Engineered Therapeutics to Reprogram the Tumor Microenvironment

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President, BeNeLux & France CRS Local Chapter

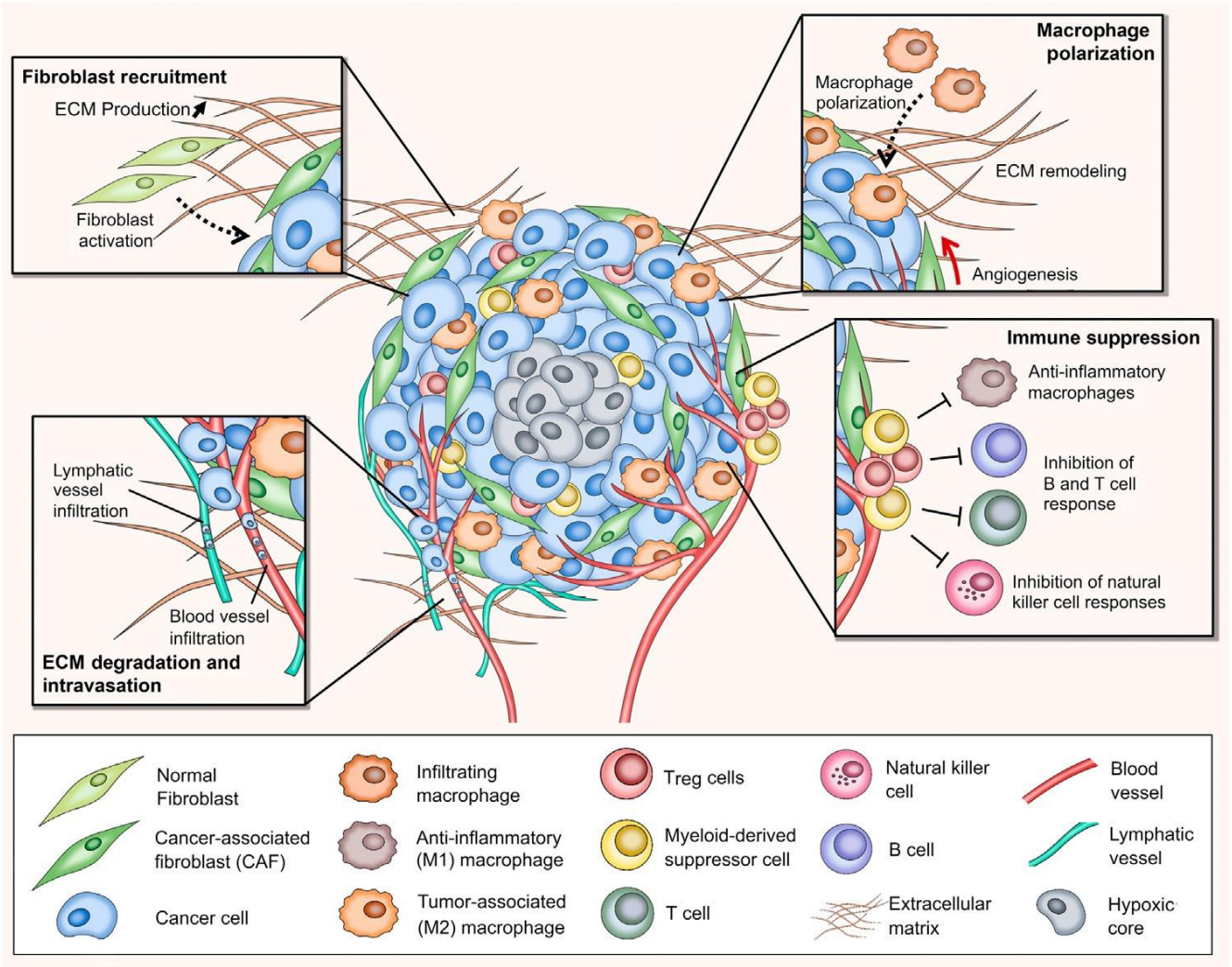
CRS 2022 Annual Meeting & Expo

July 11 – 15, 2022 | Montreal Congress Center, Montreal Canada

Advanced Delivery Science

The Tumor Microenvironment (TME)

Tumor fibrotic microenvironment



Tumor immune microenvironment

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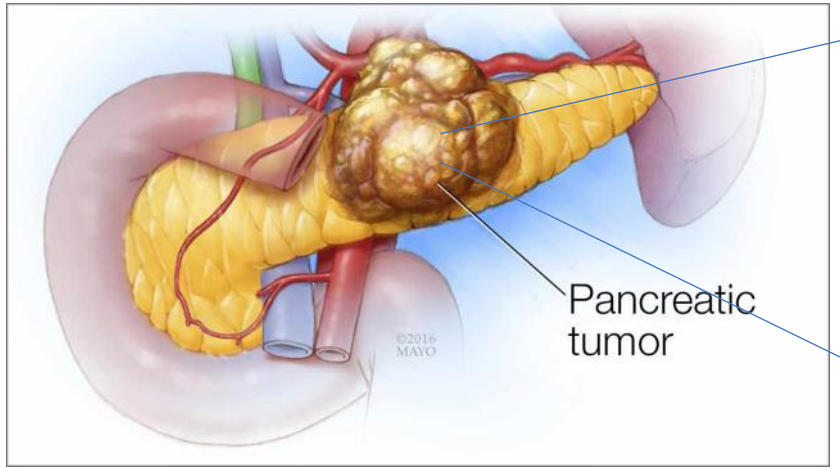
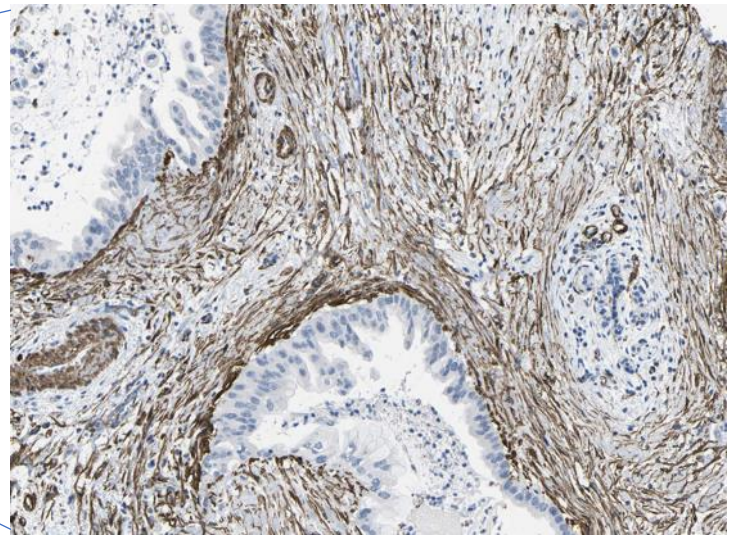
Rodrigues, Heinrich…. Prakash, Trends in Cancer, 2021

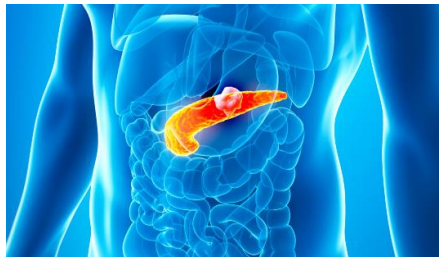
Pancreatic cancer

- Pancreatic ductal adenocarcinoma (PDAC) is the deadliest cancer type with the 5 year survival rate of <8%
- There is hardly any improvement in the patient outcome in the last 30 years
- PDAC consist of abundant tumor stroma (80-90%)

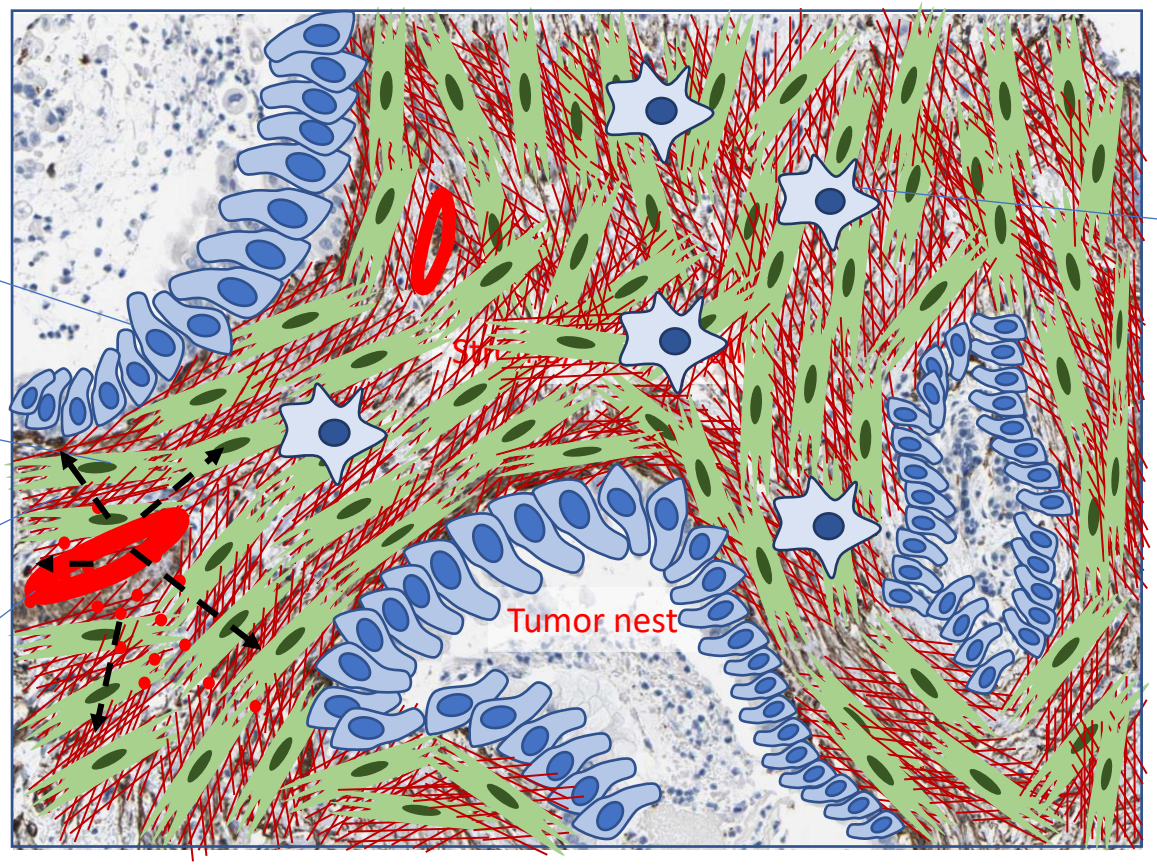




Pancreatic tumor stroma



Human pancreatic tumor

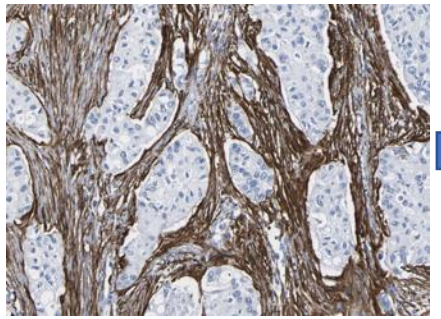


(up to 90% stroma)

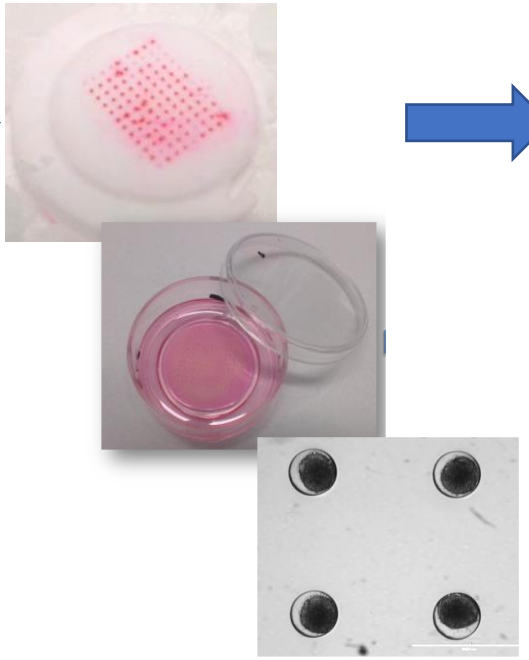
Prakash J. Book: Tumor Stroma: Biology and Therapeutics, 2022

Stroma as a physical barrier for nanoparticle penetration

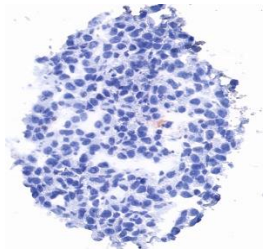
Human patient



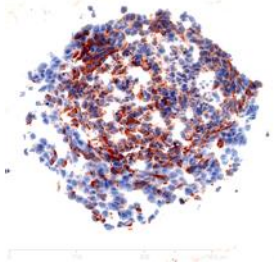
3D spheroids



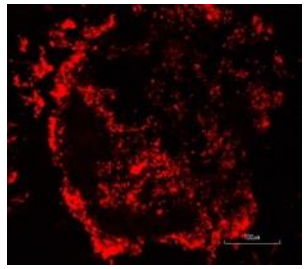
Homospheroid

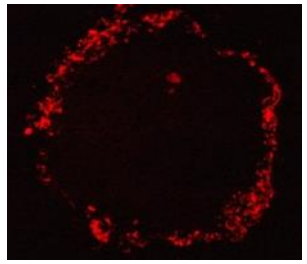


Heterospheroid



Nanoparticle penetration





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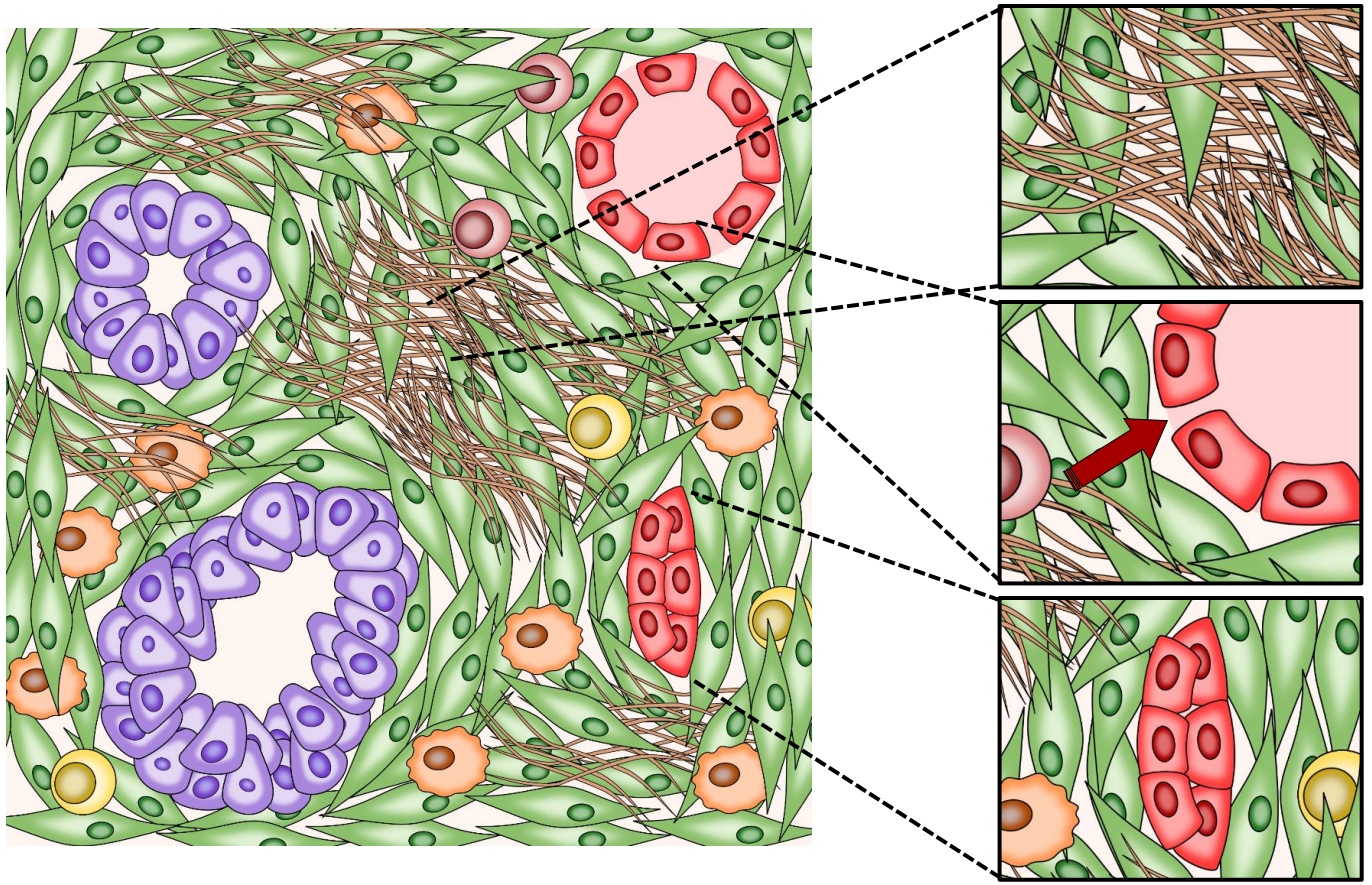
Priwitaningrum…. Prakash. J Cont Release 2016

