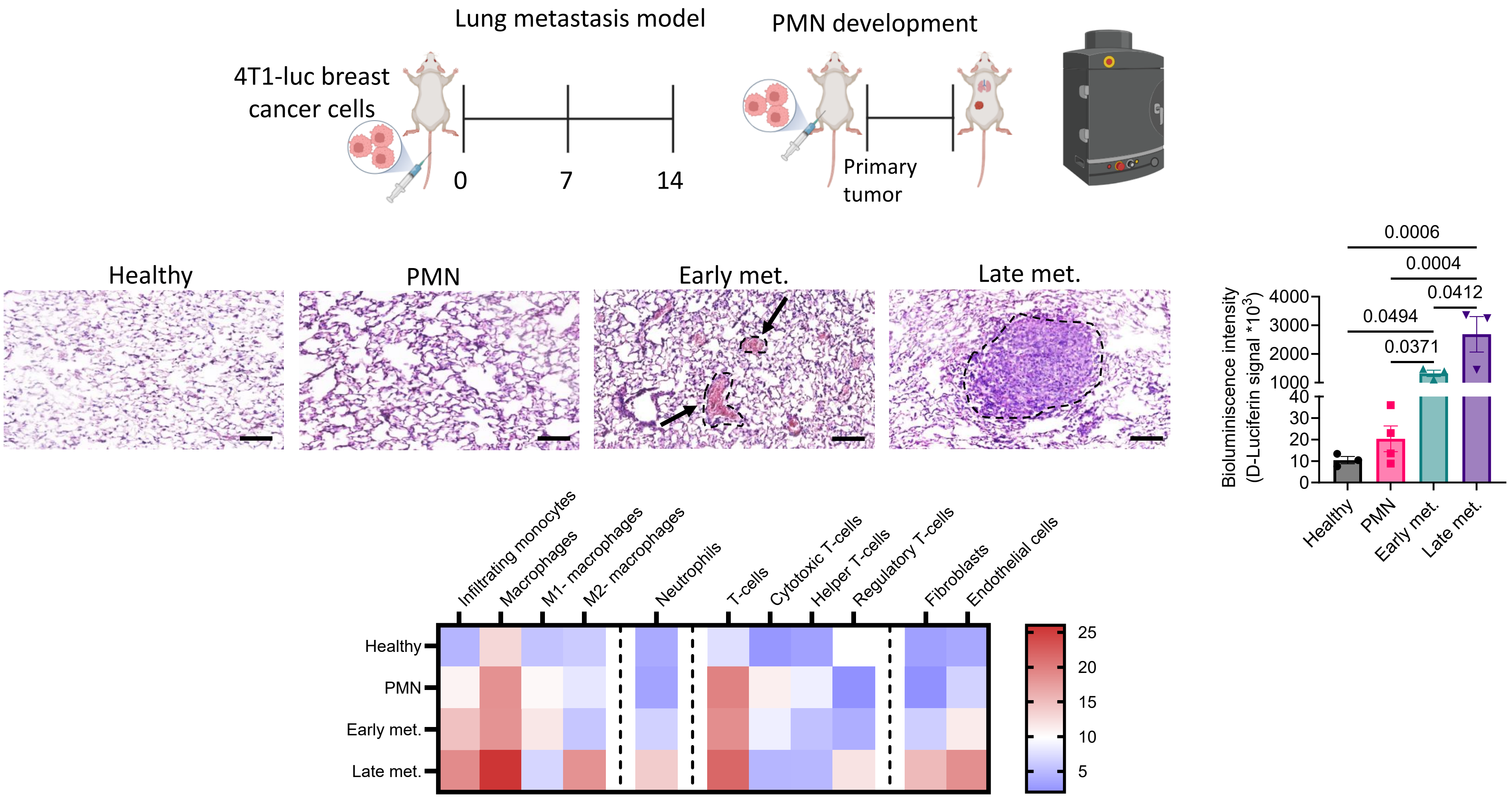
Kuninty….Prakash. Nat. Commun. 2022

Metastasis-associated Macrophages



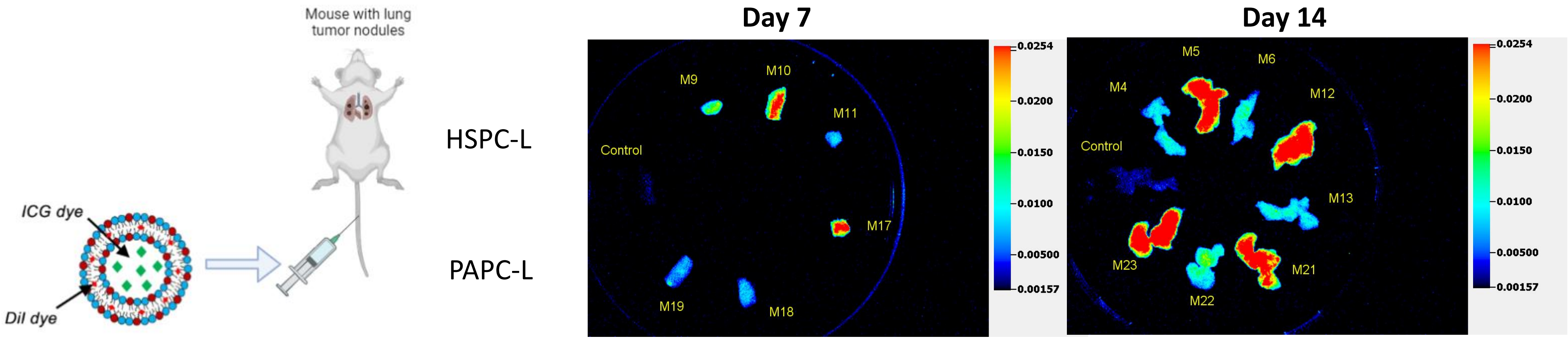
Robinson et al, Trends in Immunol 2021

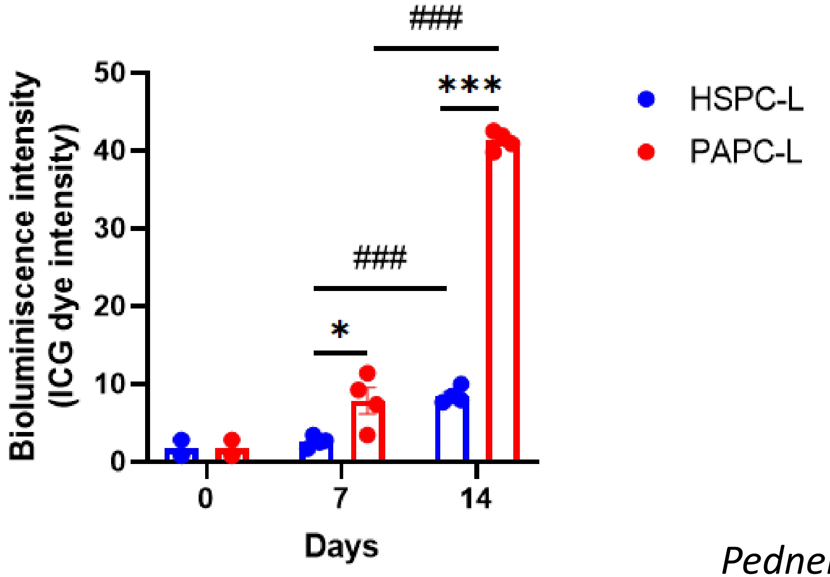
Lung metastasis model



Pednekar et al. unpublished - do not post

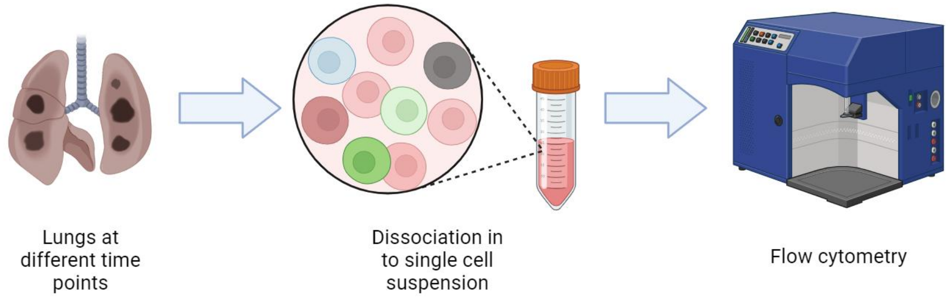
Targeted PAPC-L accumulate into metastatic lungs

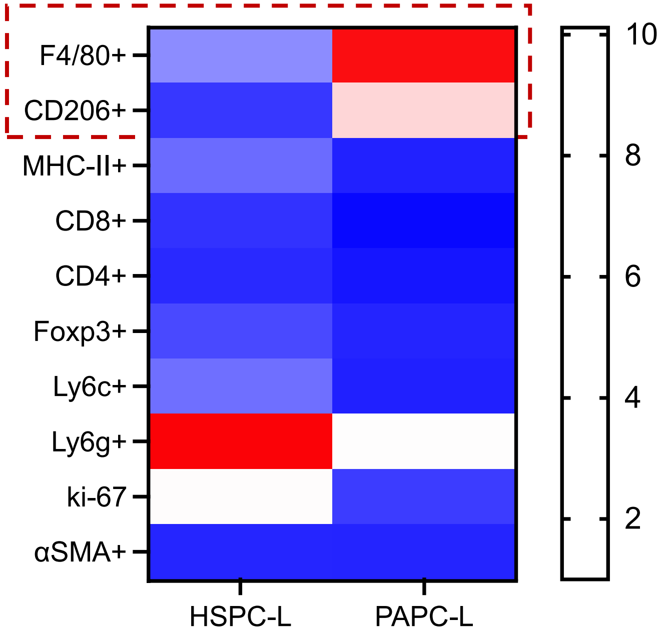


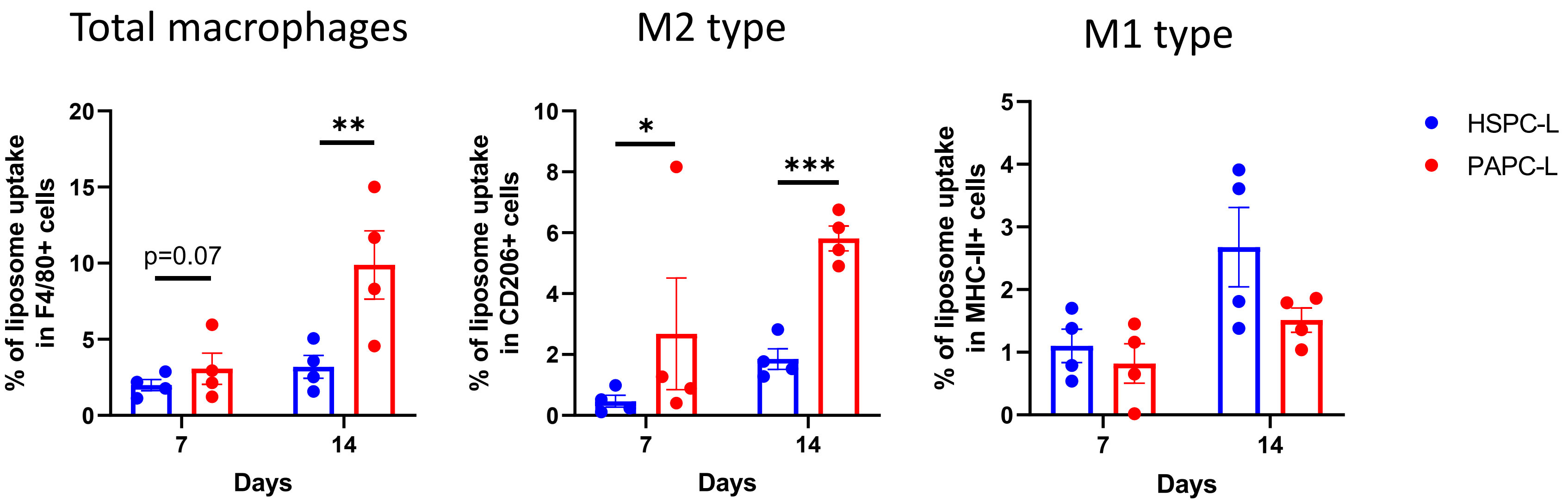


Pednekar et al. unpublished - do not post

PAPC-L are internalized by M2 macrophages in metastasis

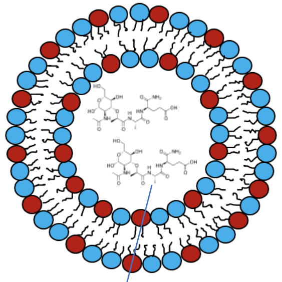




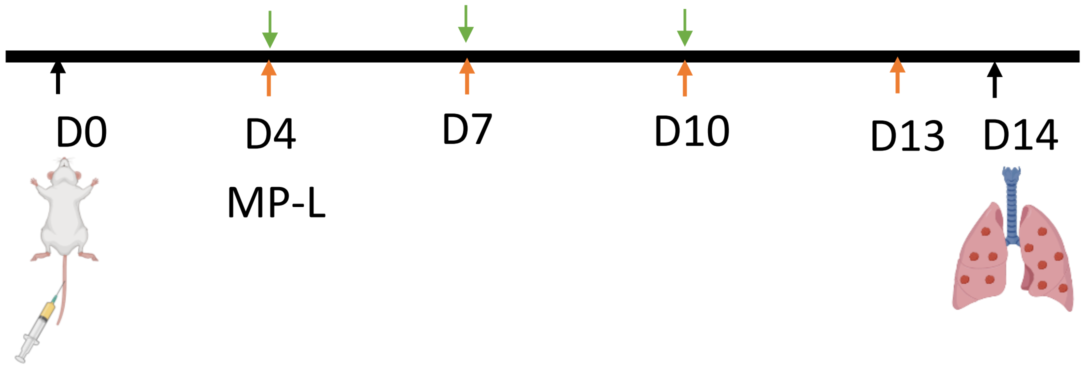


Pednekar et al. unpublished - do not post

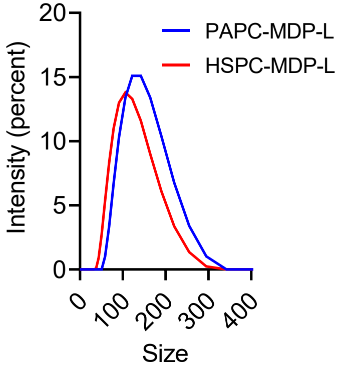
Targeting MDP to lung metastasis using PAPC-L