Stroma in PDAC reduces drug perfusion and delivery



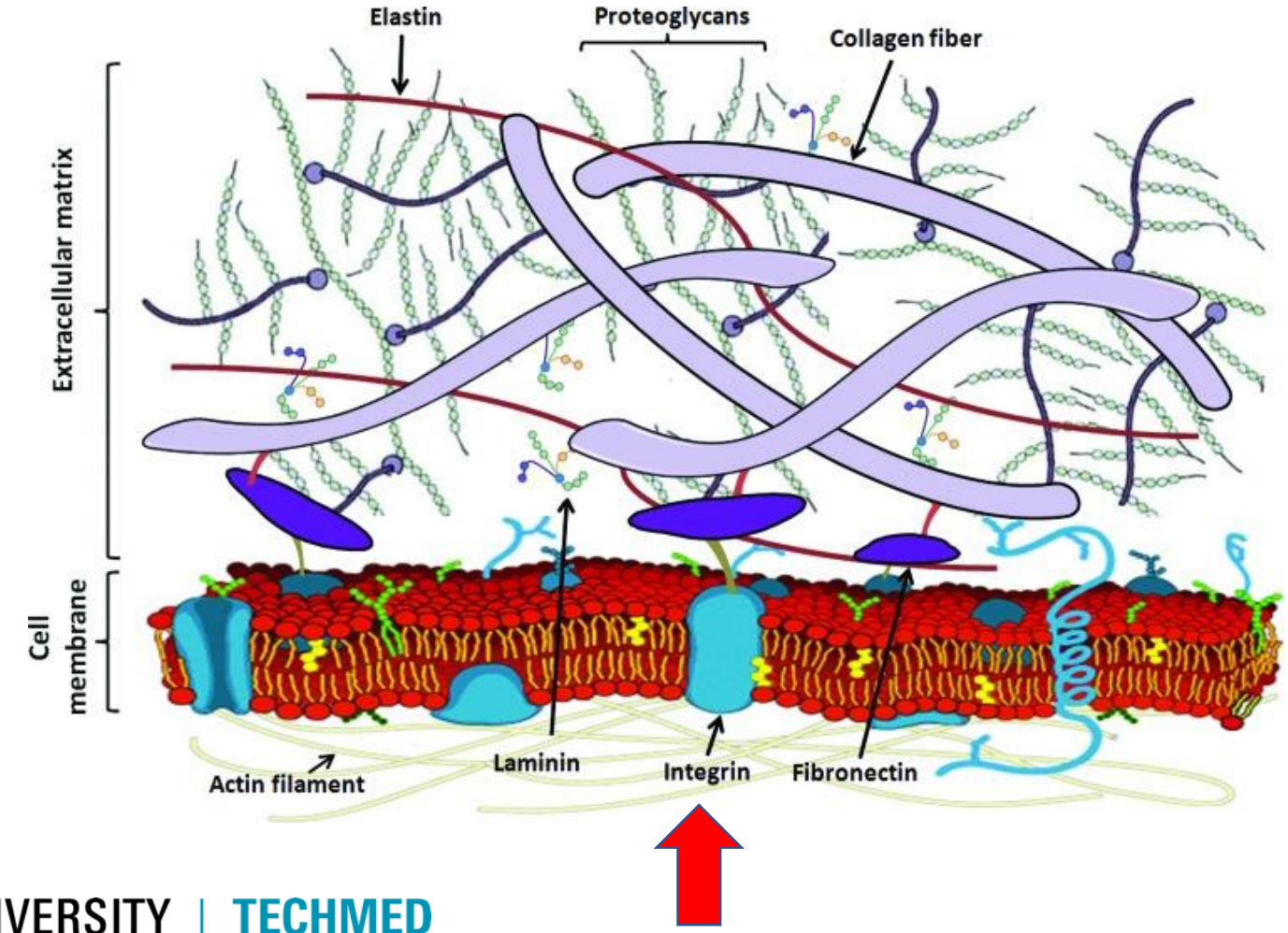
High desmoplasia

High interstitial pressure

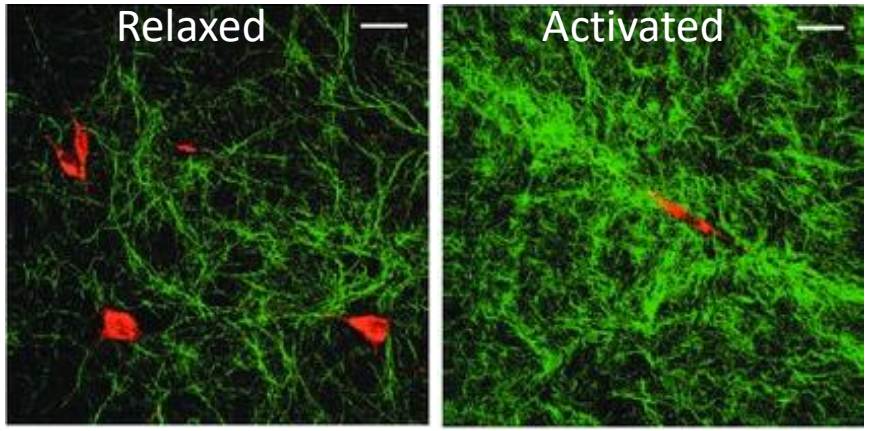
Blood vessel collapse

Heinrich….Prakash., Adv. Drug Deliv. Rev. 2021

Fibroblast-ECM interaction within tumor stroma



Matrix/ fibroblast



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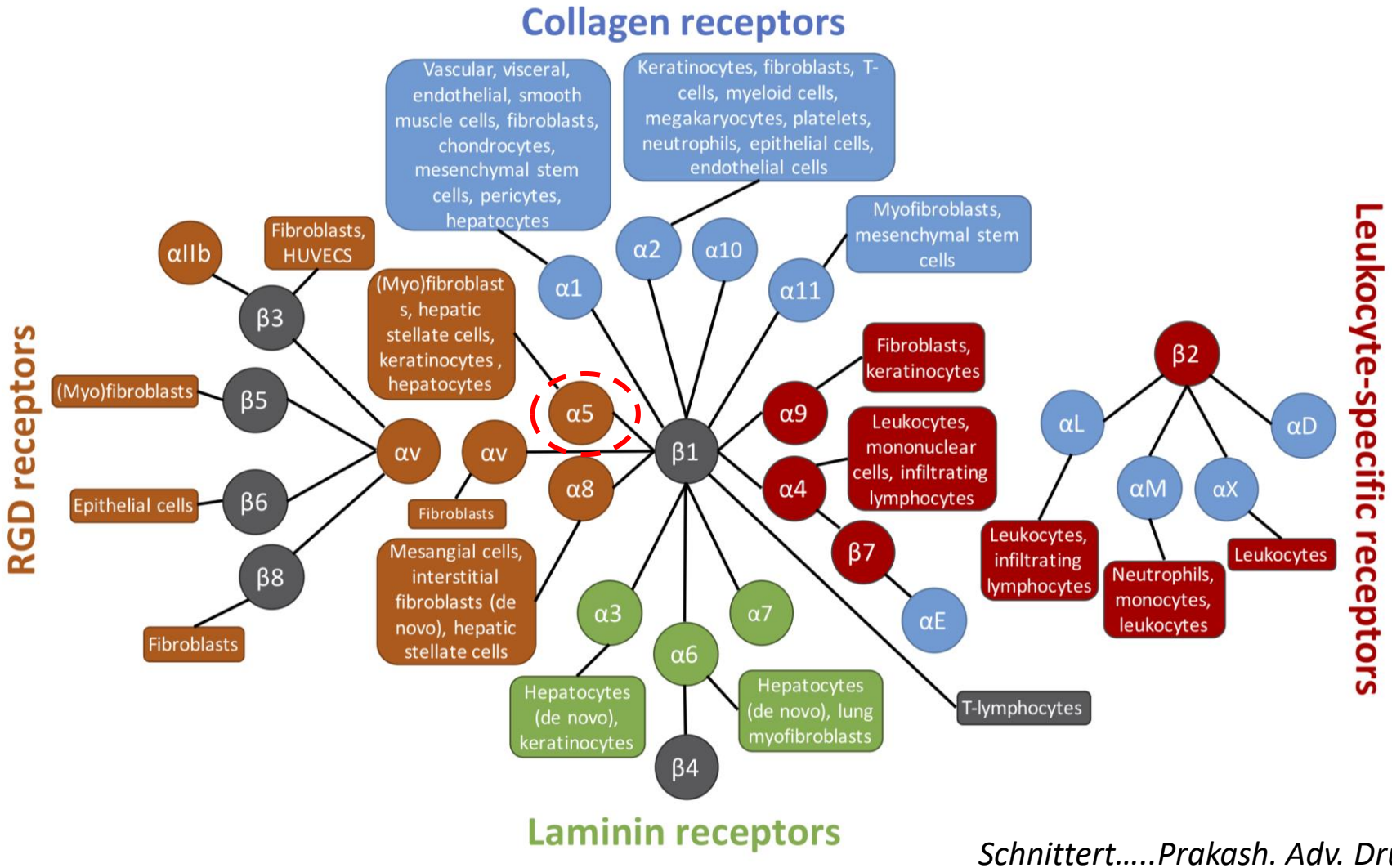
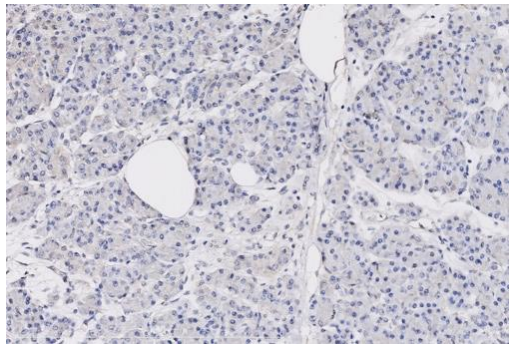
Integrin receptors



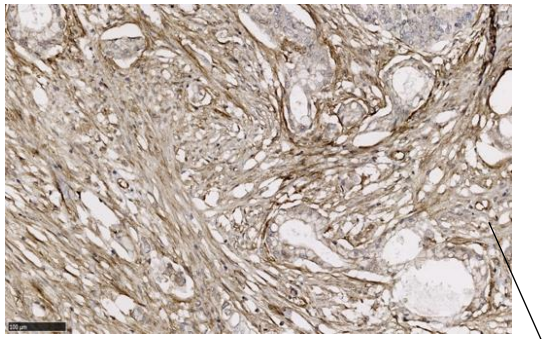
Schnittert…..Prakash. Adv. Drug Del. Rev. 2018

Integrin alpha5 (ITGA5) expression in PDAC patients

Healthy Pancreas



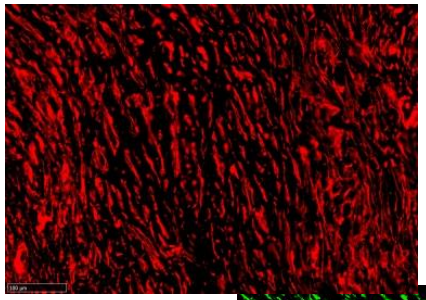
Pancreatic cancer



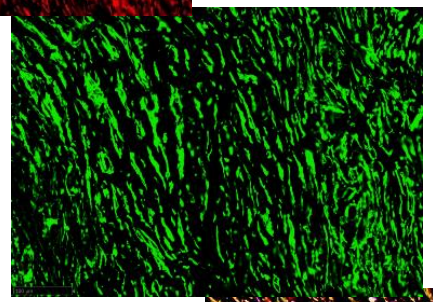
Tumor

Stroma

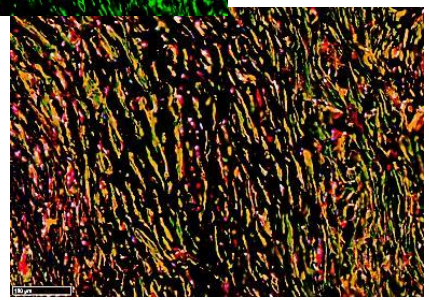
ITGA5

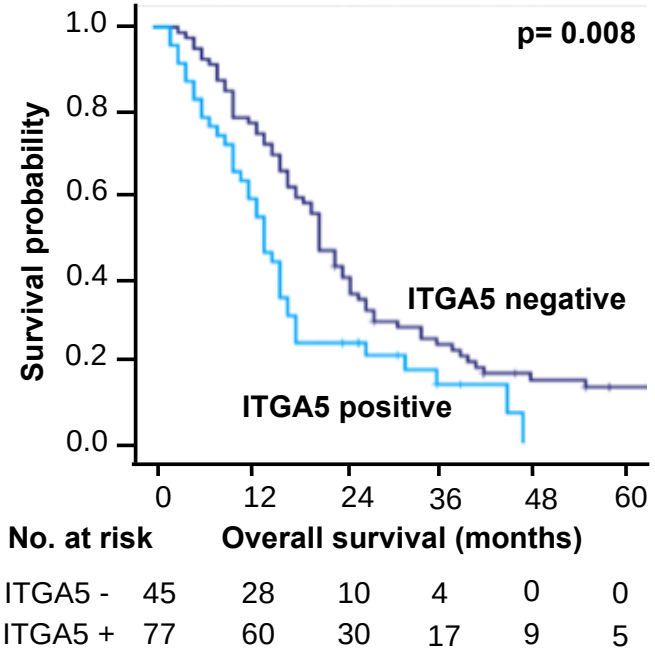


α-SMA



merge





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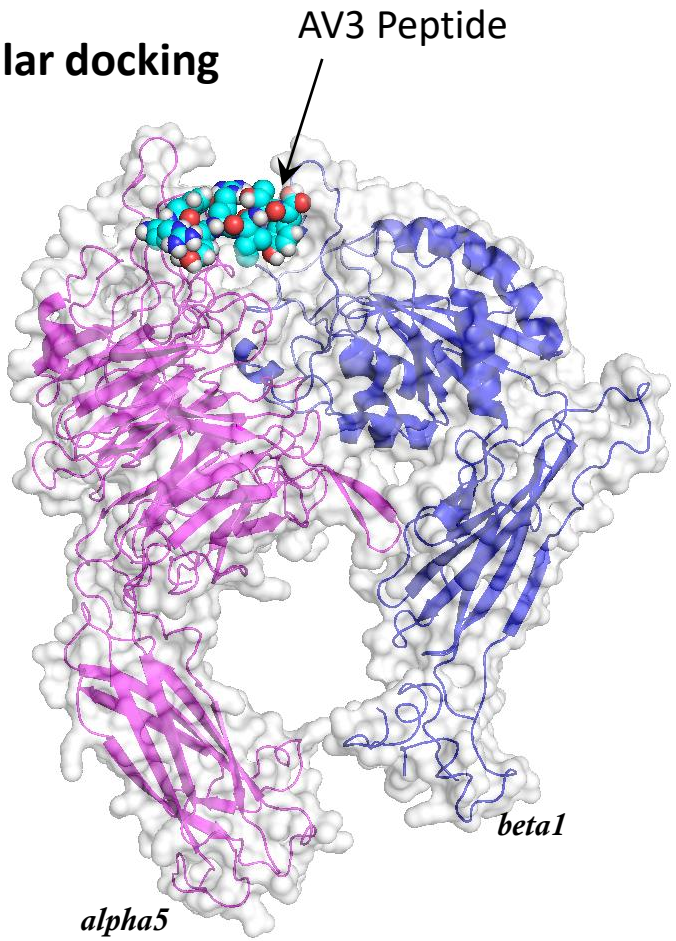
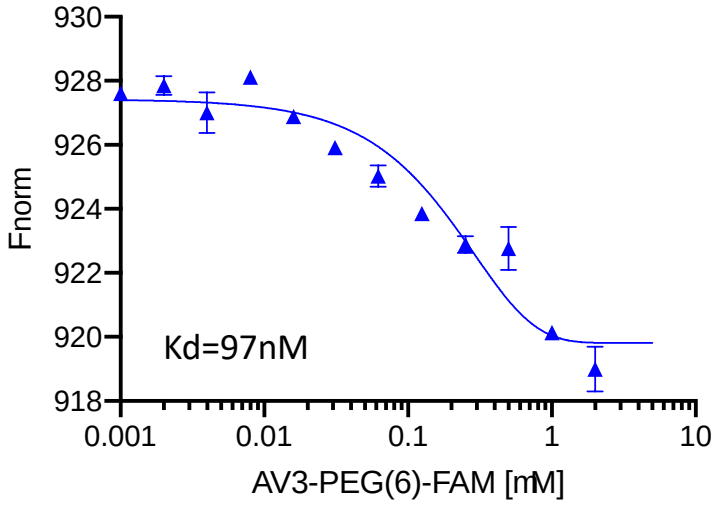
Kuninty…….Prakash, Science Advances 2019

AV3 peptide against ITGA5

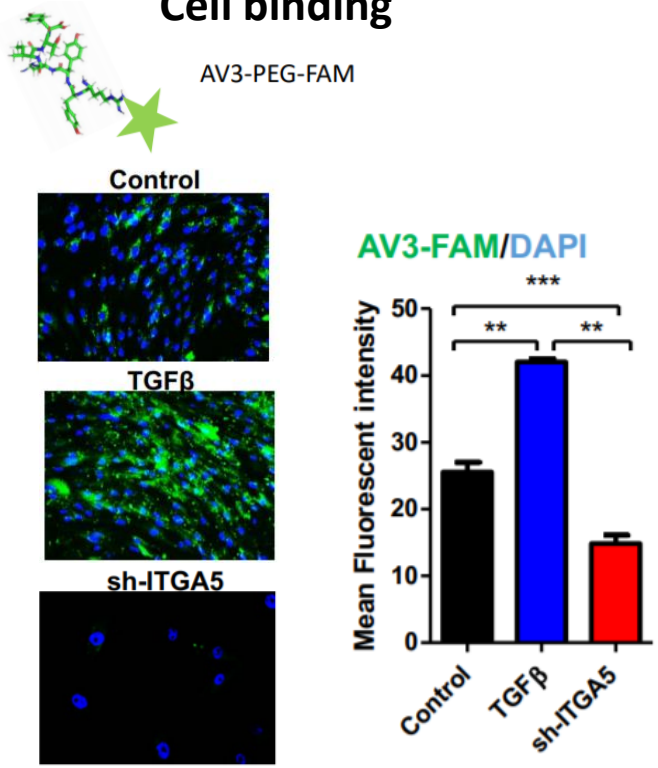
Molecular docking



Receptor binding



Cell binding



Binding of Fluorescently-Labeled AV3

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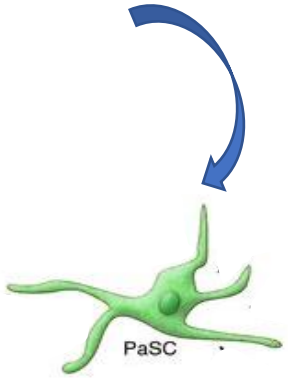
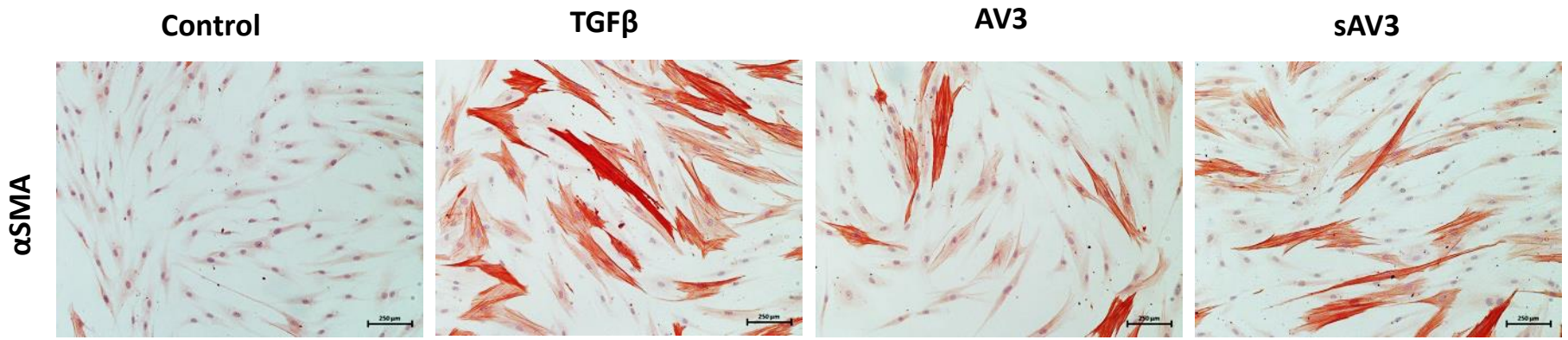
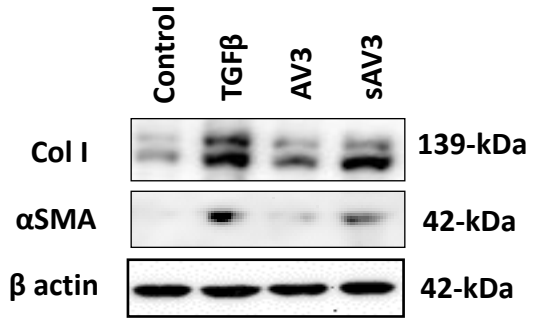
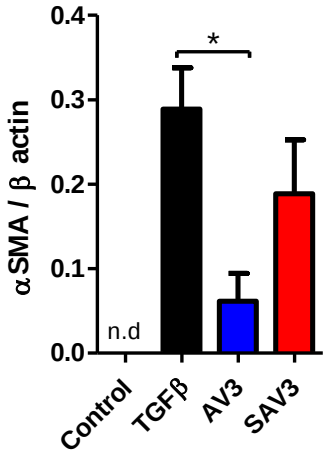
AV3 peptide inhibits PSC activation and ECM production