Muramyl dipeptide (MDP)



4T1 cell injection
(n = 6-8 mice/gp)

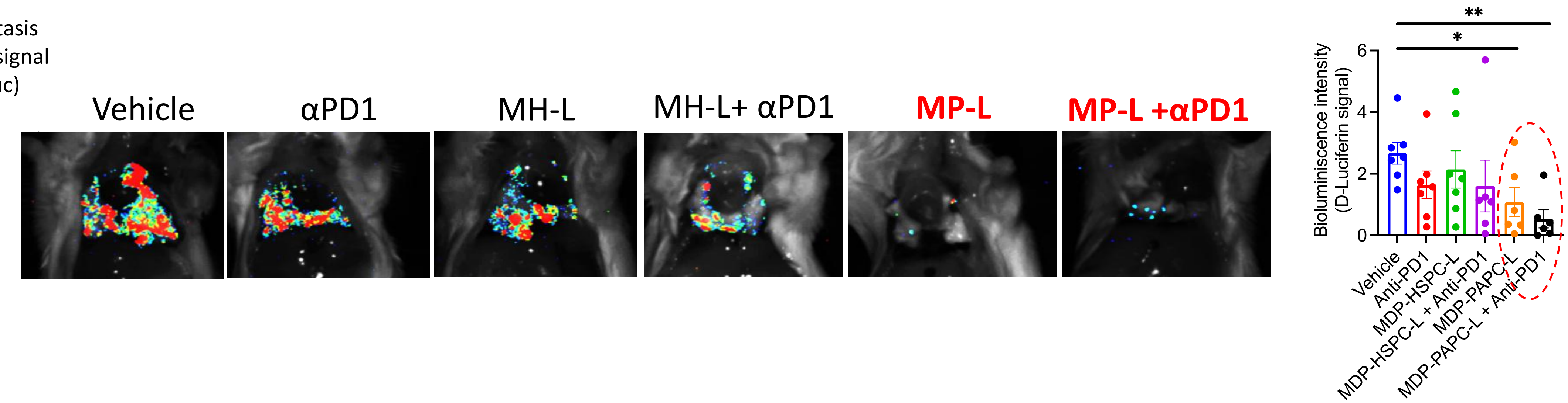


Liposomes	Size	%EE
MDP-HSPC-L	105 nm	41%
MDP-PAPC-L	122 nm	39%

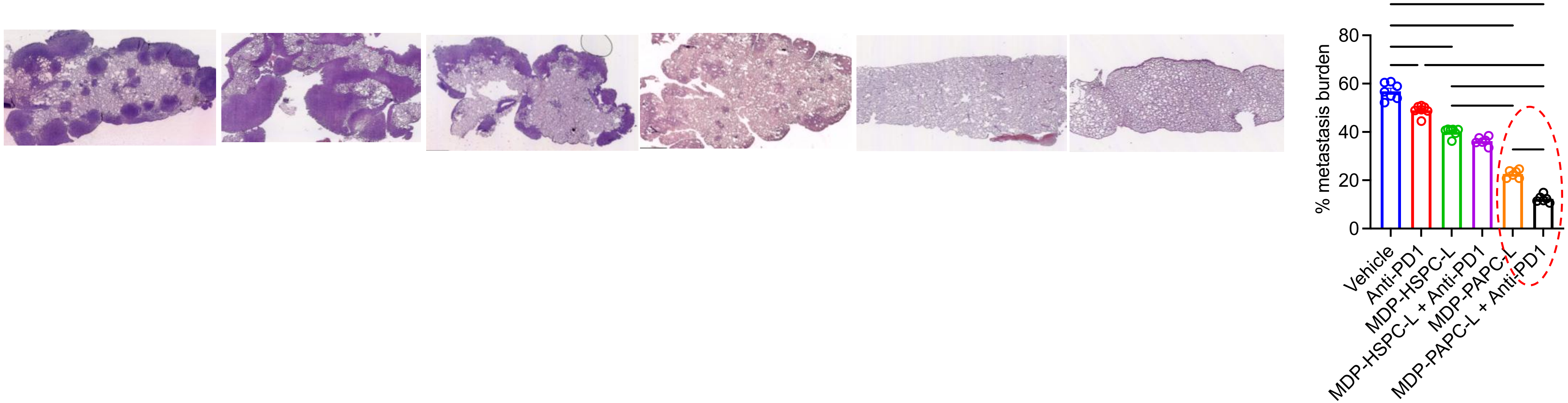
Pednekar et al. unpublished - do not post

MP-L reduces metastasis in combination with immune checkpoint inhibitor

Lung metastasis
(Luciferase signal
from 4T1-Luc)

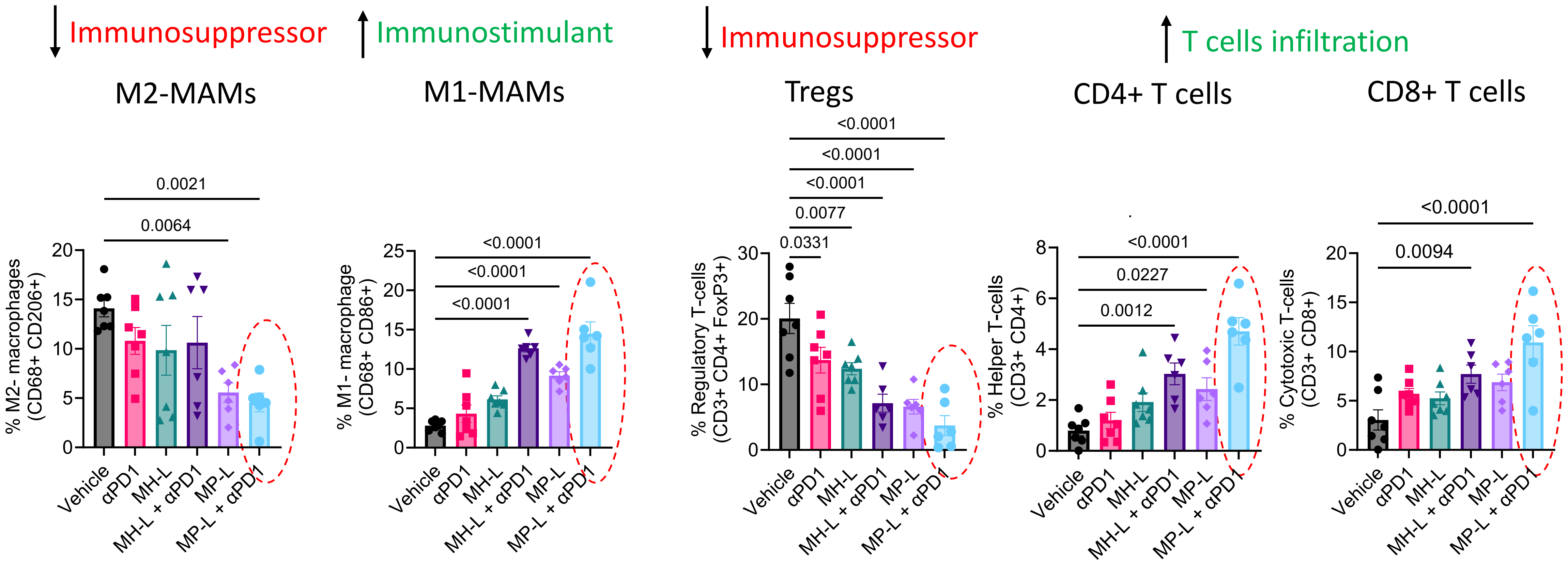


H&E



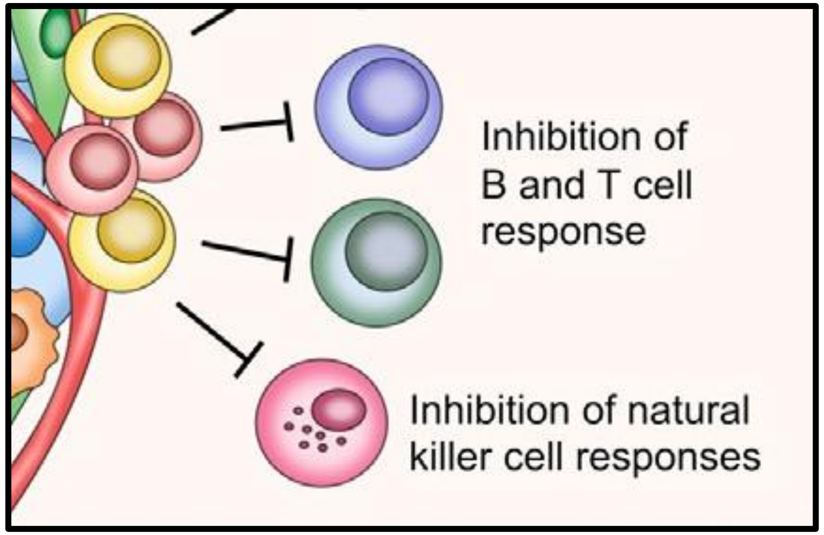
Pednekar et al. unpublished - do not post

MP-L reprograms the immuno-microenvironment

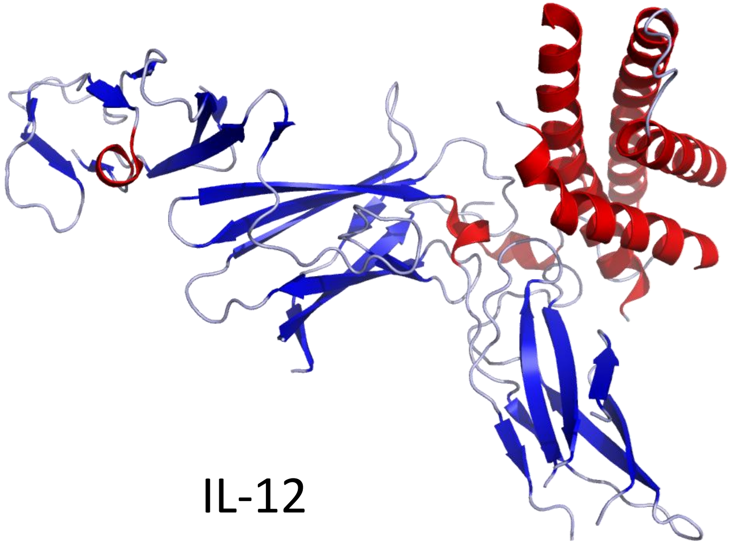


Pednekar et al. unpublished - do not post

Deliver cytokines to activate cytotoxic immune cells



Interleukin-12



IL-12

- Molecular weight is 70kDa
- Active heterodimer consist of IL-12A(p35) and IL-12B(p40)

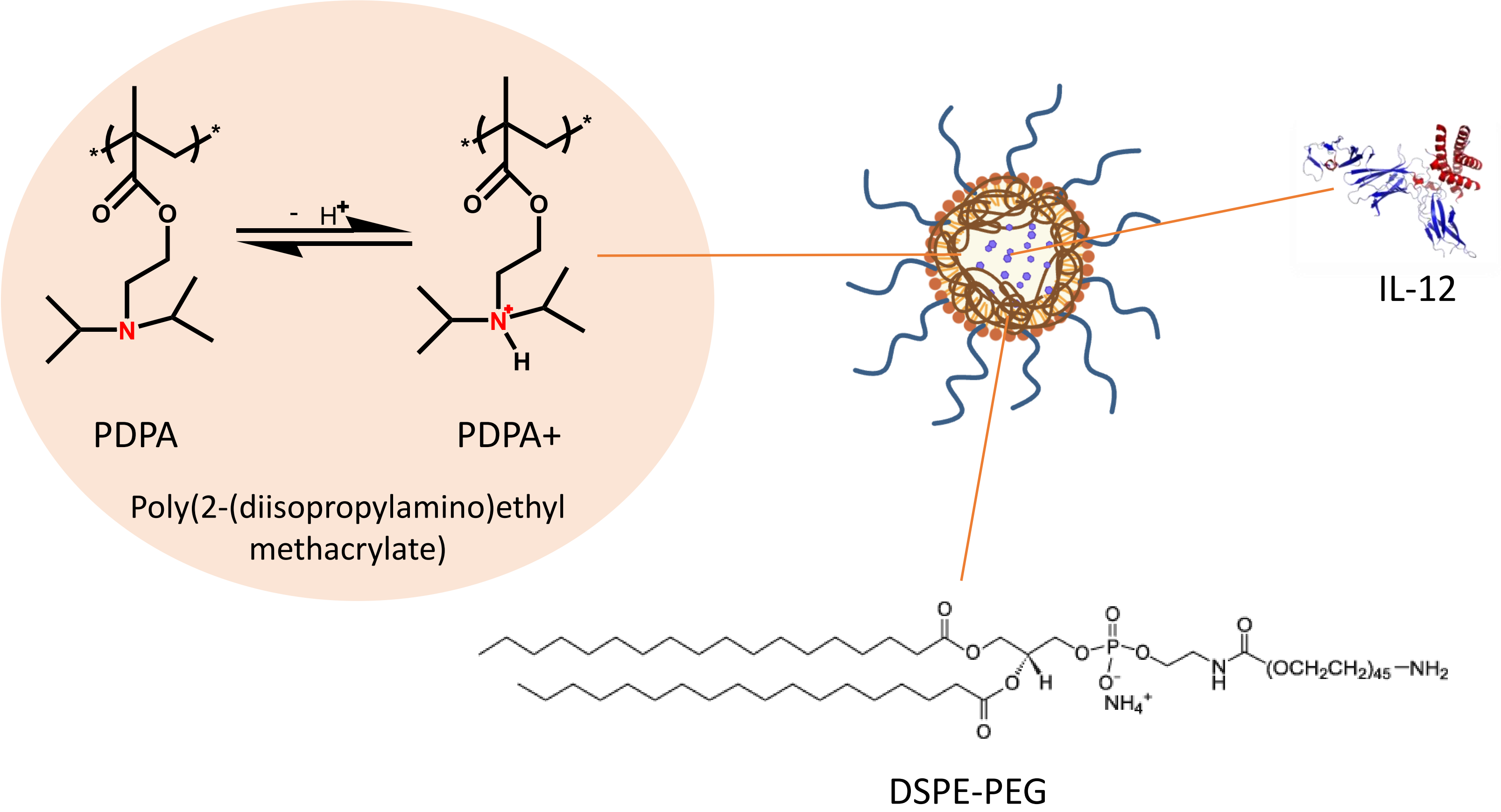
Functions:

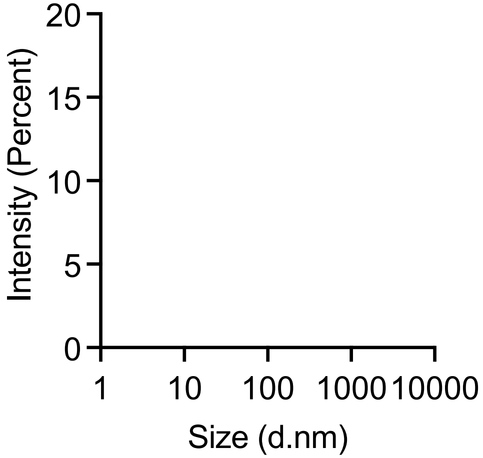
- Polarize T cells into Th1 cells
- Activate NK cells and T cells
- Anti-angiogenic activity

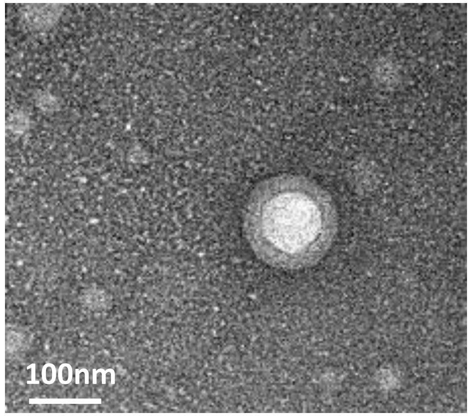
Limitations:

- Short half-life
- Systemic Side effects

pH-responsive lipid-polymer hybrid nanoparticles

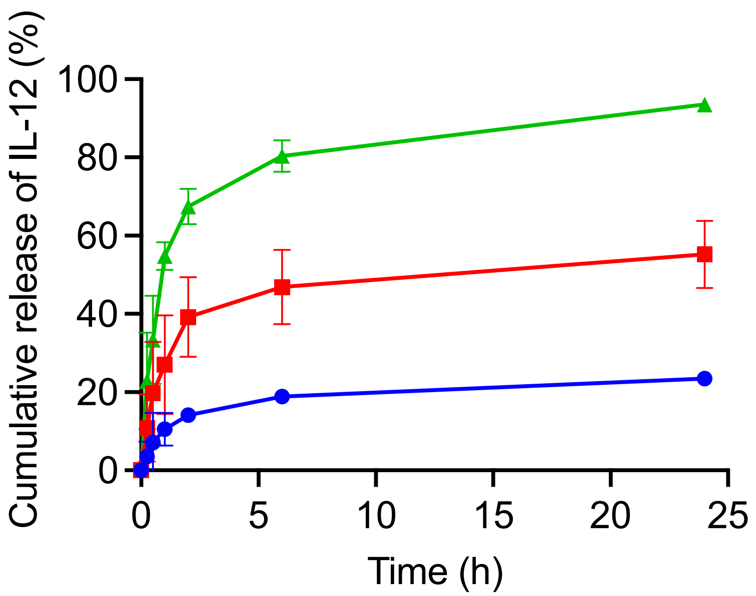


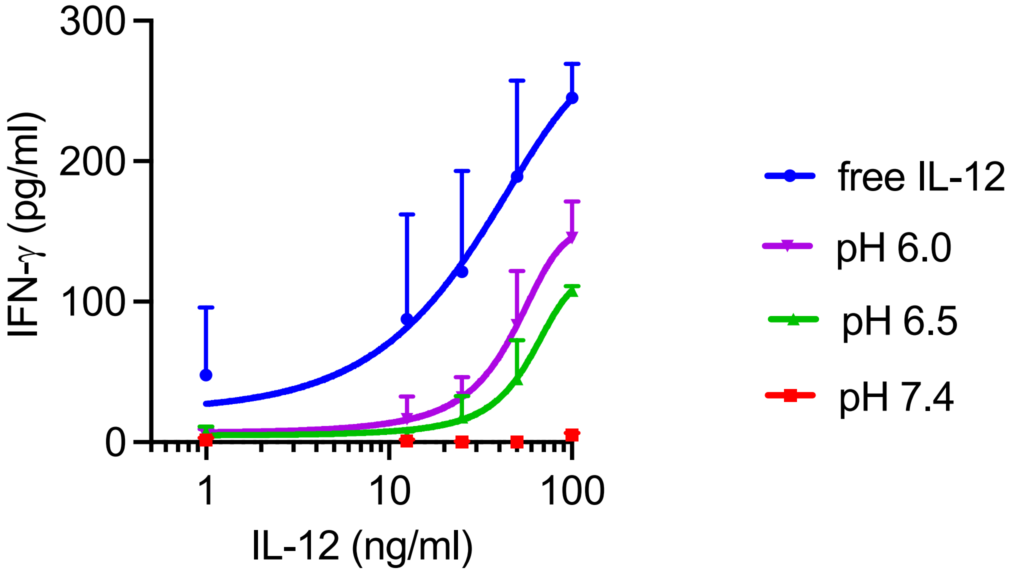




Chen et al. unpublished - do not post

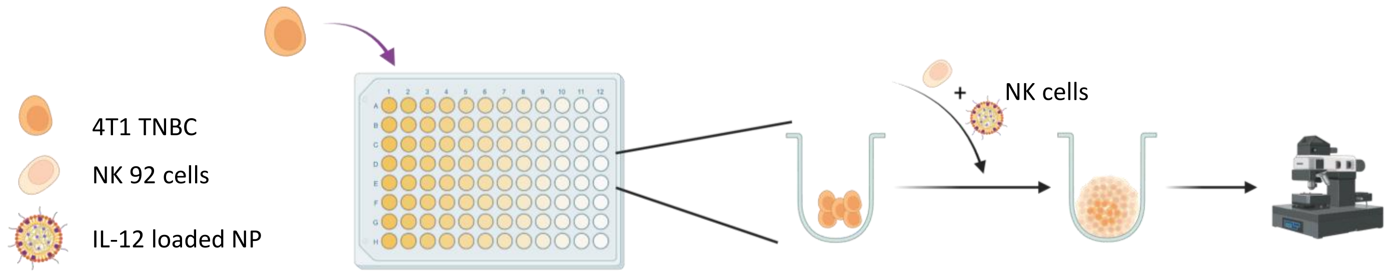
pH-dependent release of IL-12 and bioactivity