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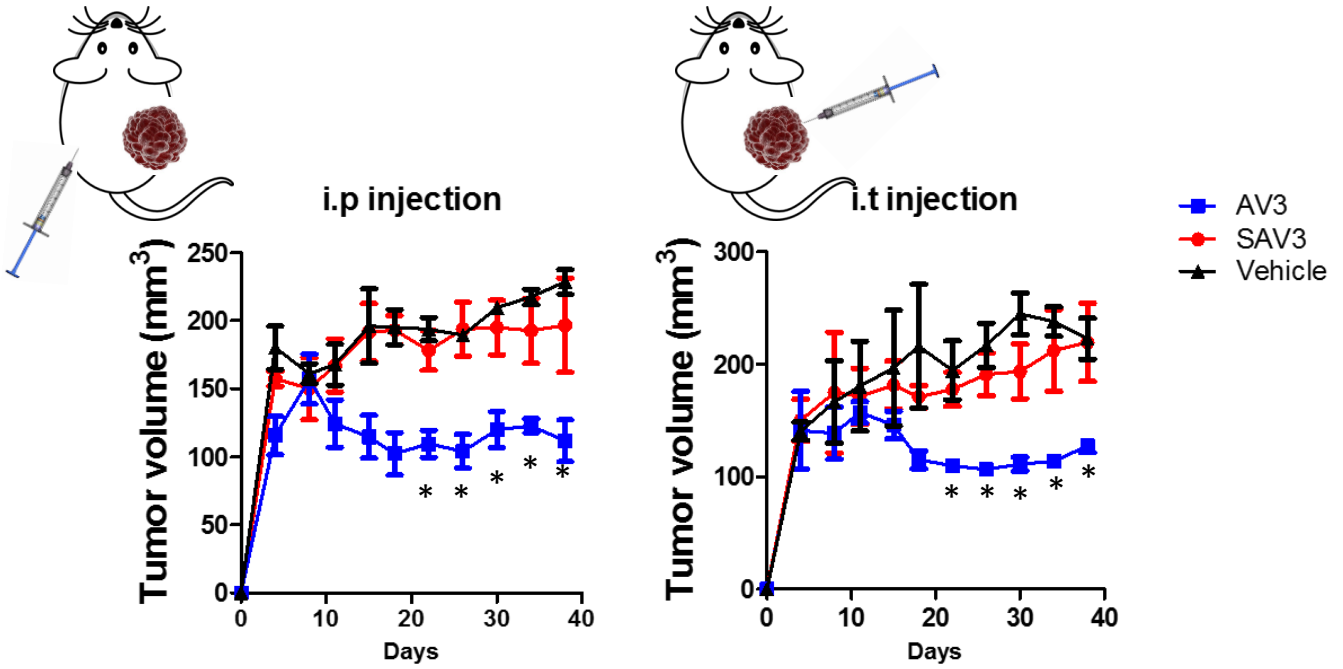
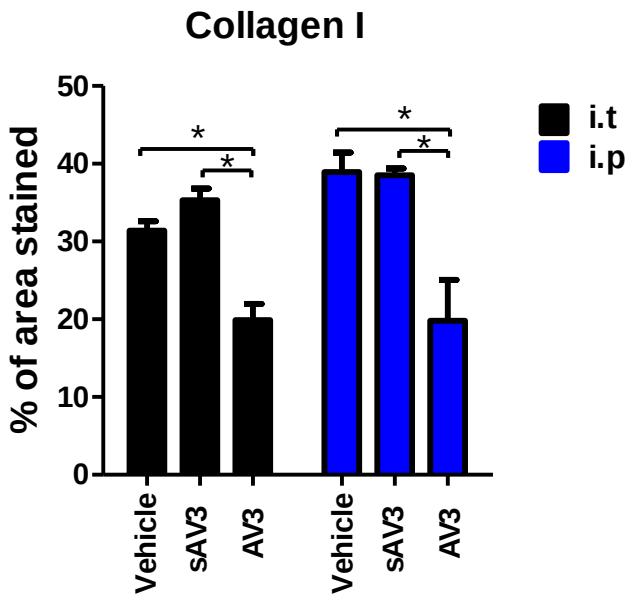
AV3 attenuates stroma-induced tumor growth



Dose: 20 mg /kg, i.p or 4 mg/kg i.t. twice a week



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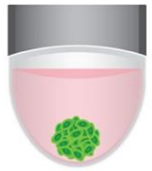
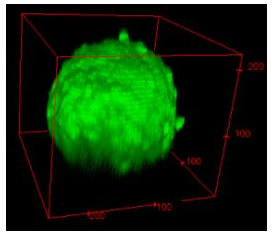
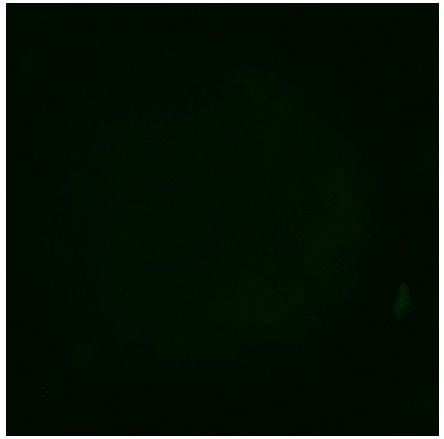
AV3 enhances the effect of gemcitabine in 3D hetero-spheroids

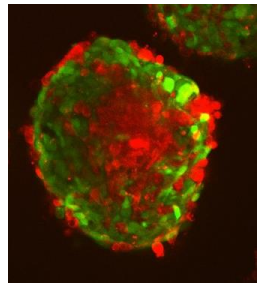
3D cell culture

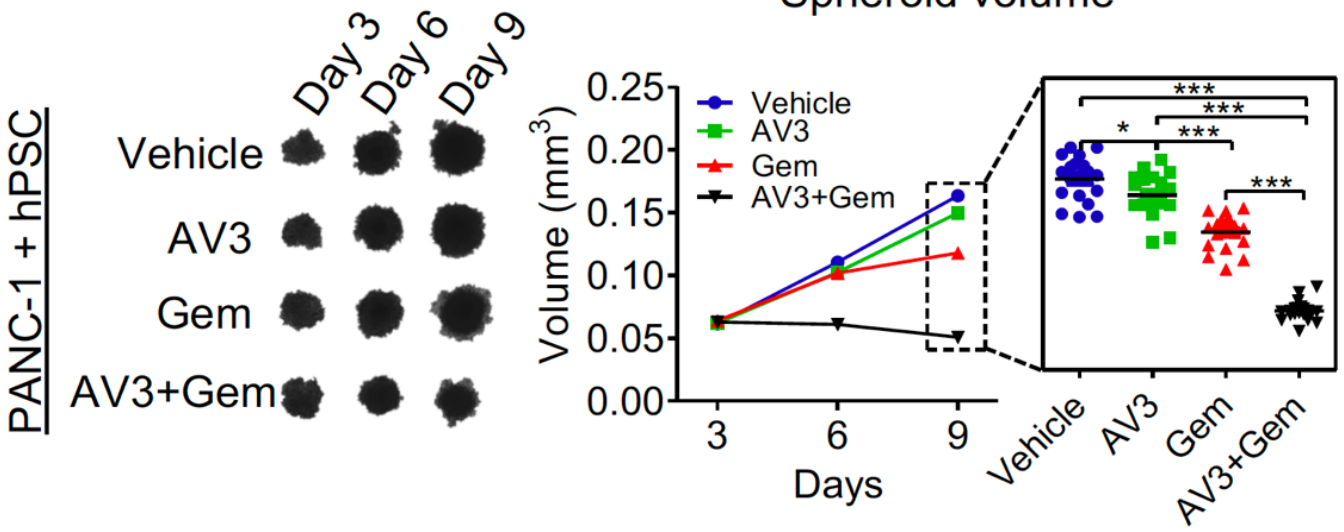


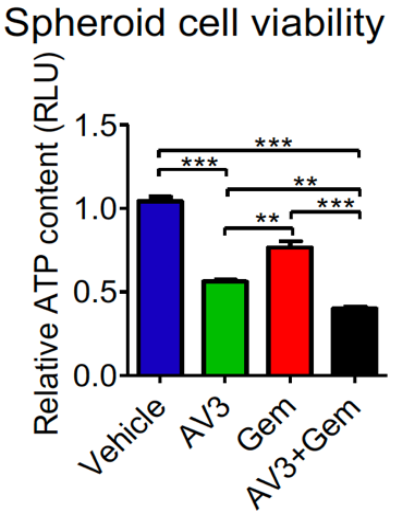




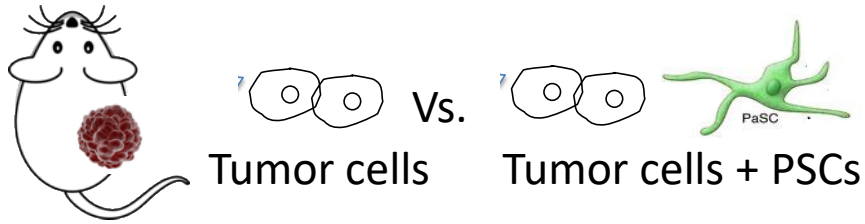
Heterospheroids

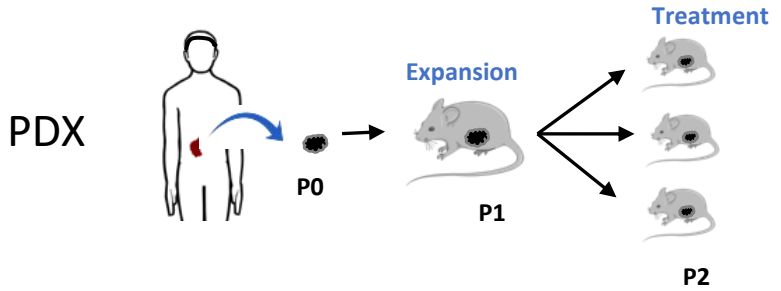


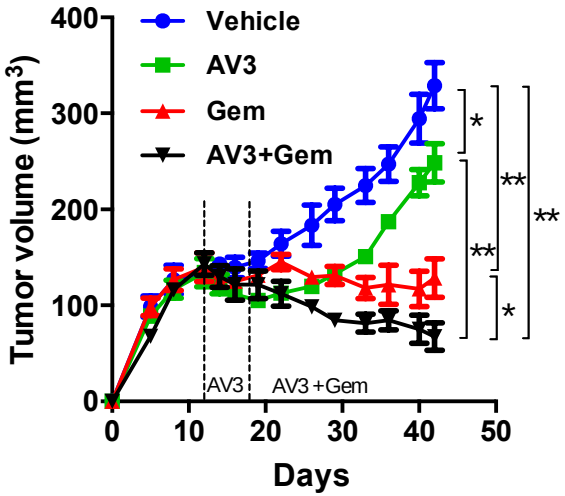


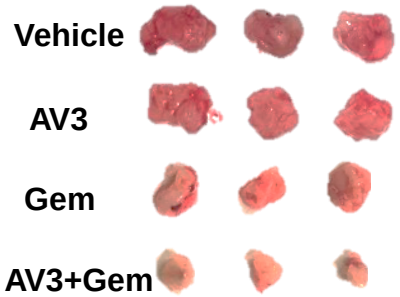


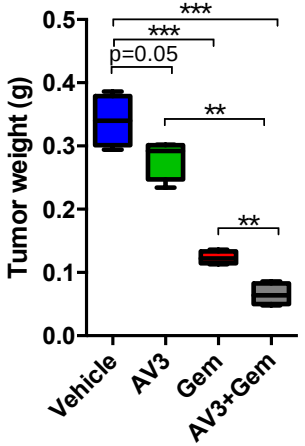
AV3 enhances the effect of chemotherapy in mouse tumor models

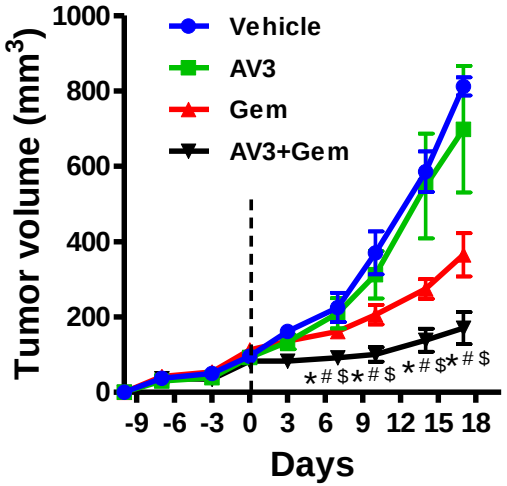


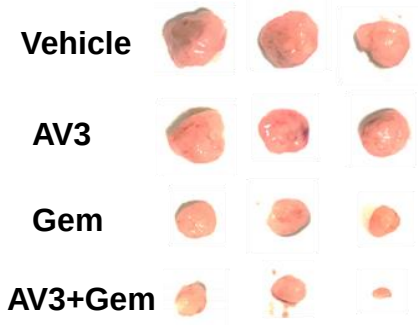


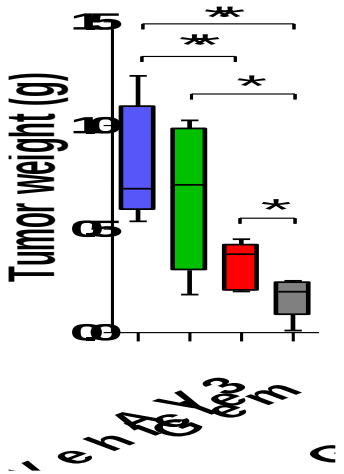












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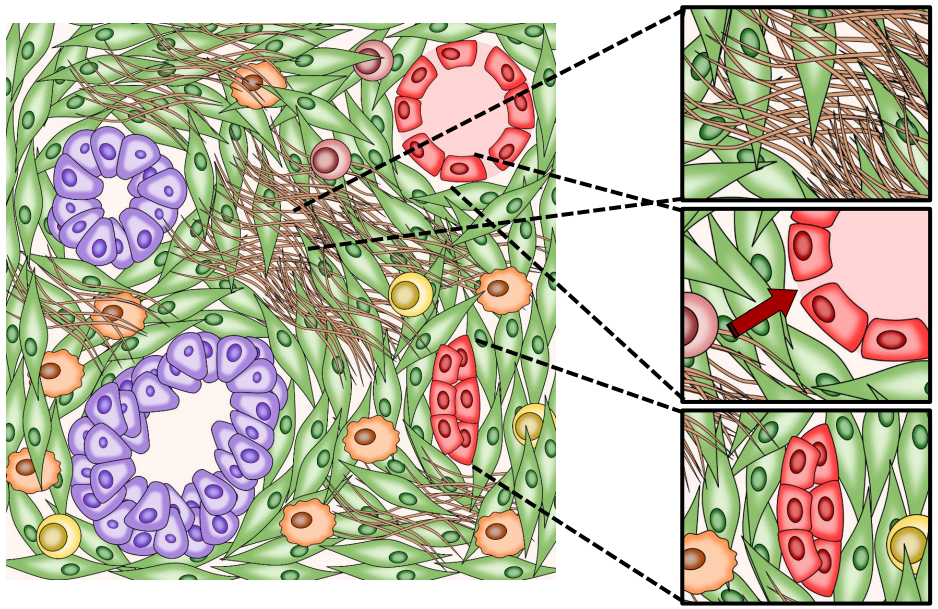
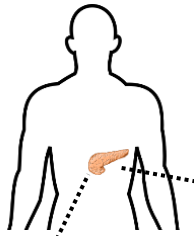
Compression of blood vessels