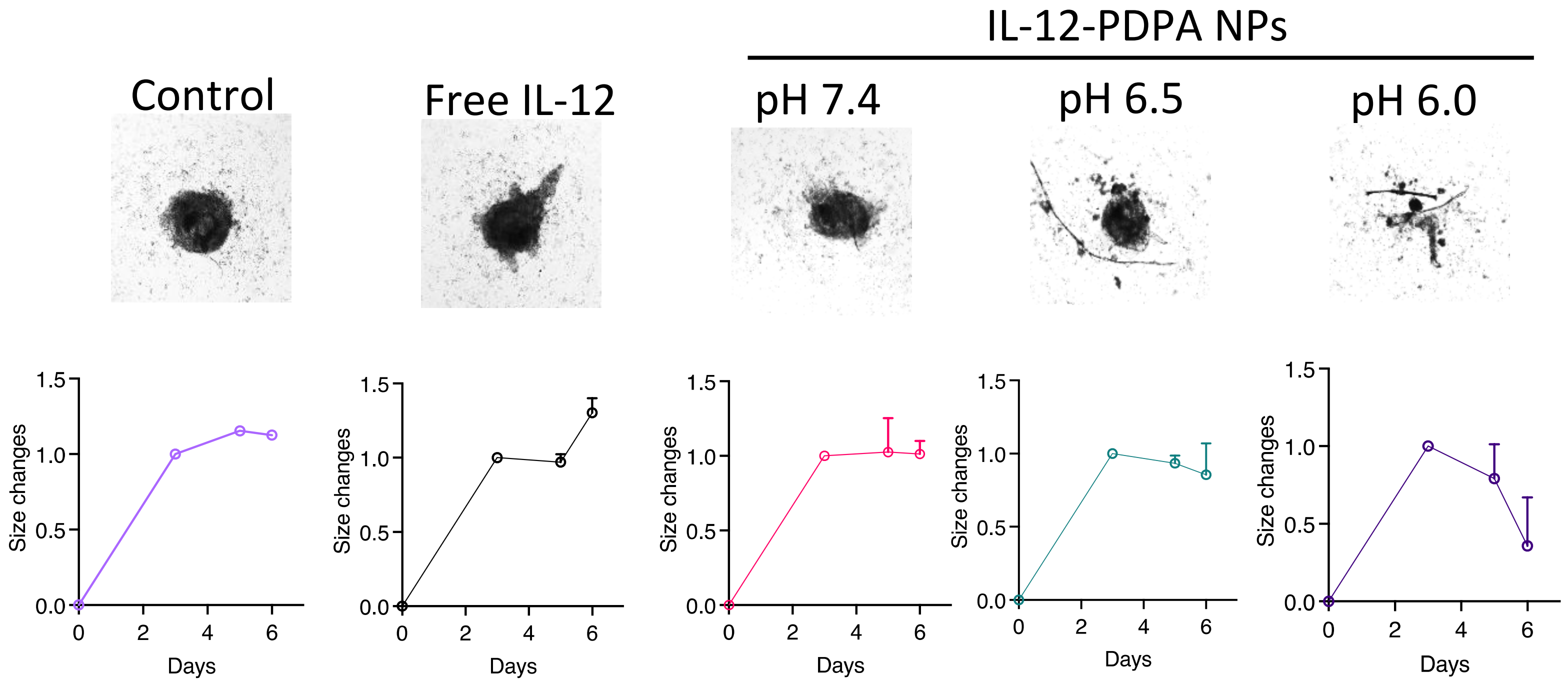




Chen et al. unpublished - do not post

IL-12-PDPA NP kill 3D tumor spheroids via NK cells





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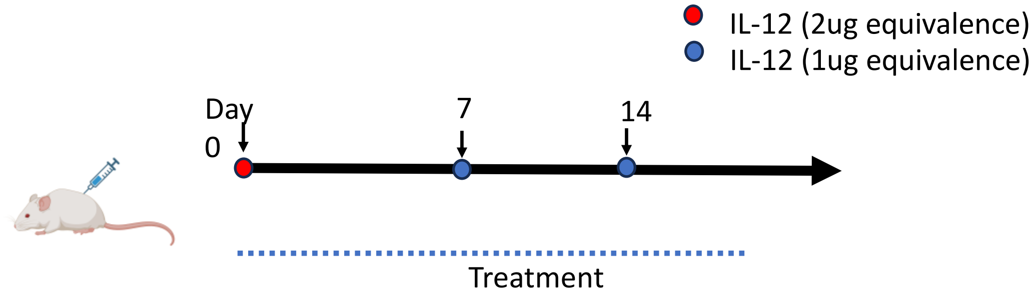
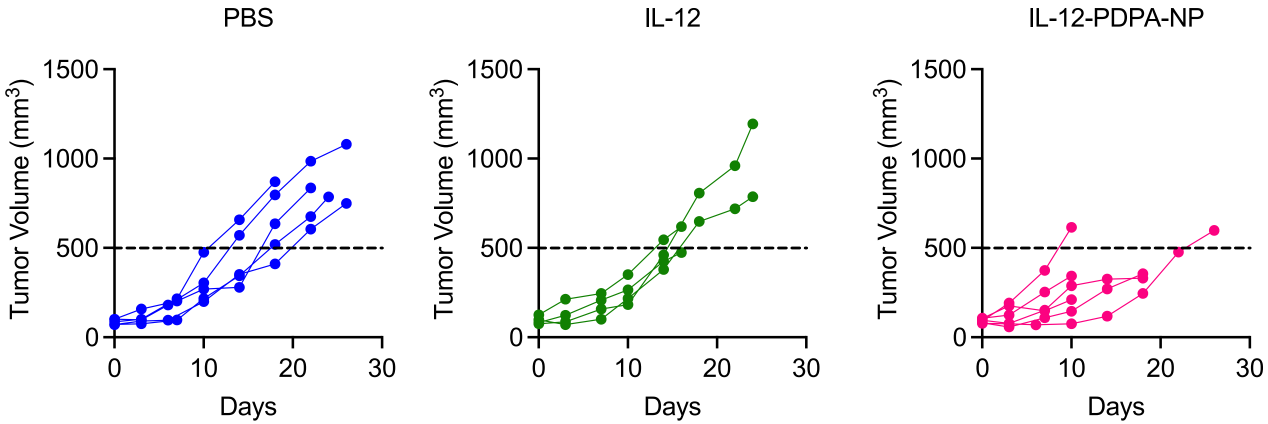
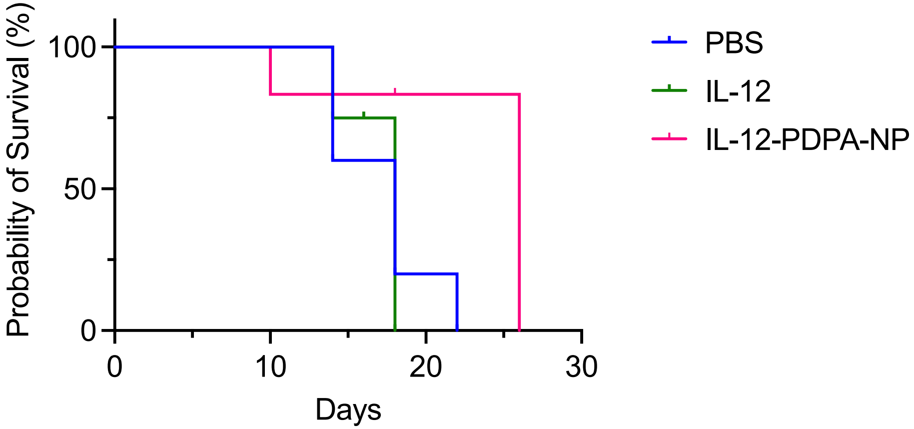
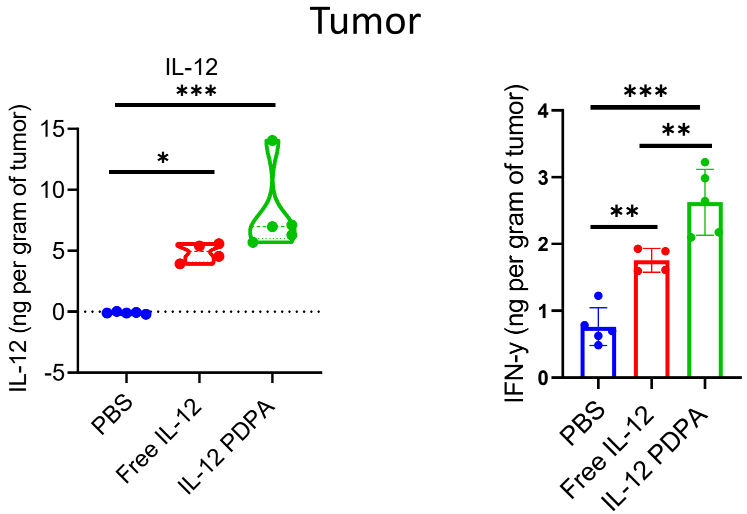
IL-12 PDPA NP reduces the tumor growth