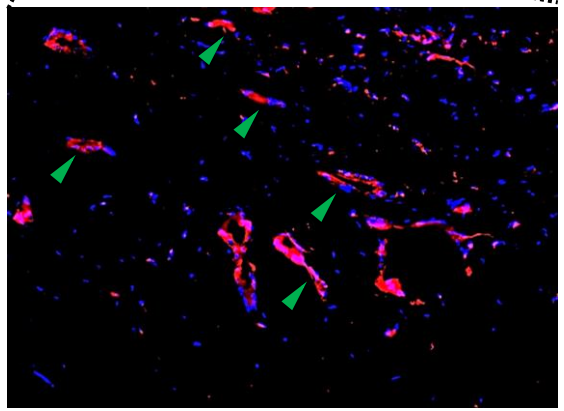
High desmoplasia

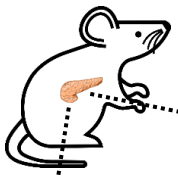
High interstitial pressure

Blood vessel collapse

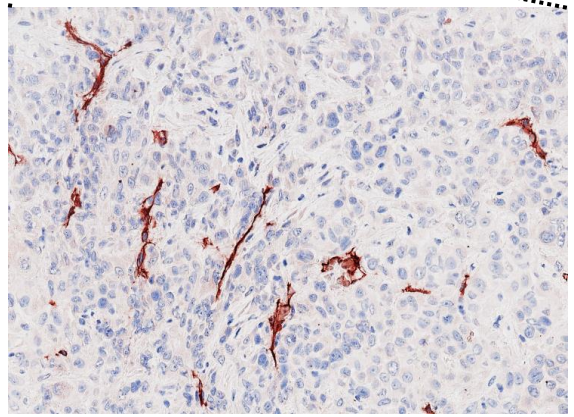


Human PDAC Tissue

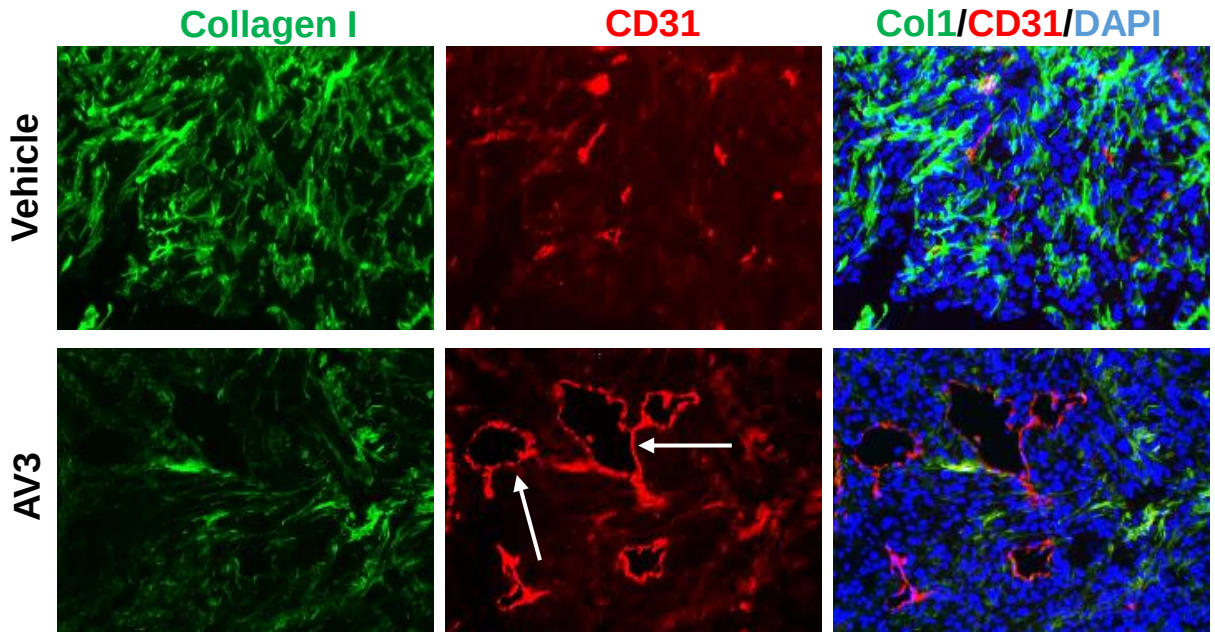


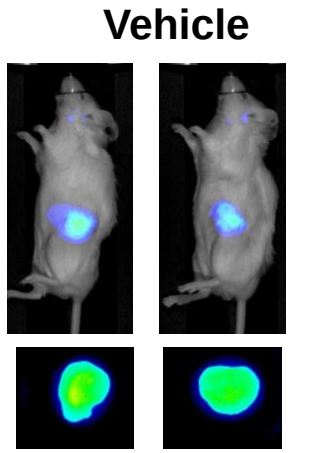


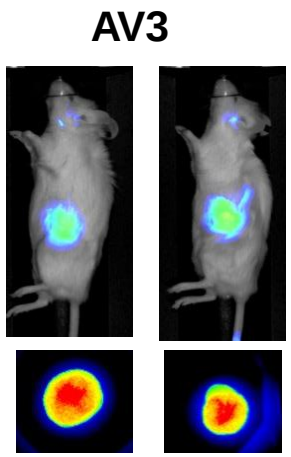
Panc-1/PSC Injection Model

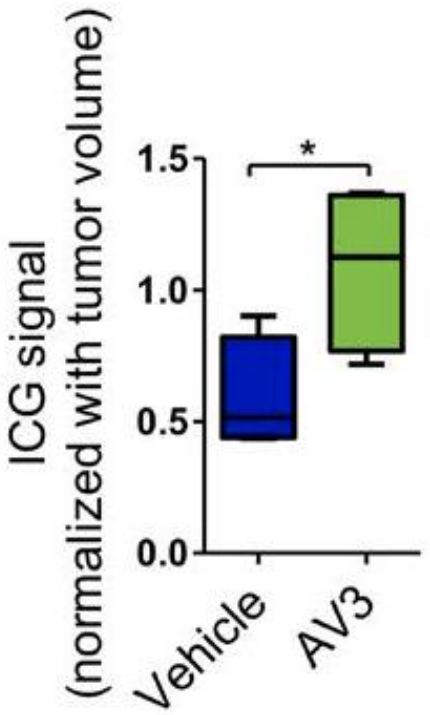


AV3 reduces collagen – decompresses vasculature – enhance drug delivery









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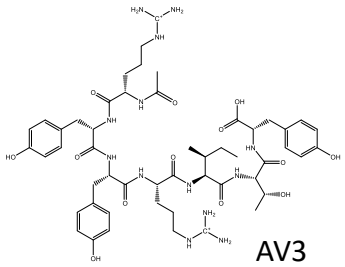
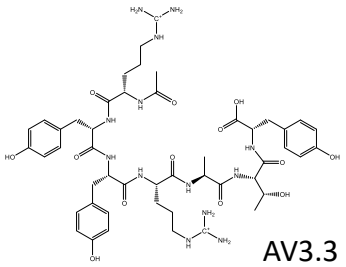
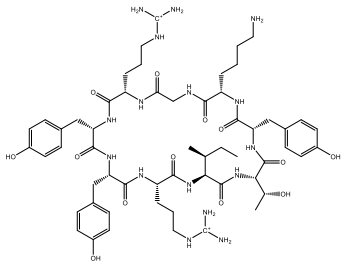
New AV3 variant peptides



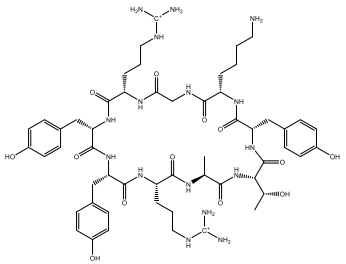
AV3



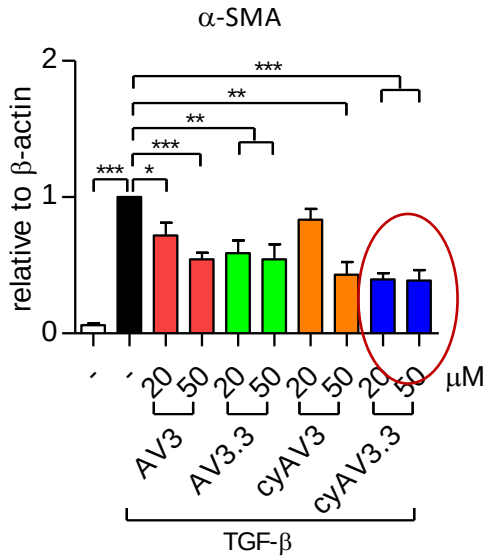
AV3.3

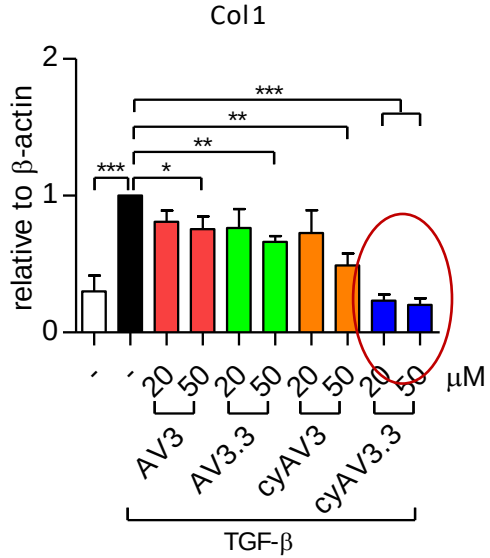


cyclic AV3 (cyAV3)



cyclic AV3.3 (cyAV3.3)





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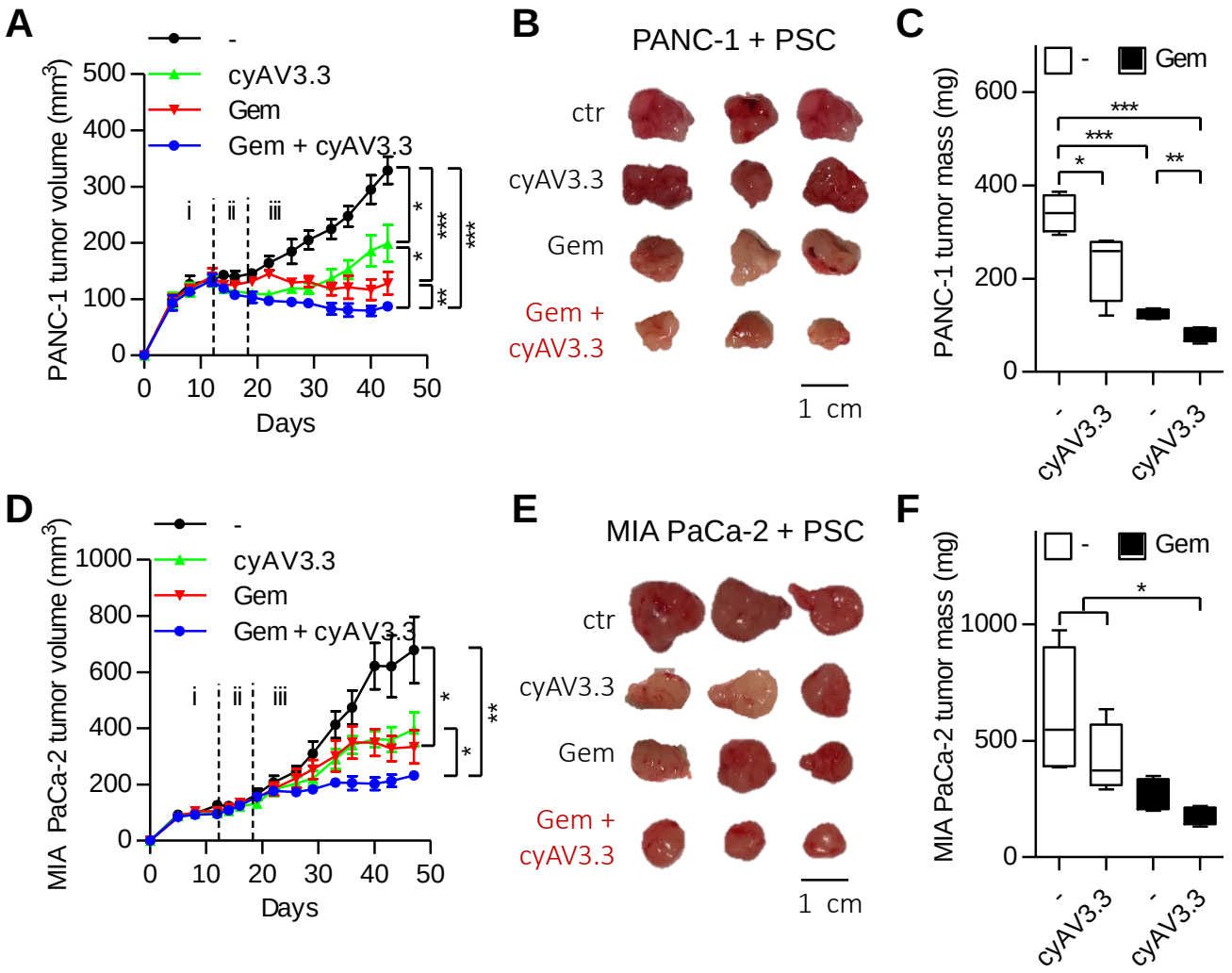
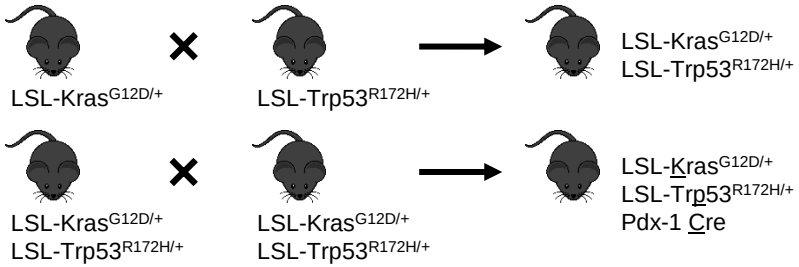
Mardhian et al, in preparation

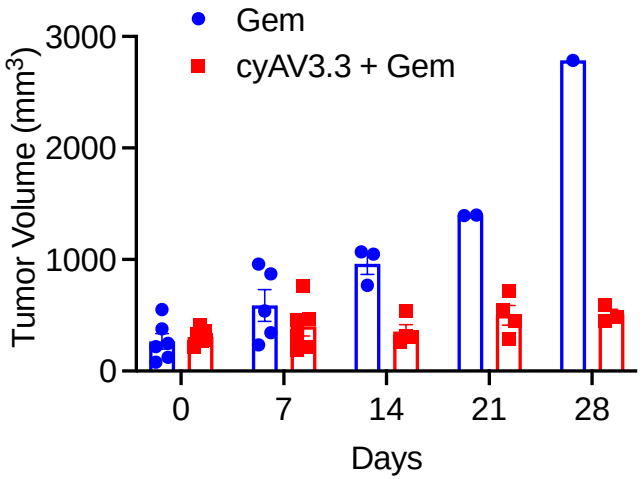
In vivo efficacy of cyAV3.3 in co-injection models

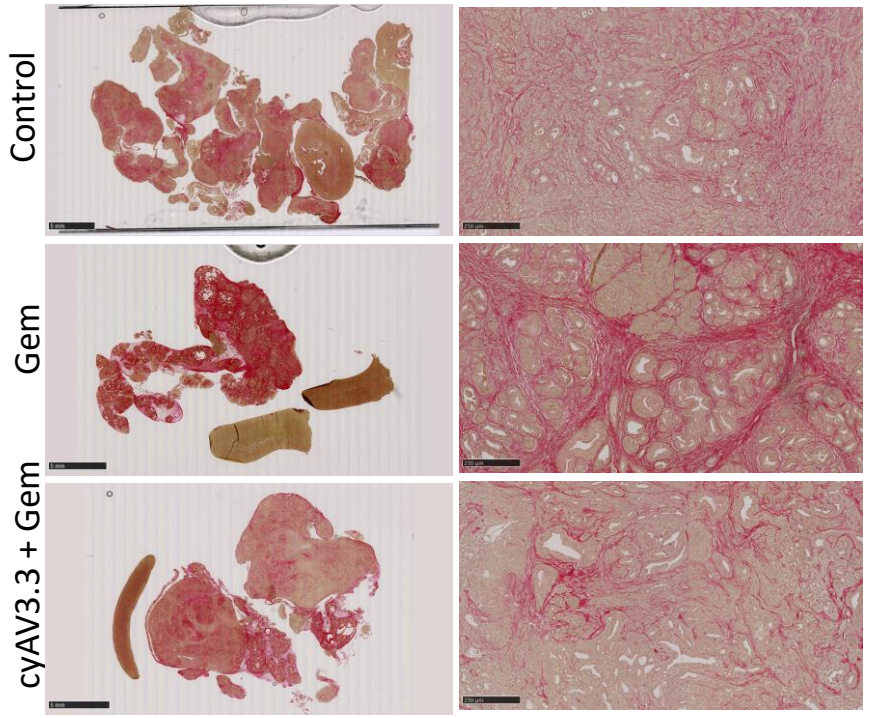


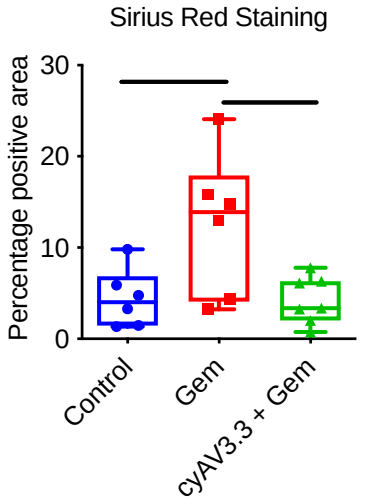
Mardhian et al, in preparation

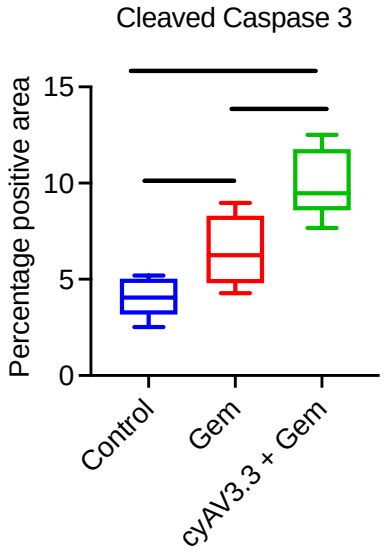
Efficacy in genetically engineered KPC mouse model