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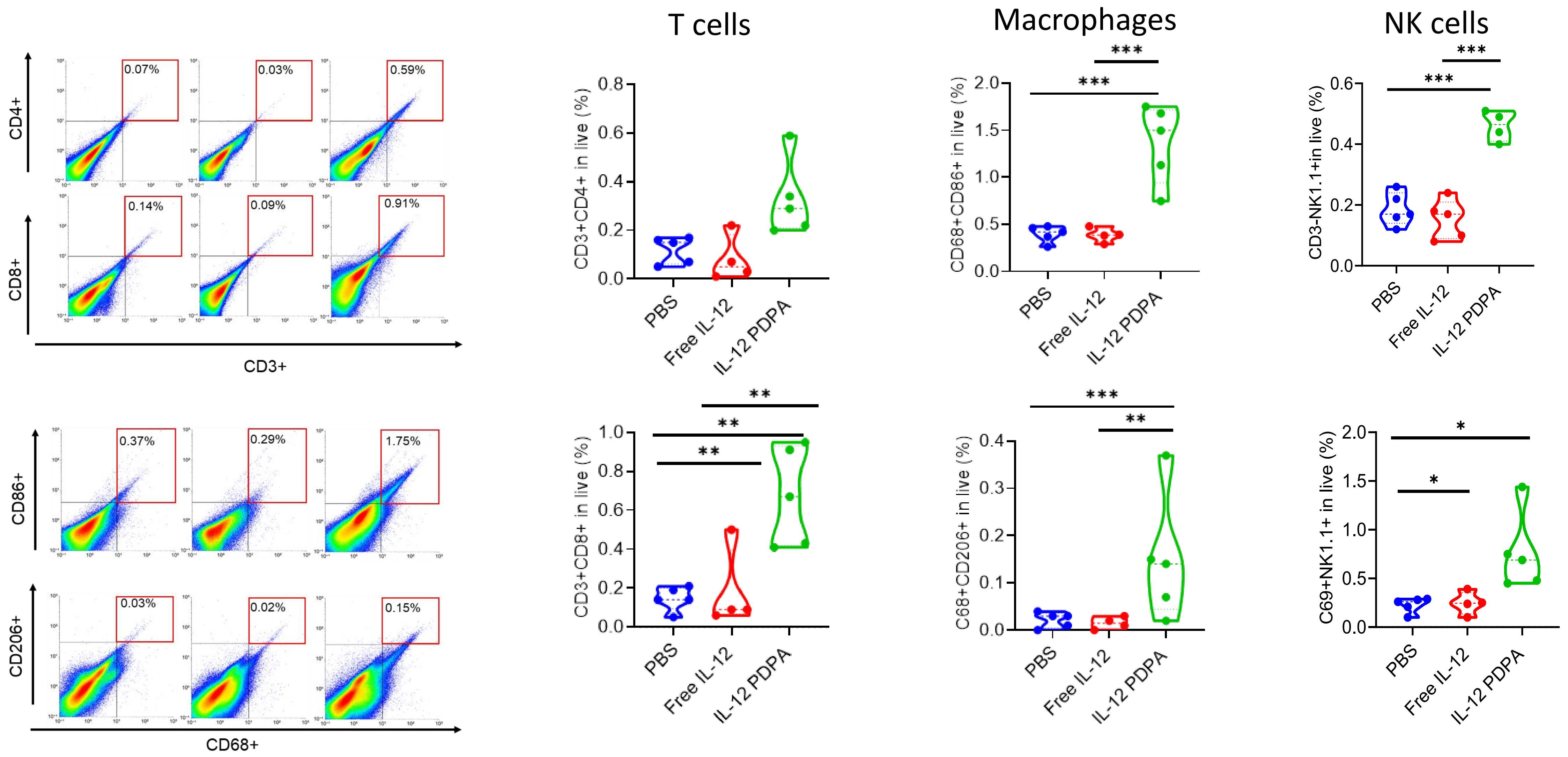
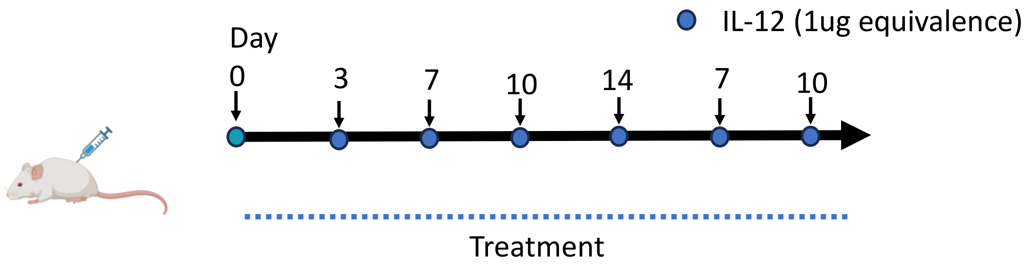
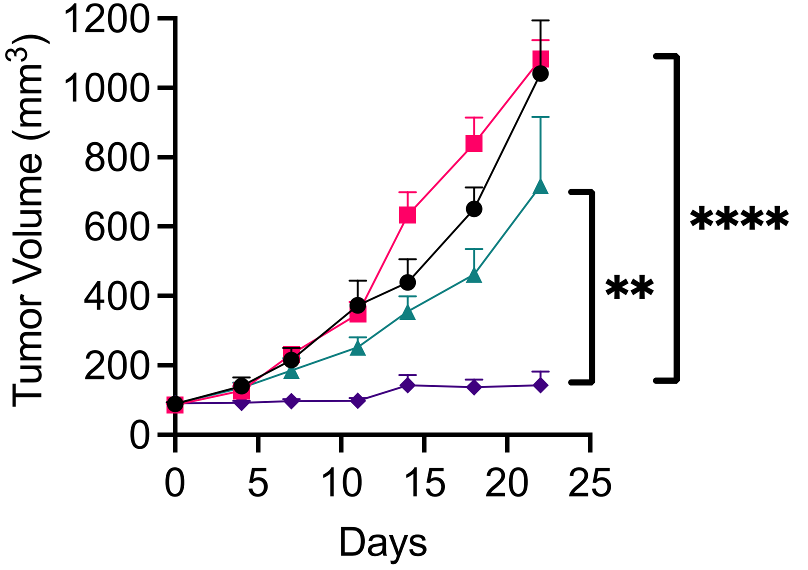
IL-12-PDPA NP reverses the tumor immunosuppression