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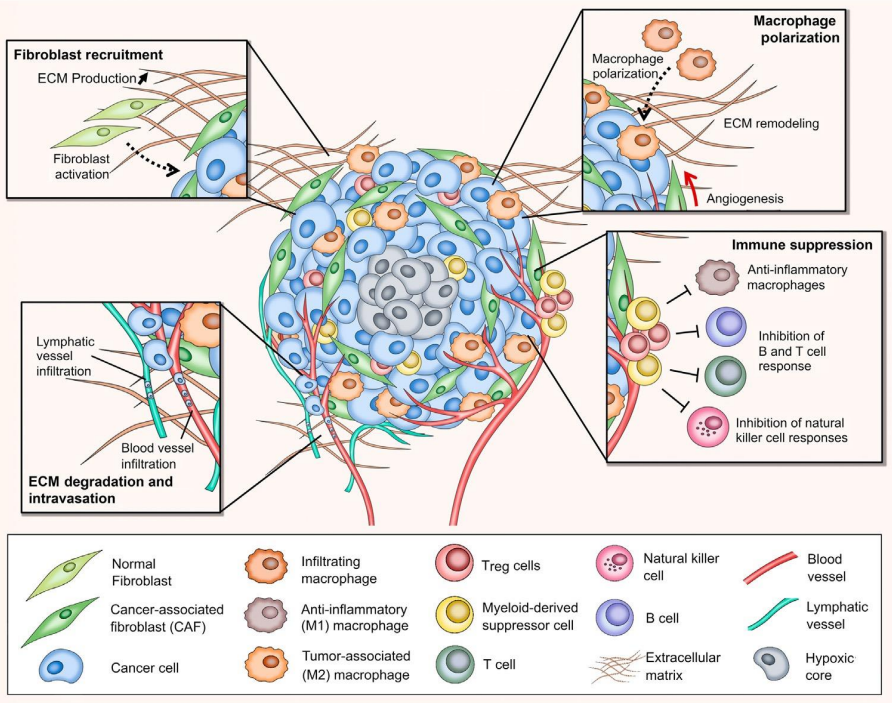
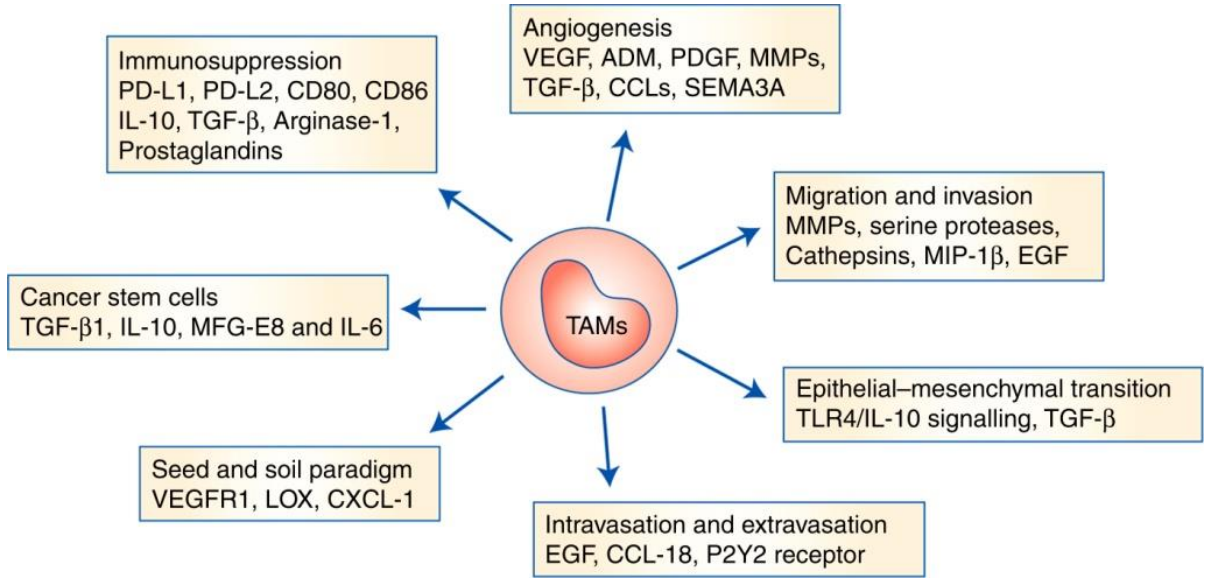
Conclusion – I

- ITGA5 is a crucial therapeutic target in controlling biomechanical activation of pancreatic tumor stroma
- Novel AV3 peptide and derivatives reduce desmoplasia and enhance the efficacy of chemotherapy *in vivo*
- To achieve higher efficacy combination with immunotherapy would be interesting

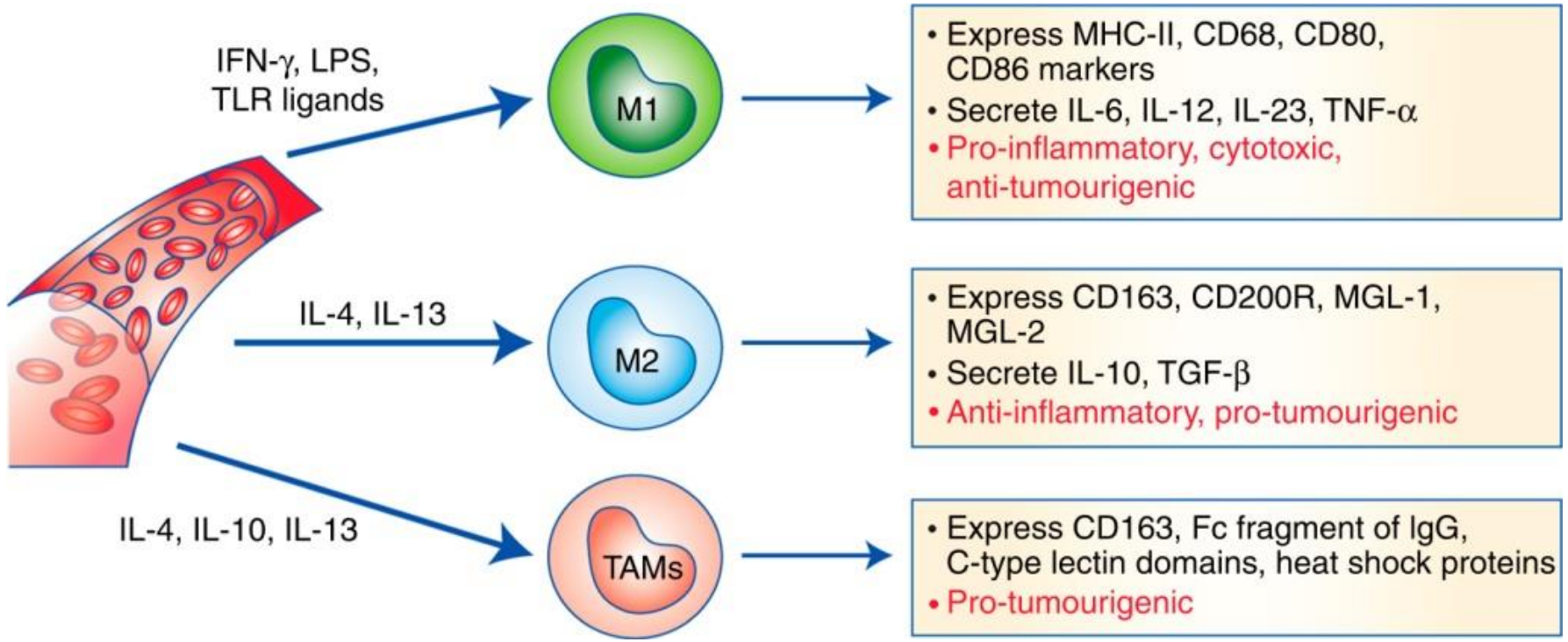
Engineering Immune microenvironment

Tumor-associated macrophages (TAM)



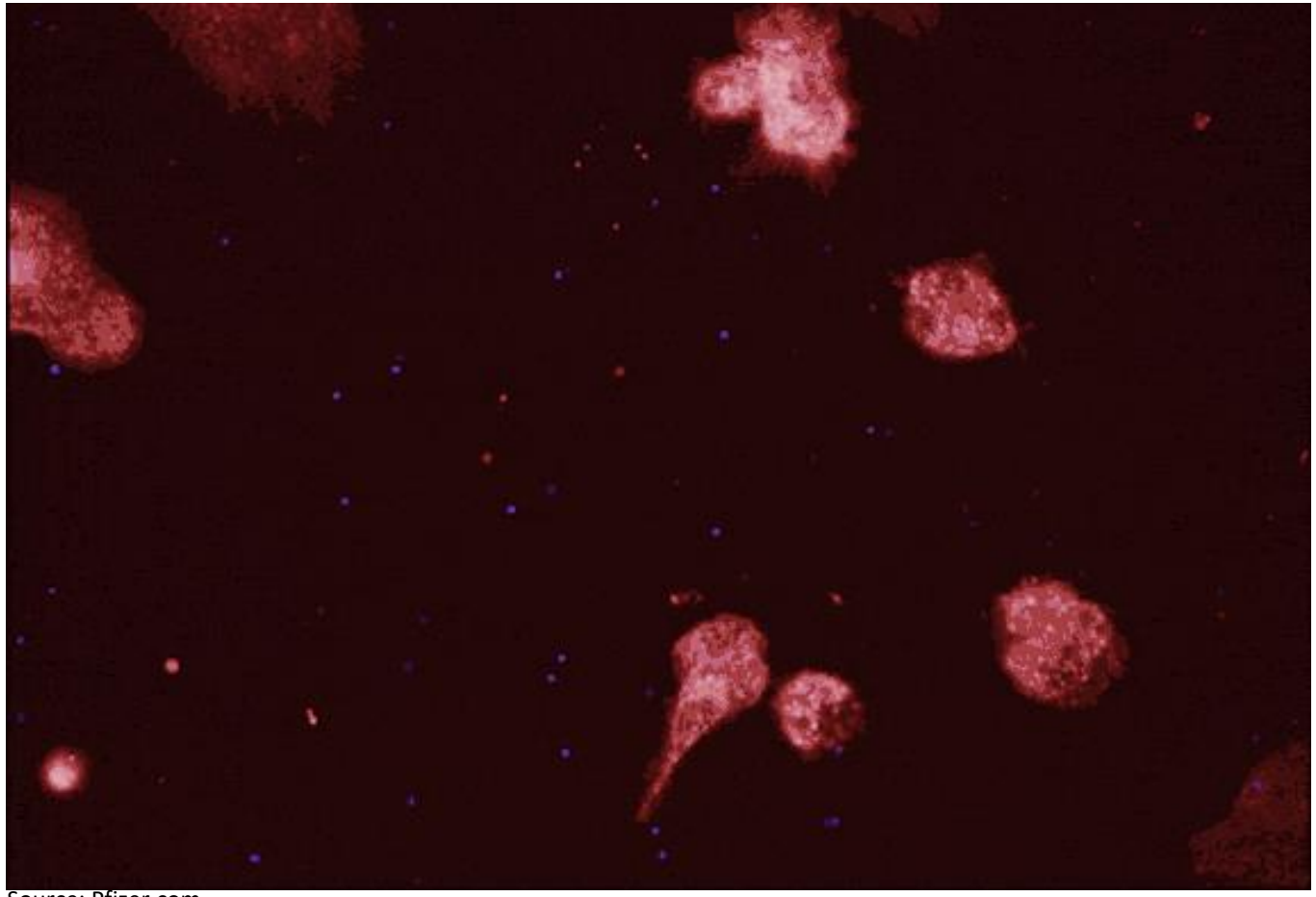


Types of macrophages

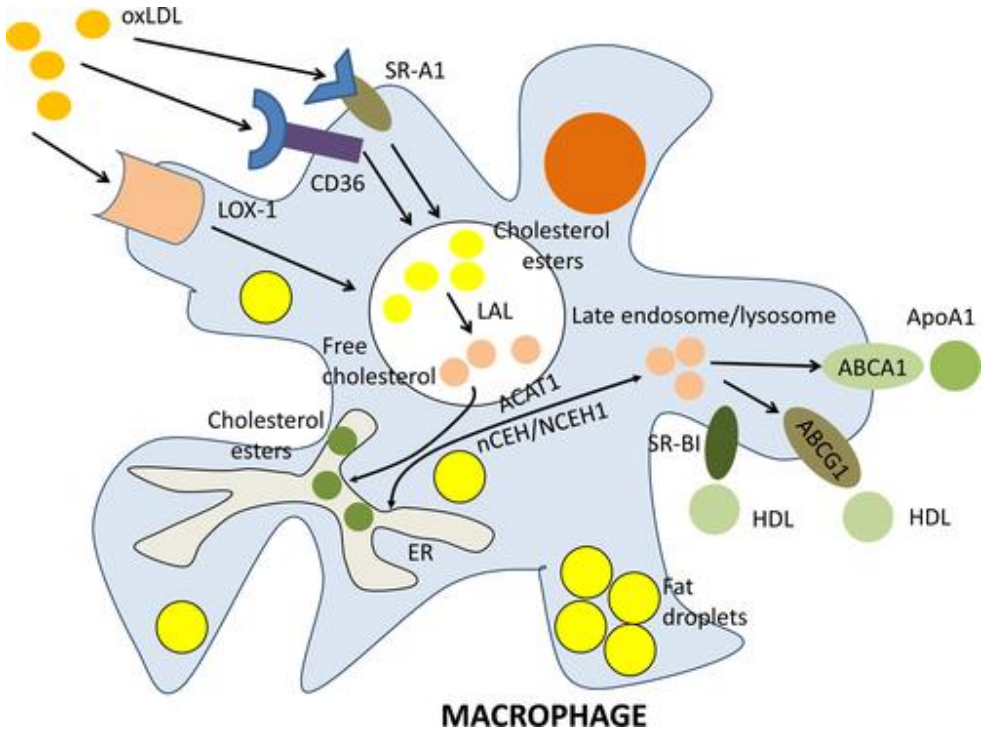


Aras and Zaidi. *Br J Cancer* (2017)

Macrophages: the scavenging machine

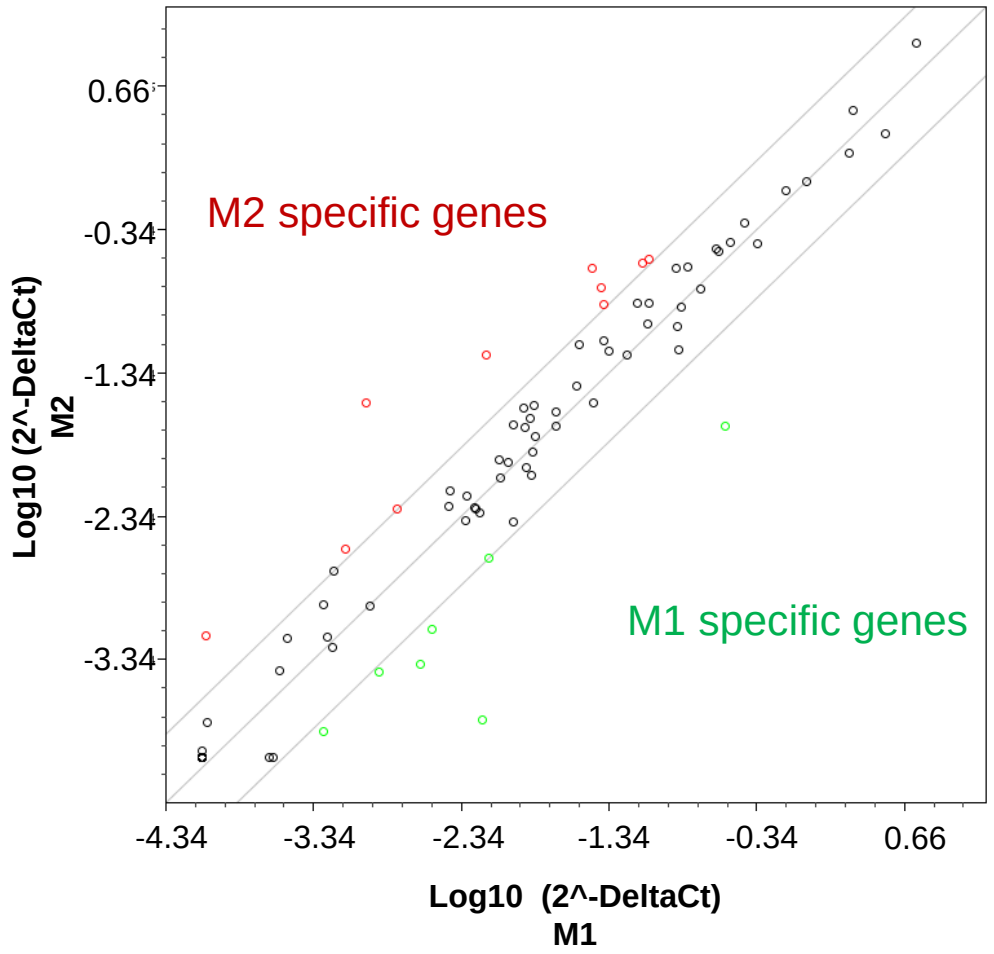


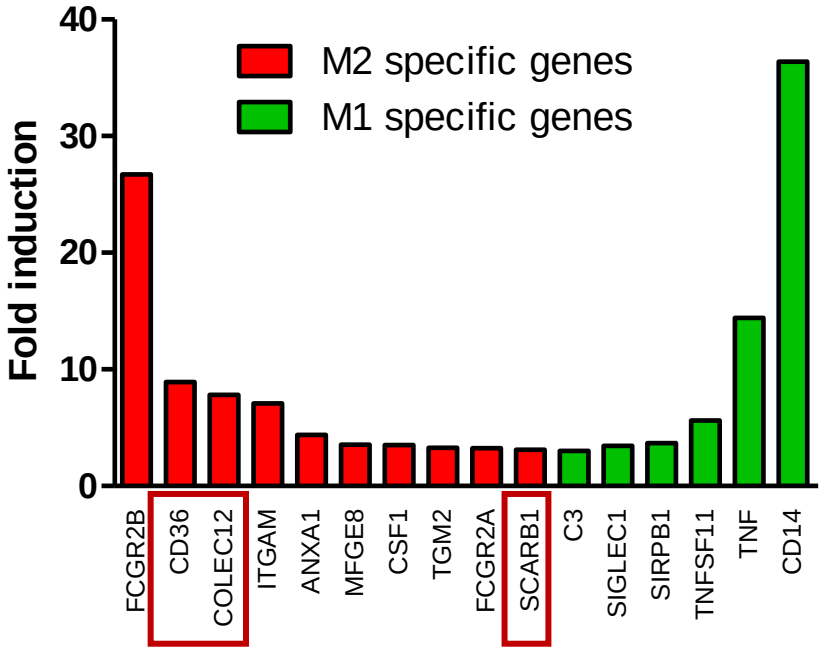
Source: Pfizer.com



doi.org/10.1111/jcmm.12689

M2-specific genes responsible for phagocytosis





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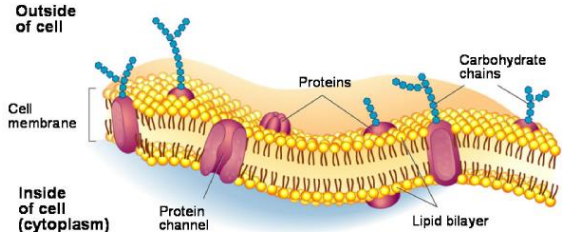
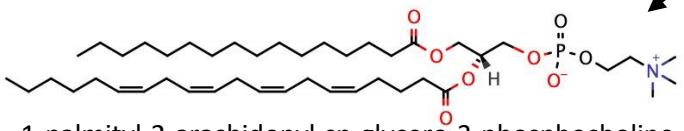
Binnemars-Postma…..Prakash. Nanomedicine 2016

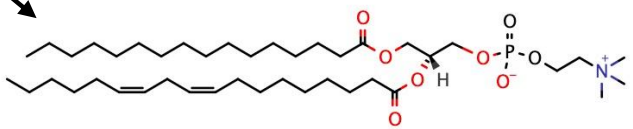
Phospholipid oxidation results in “carboxylated sn2-tail containing lipids”



Polyunsaturated fatty acids (PUFA)

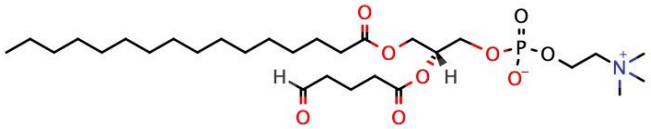


1-palmityl-2-arachidonyl-sn-glycero-3-phosphocholine



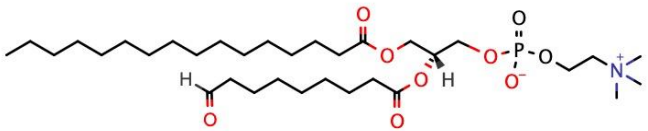
1-palmityl-2-linoleyl-*sn*-glygero-3-phosphocholine

O_2



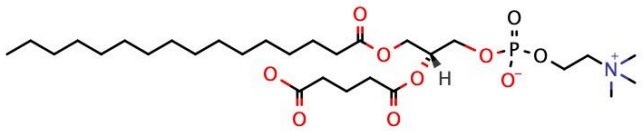
1-palmitoyl-2-(5'-oxo-valeroyl)-sn-glycero-3-phosphocholine

O_2



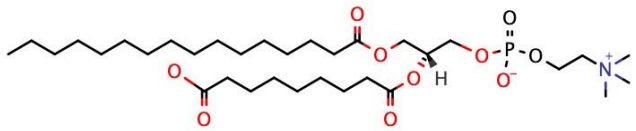
1-palmitoyl- 2-(9-oxononanoyl)-sn-glycero-3-phosphocholine

O_2



1-palmitoyl-2-glutaryl-sn-glycero-3-phosphocholine
(PGPC)

O_2



1-palmitoyl-2-azelaoyl-sn-glycero-3-phosphocholine
(PAPC)

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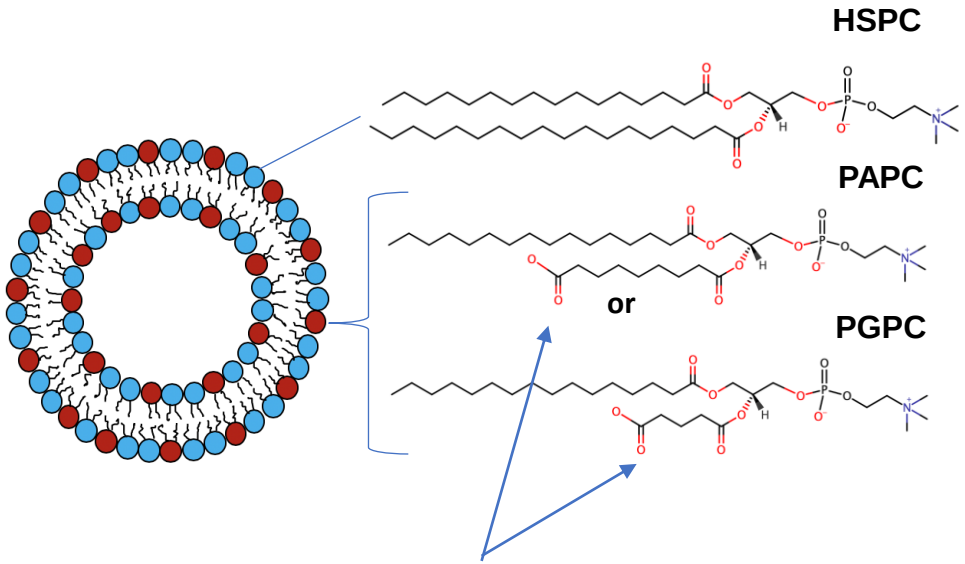
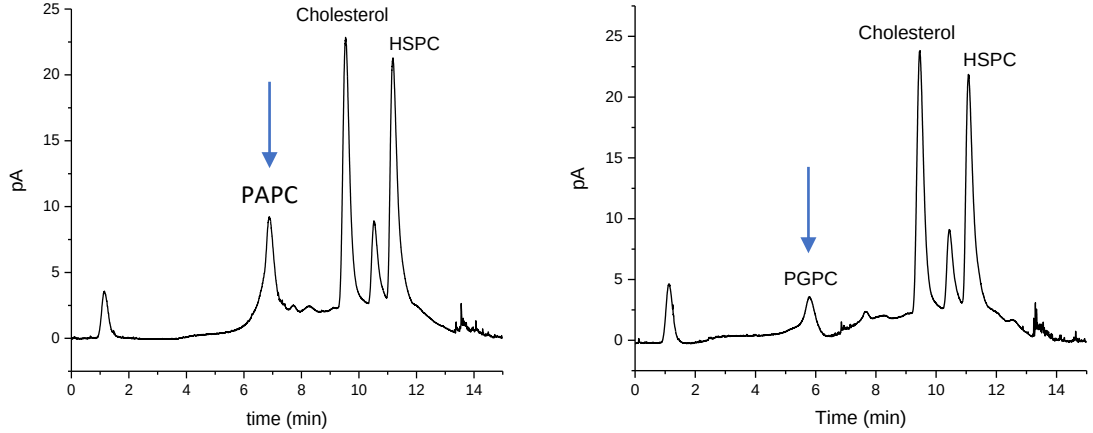
Liposomes with carboxylated phospholipids



Nanoliposomes	Size (nm ± SD)	PDI (± SD)	Zeta potential (mV ± SD)
HSPC-L (0:8:2)	115.9 ± 6.2	0.12 ± 0.05	-22.6 ± 4.8
PAPC-L (2:6:2)	107.9 ± 0.7	0.19 ± 0.06	-25.1 ± 4.9
PAPC-L (3:5:2)	105.9 ± 15.7	0.22 ± 0.04	-27.8 ± 4.6
PGPC-L (2:6:2)	80.1 ± 0.9	0.20 ± 0.10	-17.0 ± 6.0
PGPC-L (3:5:2)	113.5 ± 16.5	0.2 ± 0.08	-21.1 ± 2.8

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

UPLC-CAD



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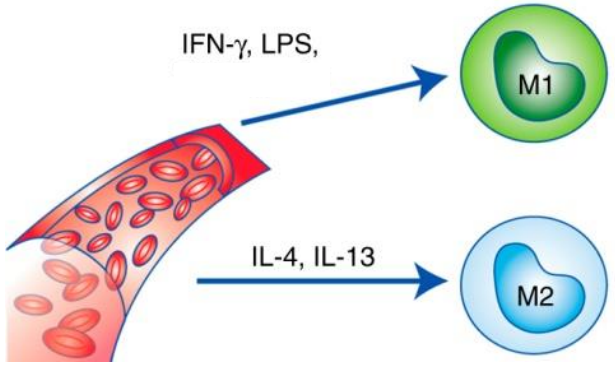
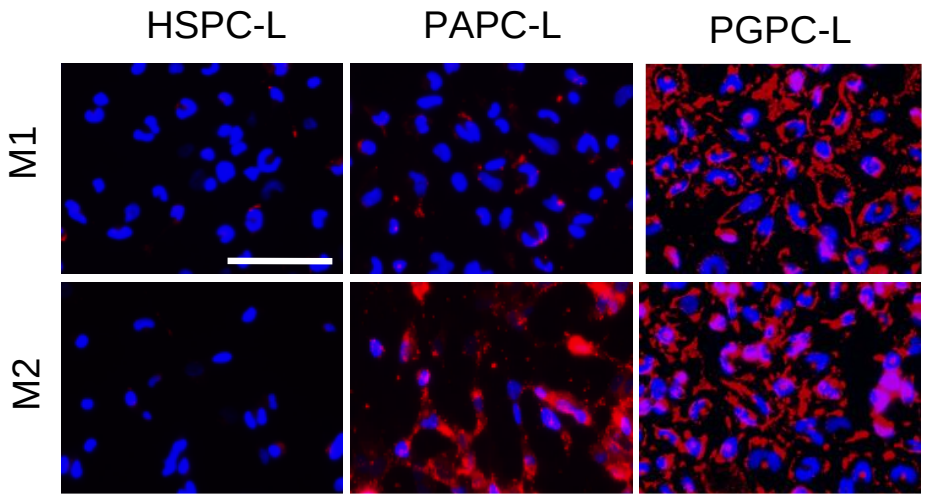
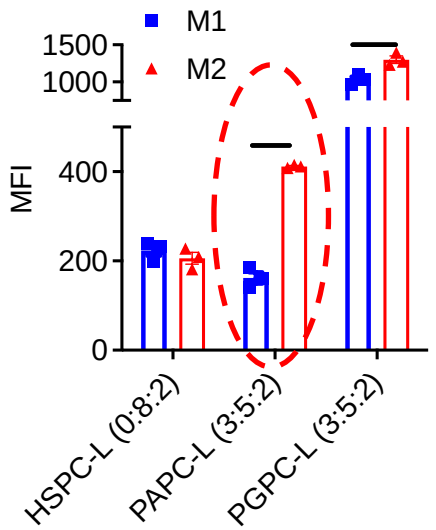
Patent: EP2019720179

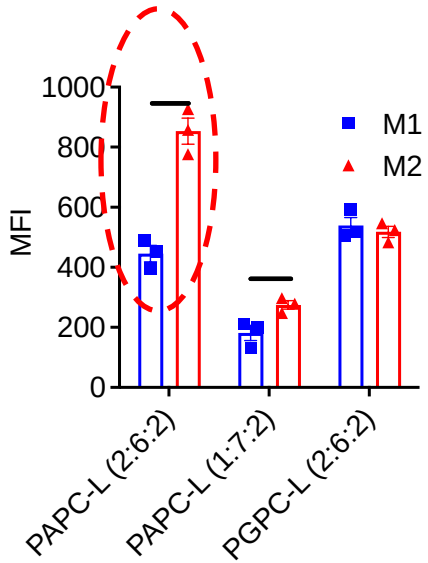
Kuninty, Binnemars-Postma, Nature Communications (accepted)

PAPC-L are preferably taken up by M2-differentiated macrophages









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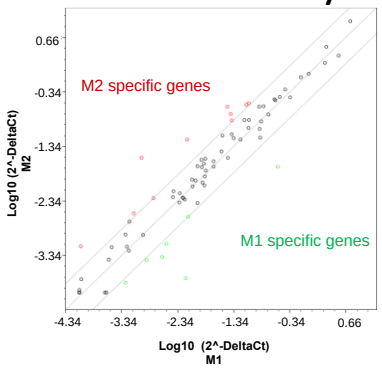
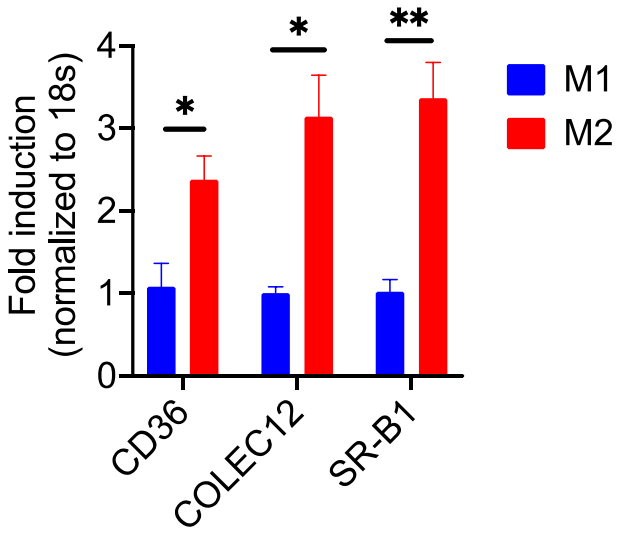
Kuninty, Binnemars-Postma, Nature Communications (accepted)

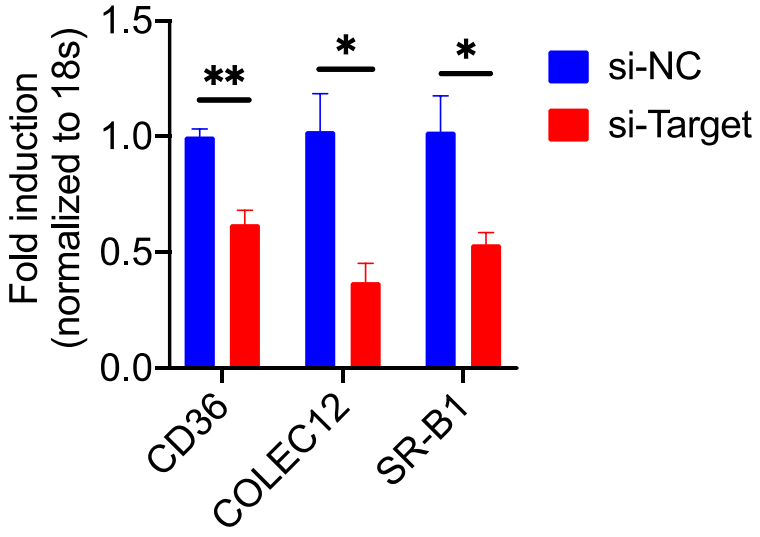
SR-B1 scavenger receptor – crucial for M2 uptake

Gene array

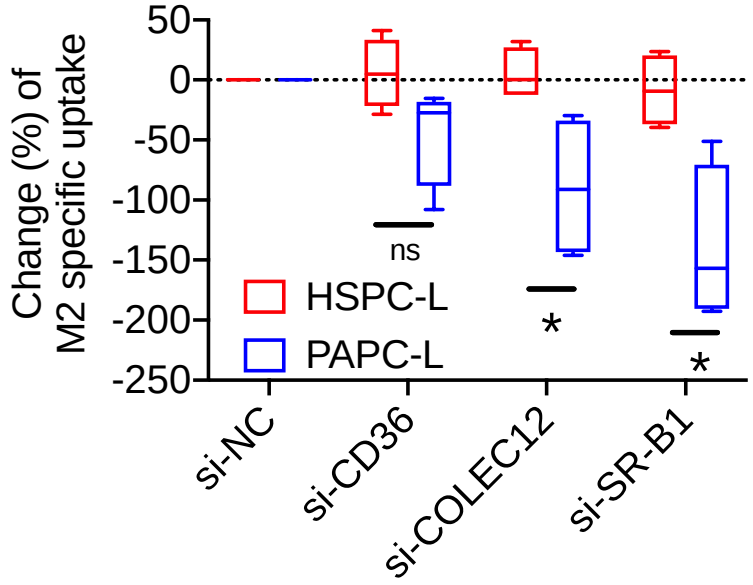




siRNA based gene silencing



Flow cytometry analysis



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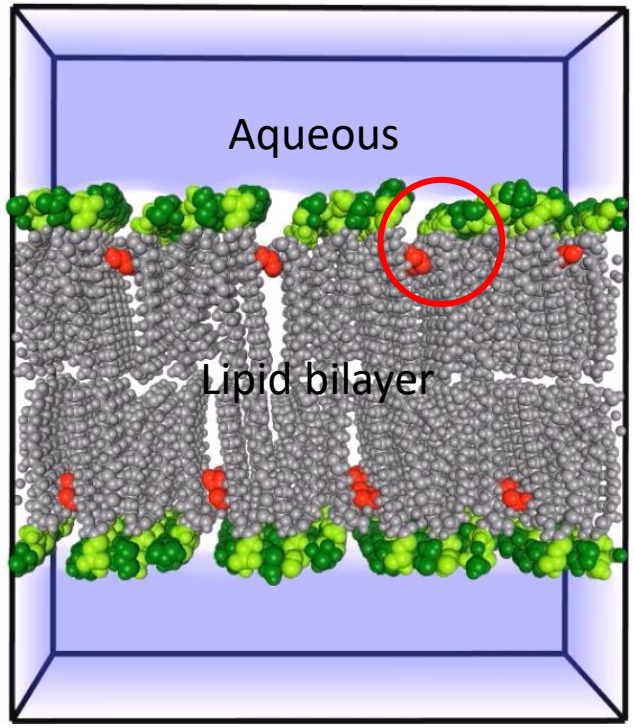
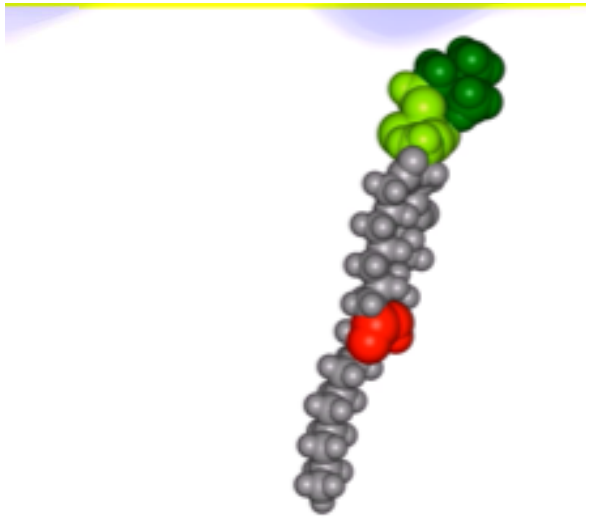
“Tail-flipping” mechanism of PAPC in lipid bilayer