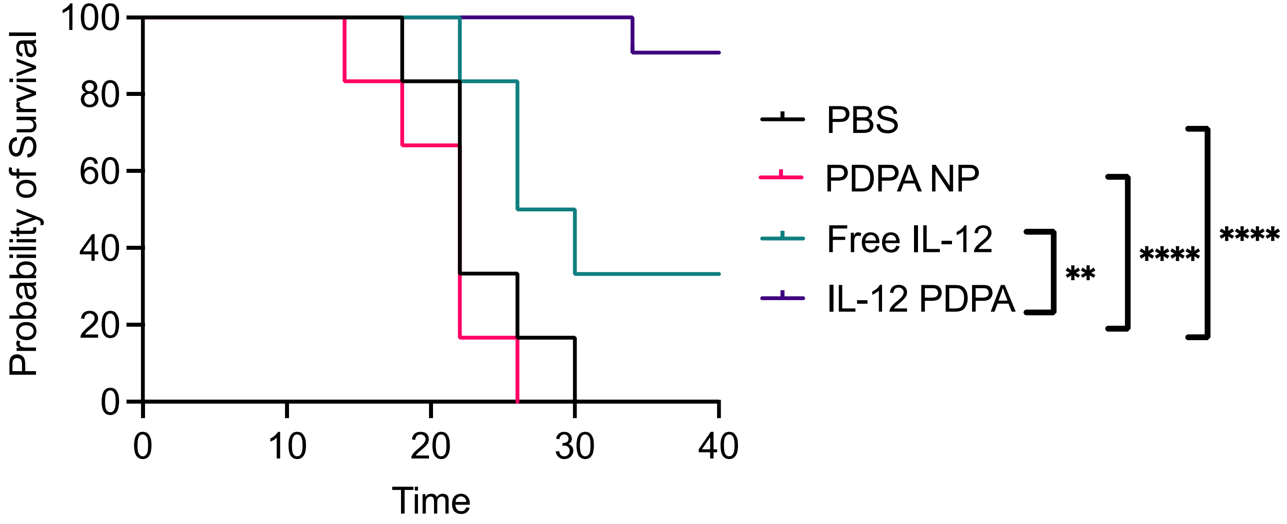


Chen et al. unpublished - do not post

IL-12-PDPA NP reduces the tumor growth and enhances the survival







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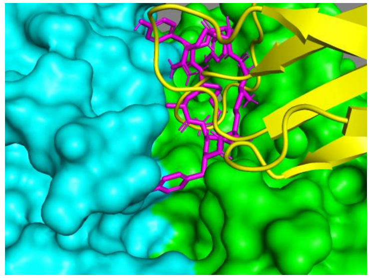
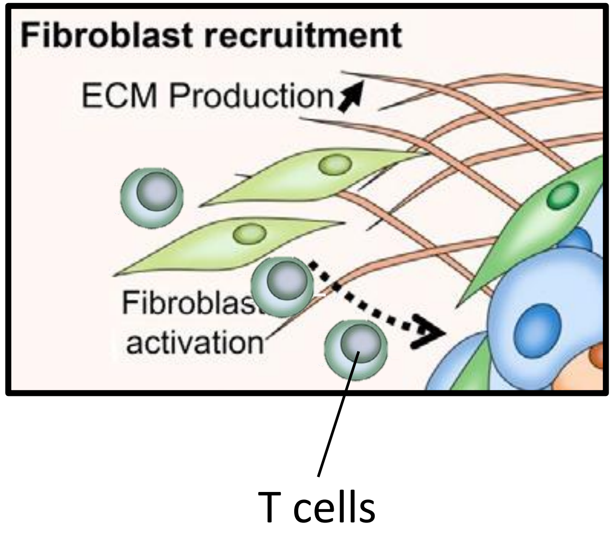
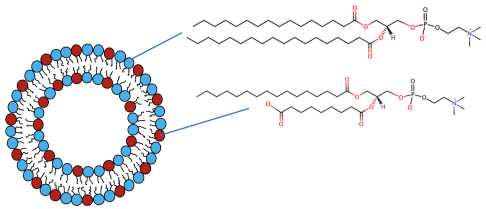
Summary & Conclusions

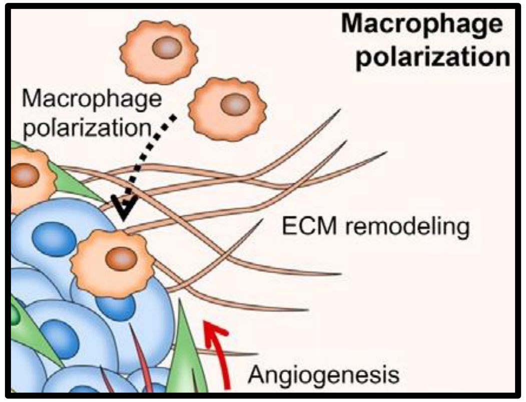


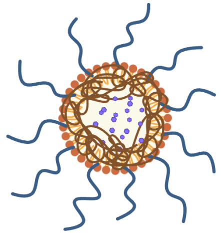
Peptide to modulate the fibrotic microenvironment



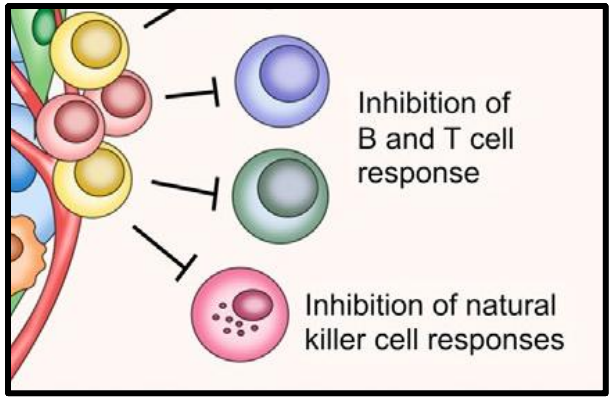


Tail-flipping nanoliposomes to repolarize macrophages





Hybrid nanosystems to deliver Il-12 to activate immune cells



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