Molecular dynamic simulation

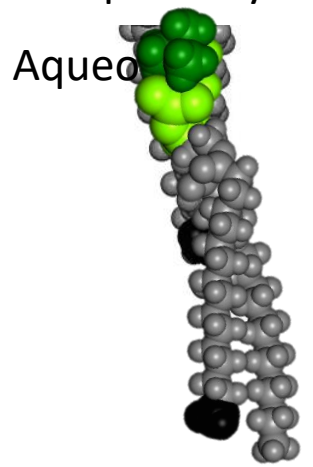
Bilayer of PAPC:HSPC



PAPC in lipid bilayer

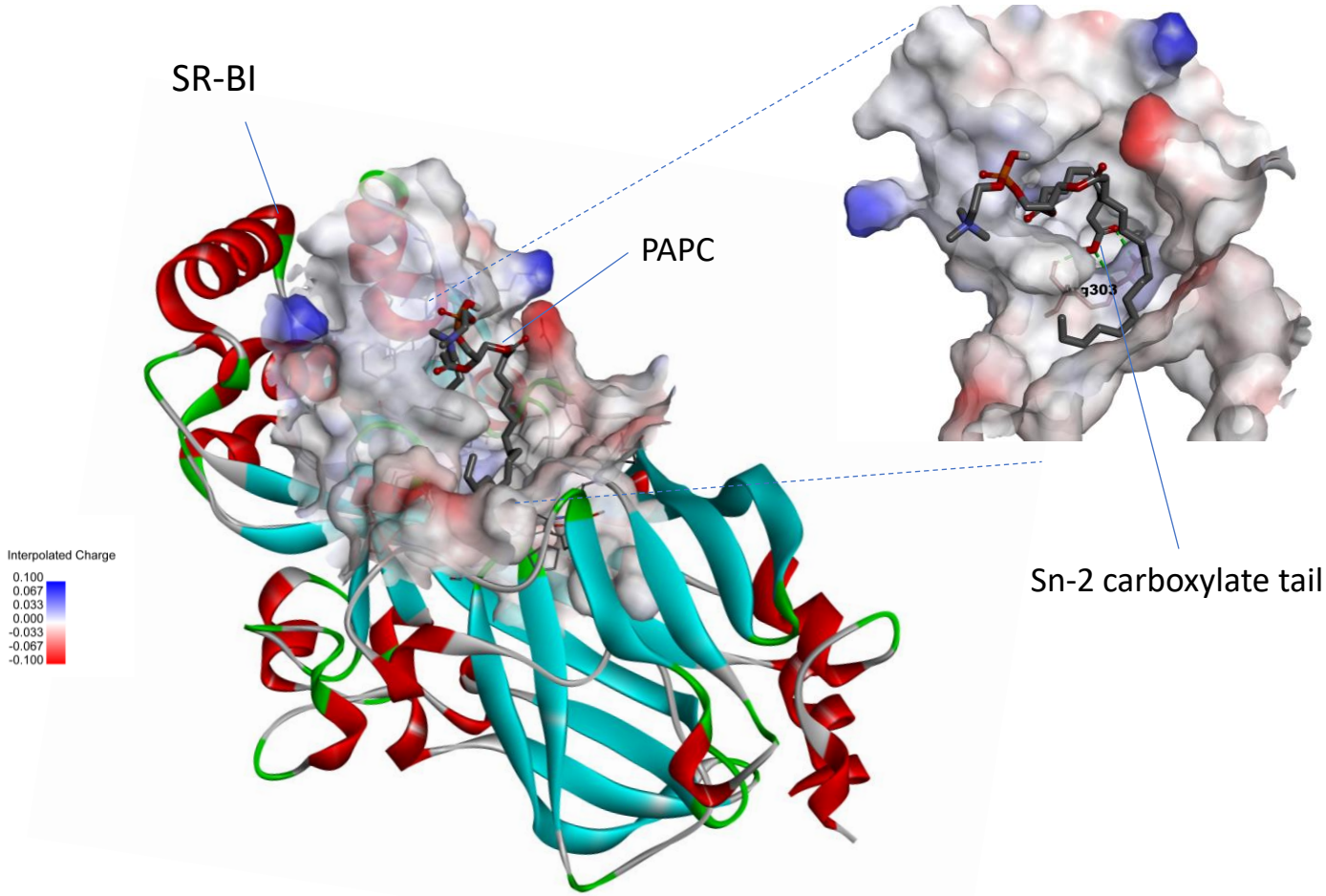


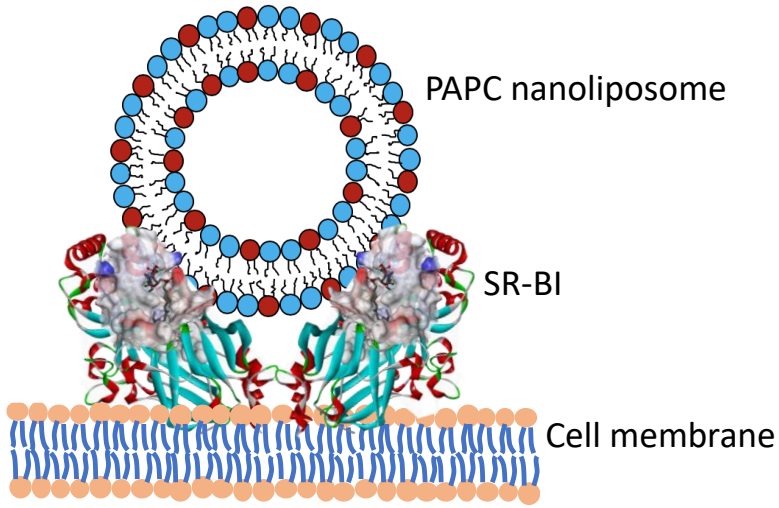
HSPC in lipid bilayer



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

PAPC “flipped tail” engages with positively charged pocket of SR-B1





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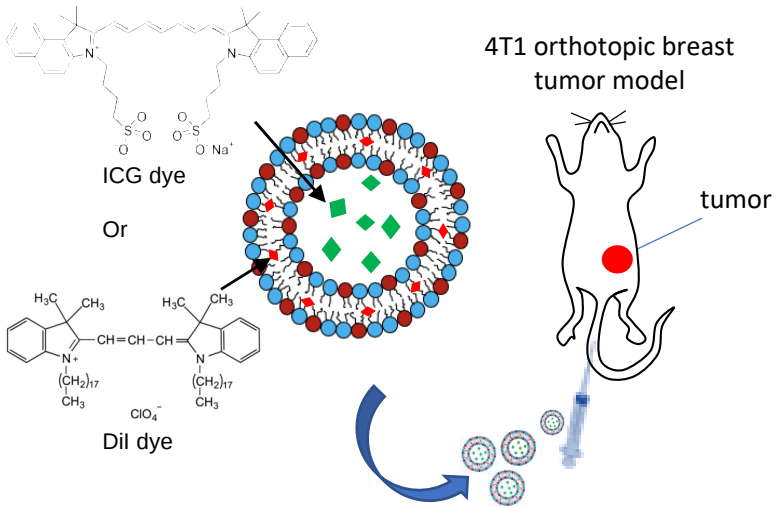
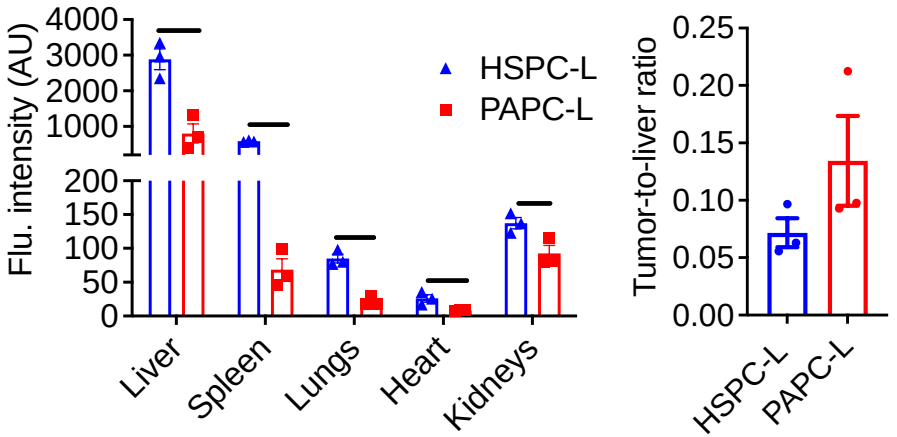
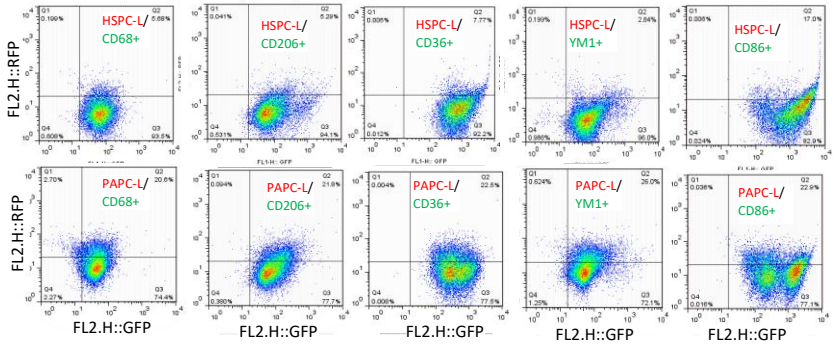
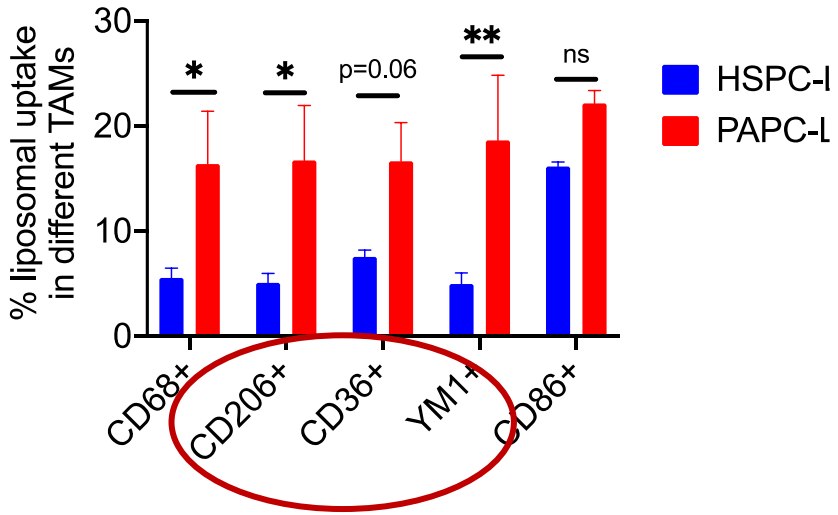
Kuninty, Binnemars-Postma, Nature Communications (accepted)

PAPC-L distributes to M2-TAM in 4T1 tumor model









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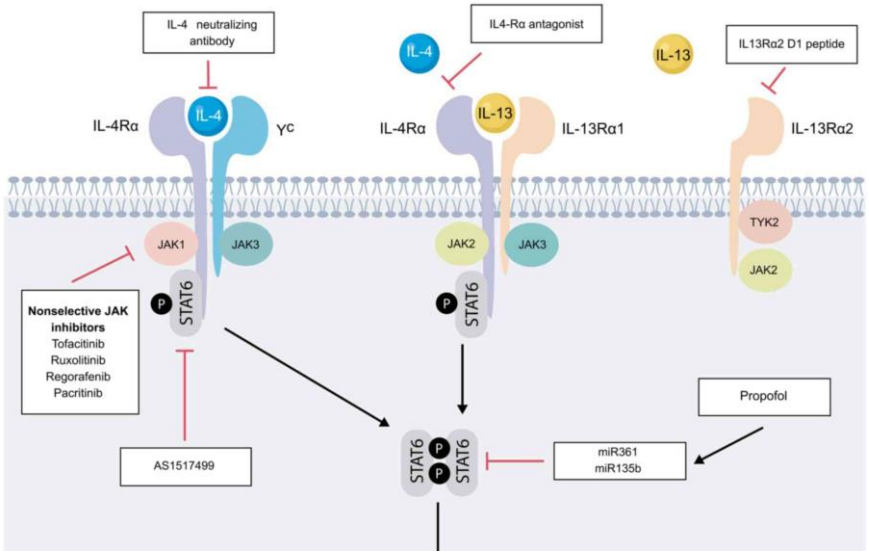
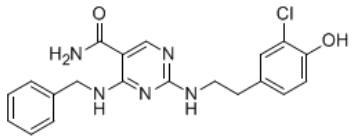
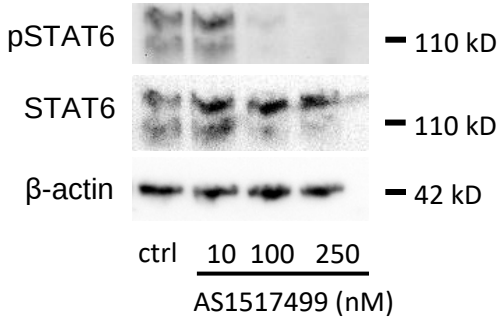
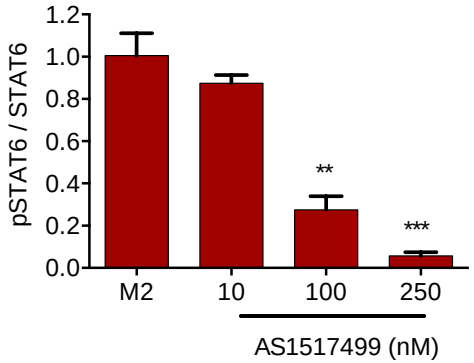
Targeting STAT6 inhibitor to M2-TAMs

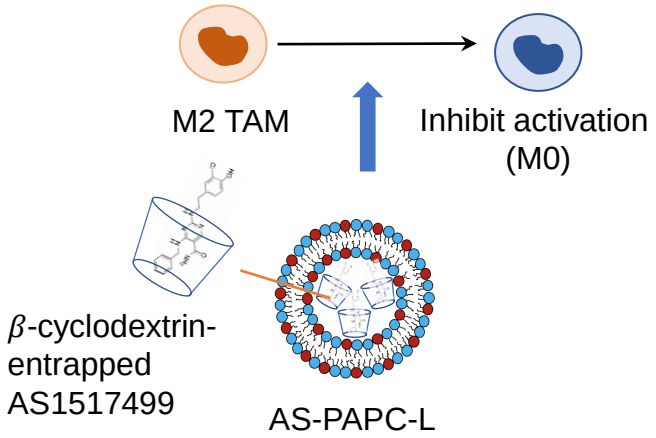




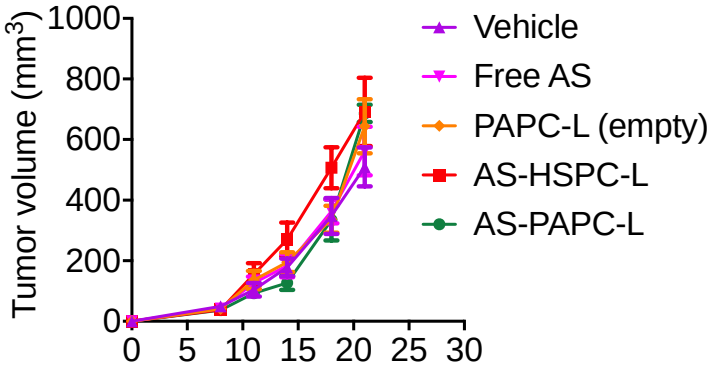




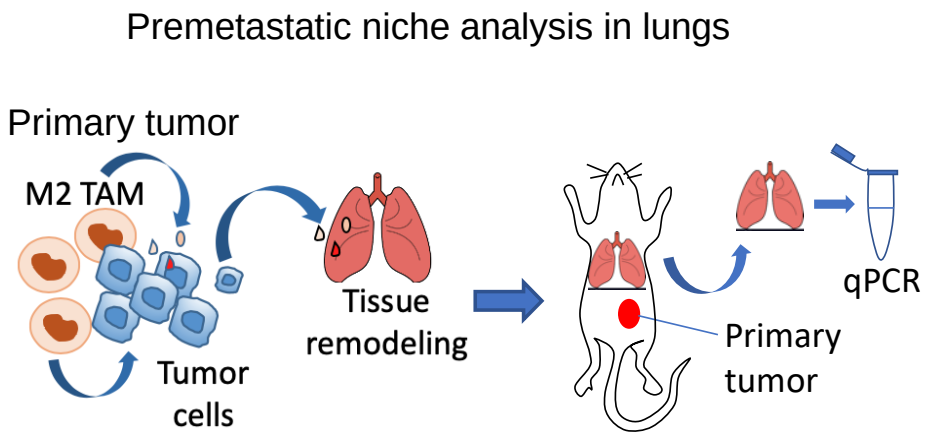
Binnemars-Postma….Prakash, FASEB J 2017

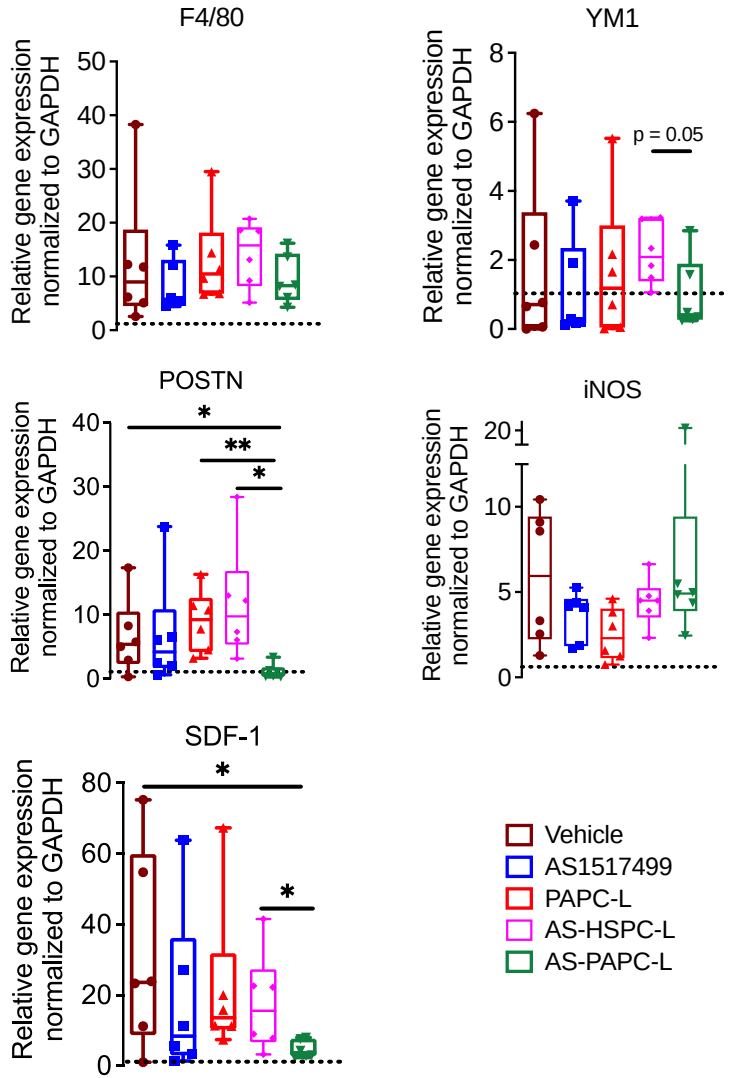


Nano-liposomes	Size (nm)	PDI	% EE
AS-HSPC-L	118	0.09	29%
AS-PAPC-L	115	0.15	46%



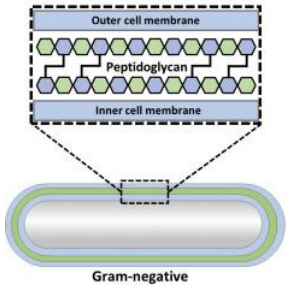
AS-PAPC-L inhibited premetastatic niche formation in lungs

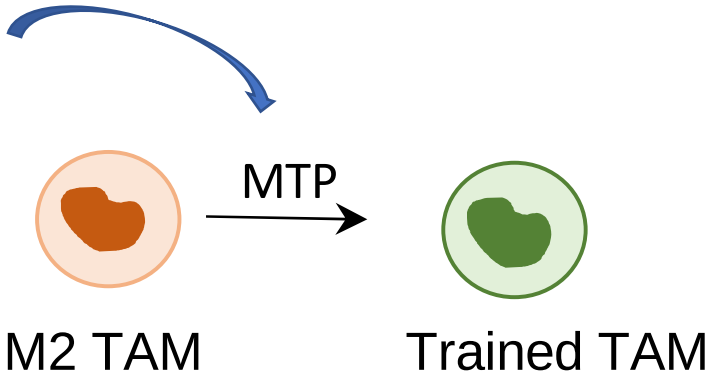


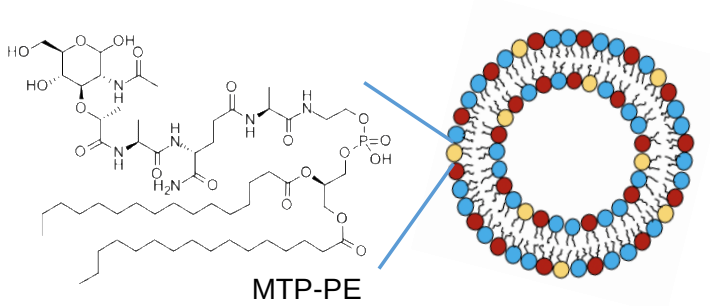


Kuninty, Binnemars-Postma, Nature Communications (accepted)

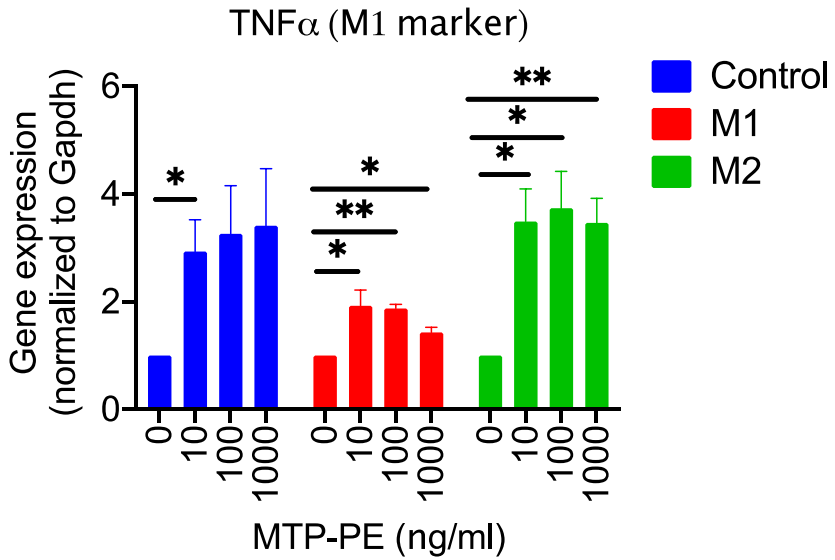
Targeting of muramyl tripeptide (MTP) using PAPC-L

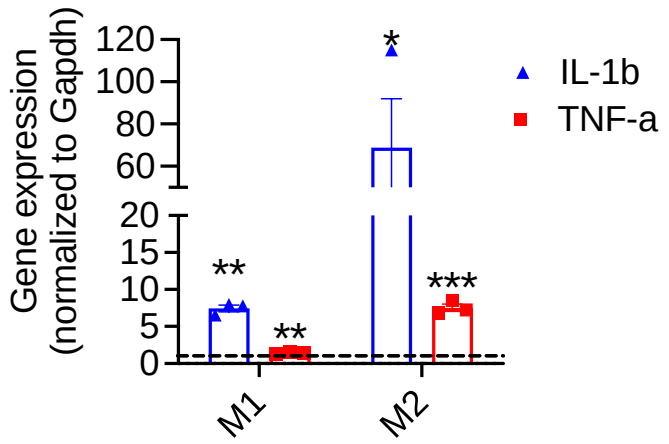




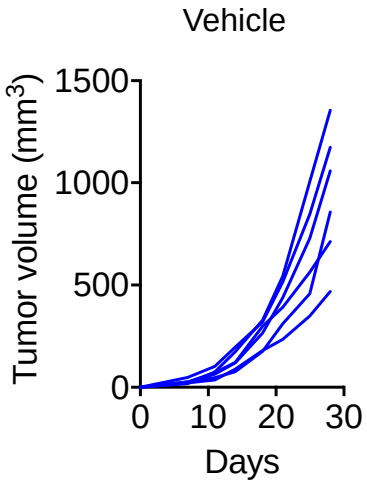


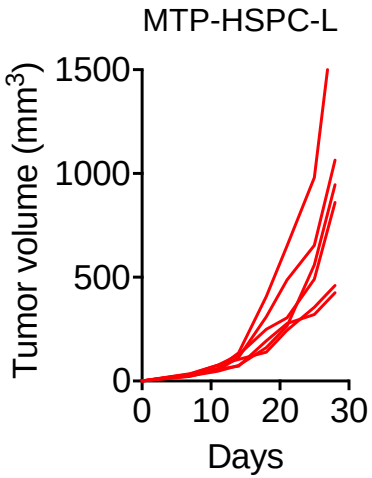
MTP-PAPC-L

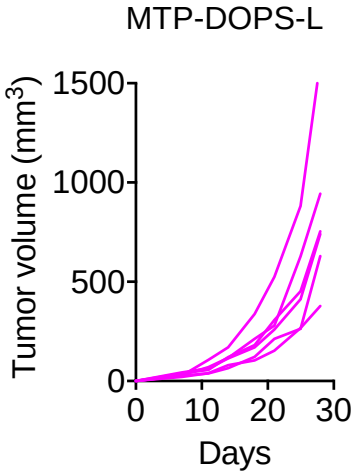


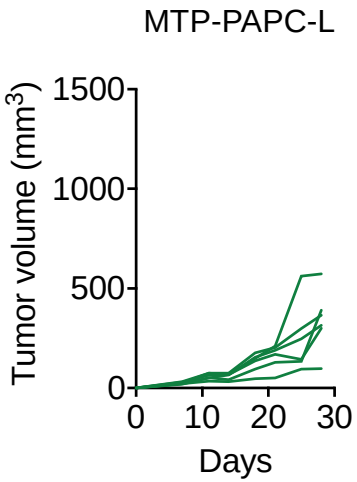


Targeting of MTP to M2-TAMs reduces tumor growth



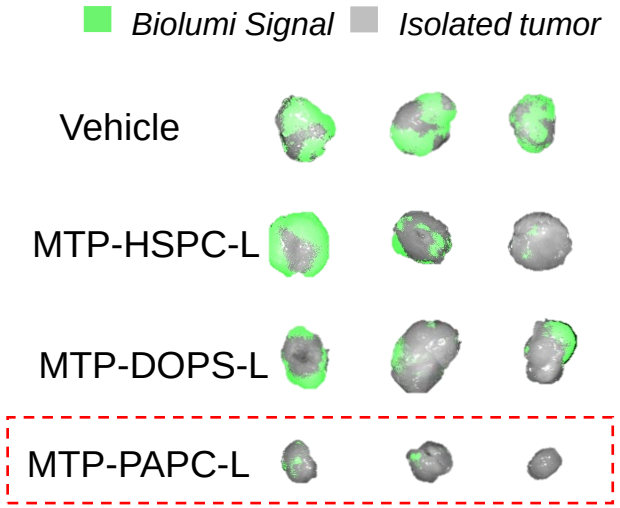


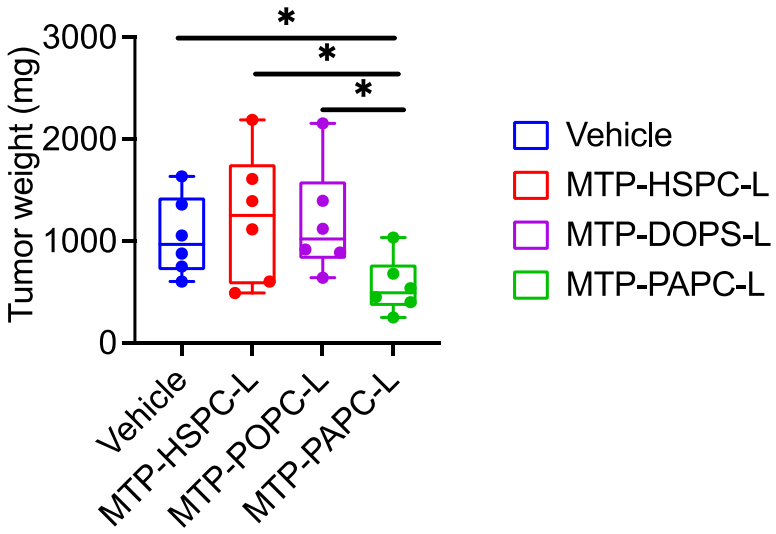




~70% tumor reduction

4T1 orthotopic tumor model
i.v. twice a week





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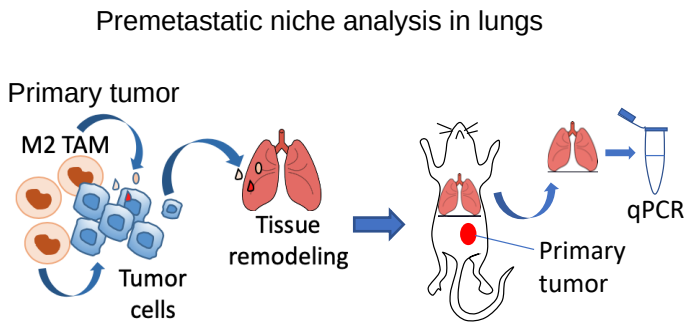
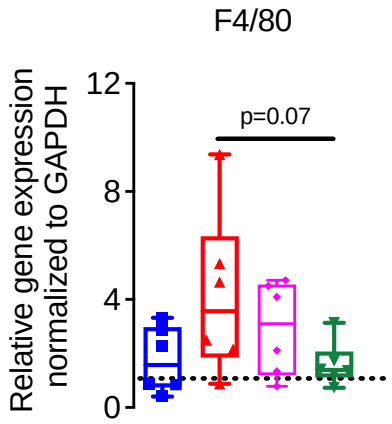
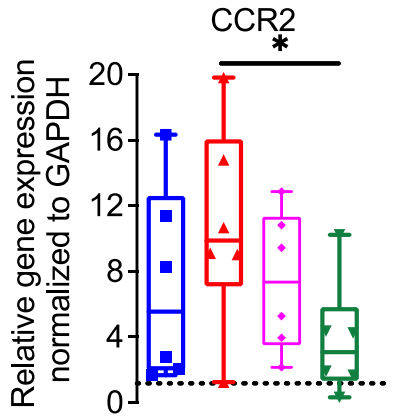
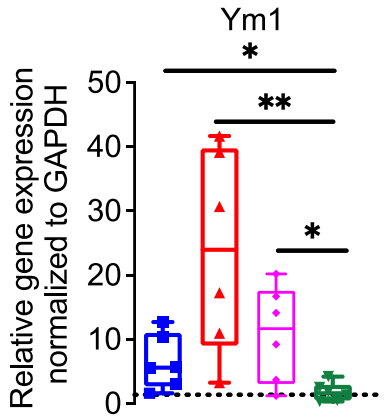
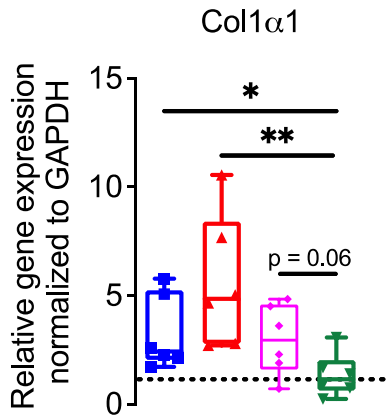
MTP-PAPC-L inhibit pre-metastatic niche formation in lungs

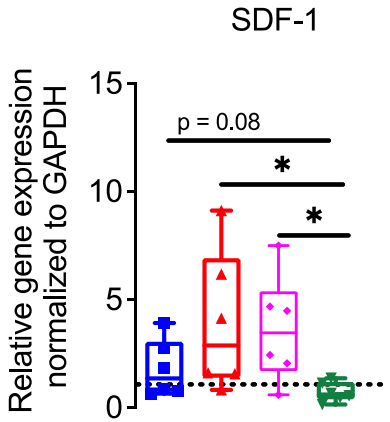


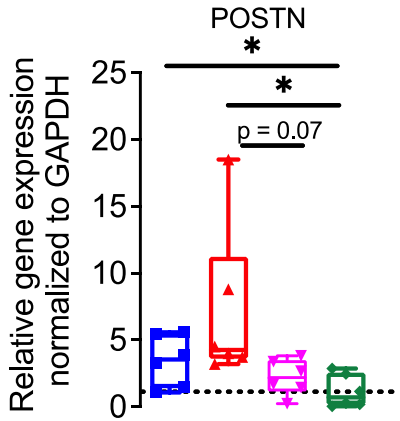


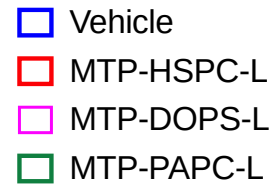












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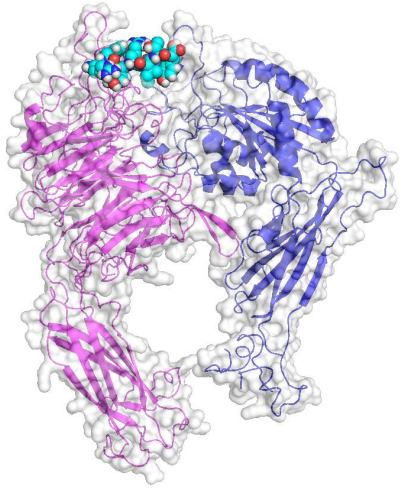
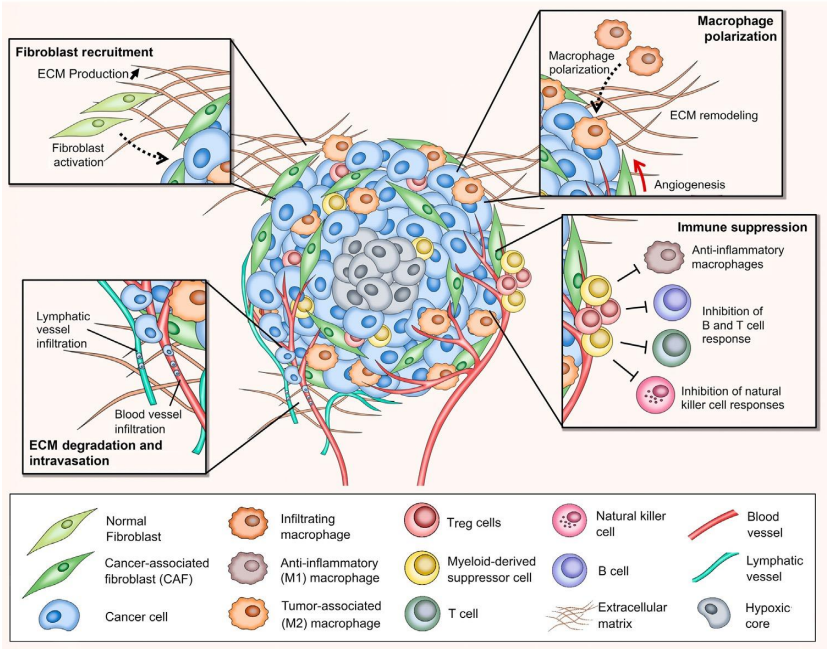
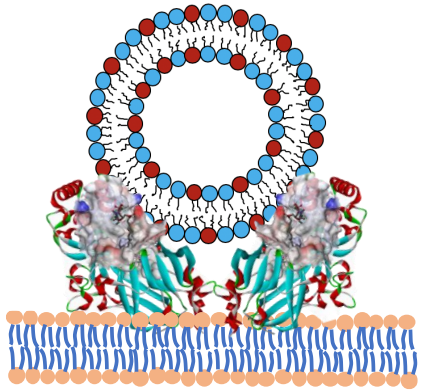
Conclusion

Engineering fibrotic microenvironment





Engineering Immune microenvironment



- The TME is highly heterogeneous and dynamic – “One does not fit all”
- Both fibrotic and immune components need to be targeted to achieve the best effects
- Combination with potent chemo-/immuno-therapeutics

Acknowledgements

Praneeth Kuninty

Karin Postma

Collaborations

- Arne Östman (Karolinska Institutet, Sweden)
- Gert Storm (Utrecht University)
- Wim Hennink (Utrecht University)
- Kees Sier, Alex Vahrmeijer (LUMC, Netherlands)
- Jen Morton (Cancer Research UK)
- Hanneke van Laarhoven and Maarten Bijlsma (AMC)
- Peter van Hoogevest (Phospholipid research centre)
- Wouter den Otter and Ahmed Jarray (UT)
- Yu Shrike Zhang – (Harvard/Brigham, US)
- Miles Miller – (MGH/Harvard Medical School)
- Peter Friedl – MD Anderson/ Radboud UMC
- Karthik Jain (University of Twente)
- Joop van Baarlen (LabPON, Netherlands)
- Twan Lammers (RWTH, Aachen)

Vetenskapsrådet

MARIE CURIE ACTIONS

MIRA BIOMEDICAL TECHNOLOGY AND TECHNICAL MEDICINE

lpdp lembaga pengelola dana pendidikan

Phospholipid Forschungszentrum / Research Center Heidelberg

STW

NIERSTICHTING Leven gaat voor

KWF KANKER BESTRIJDING

htsm HIGH TECH SYSTEMS & MATERIALS NORTHERN NETHERLANDS

NWO Nederlandse Organisatie voor Wetenschappelijk Onderzoek

ScarTec Therapeutics

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