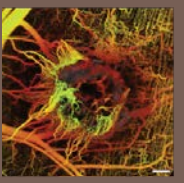


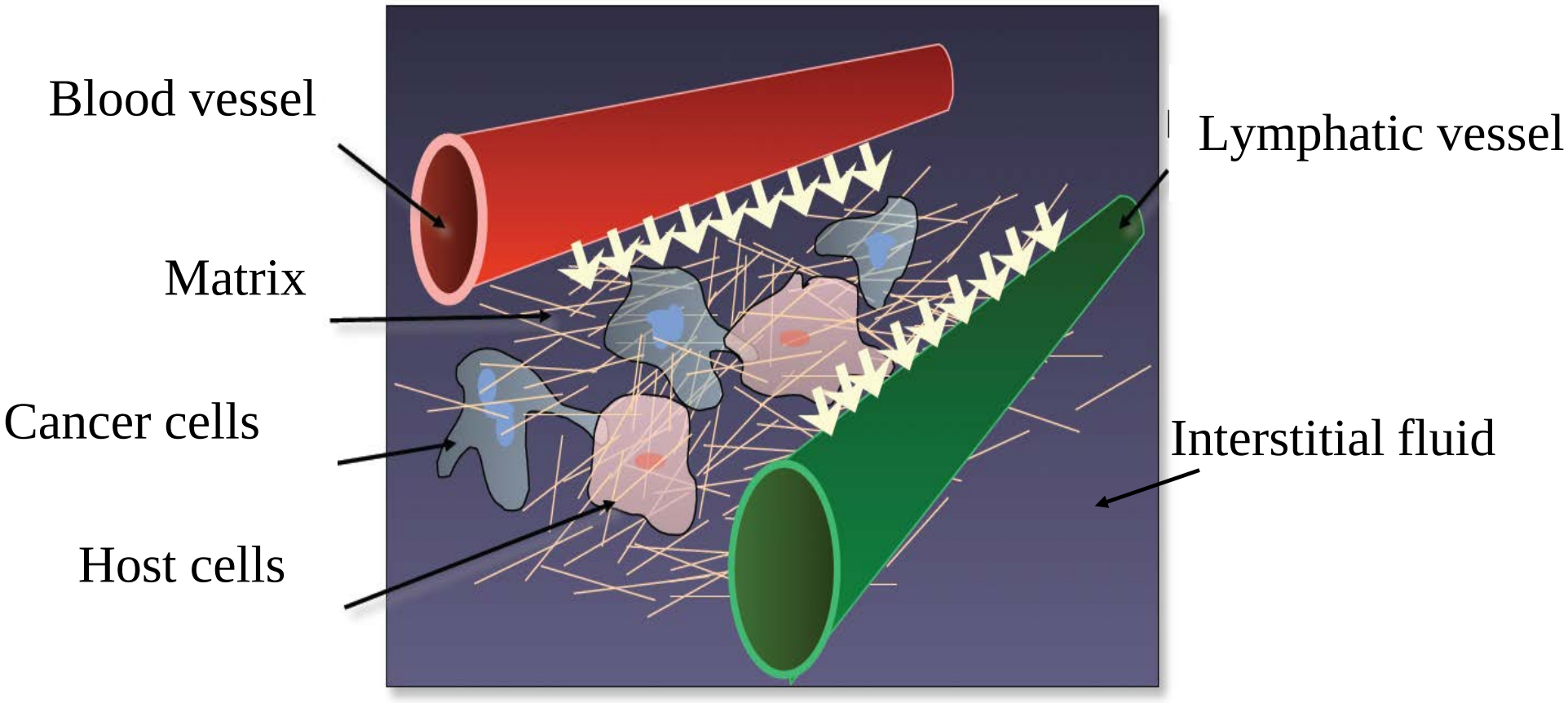
Cancer Biophysics Laboratory

University of Cyprus

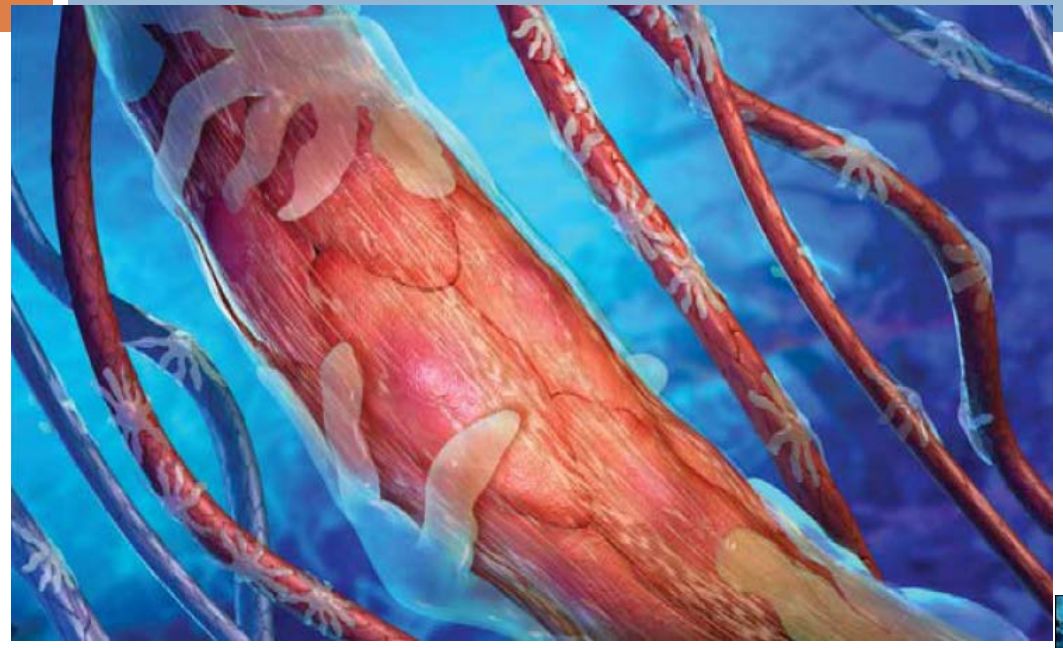
TGF-B INHIBITION COMBINED WITH CYTOTOXIC NANOMEDICINE NORMALIZES THE TUMOR MICROENVIRONMENT AND IMPROVES IMMUNE CHECKPOINT INHIBITION THERAPY

Triantafyllos Stylianopoulos, Ph.D.

The tumor micro-environment

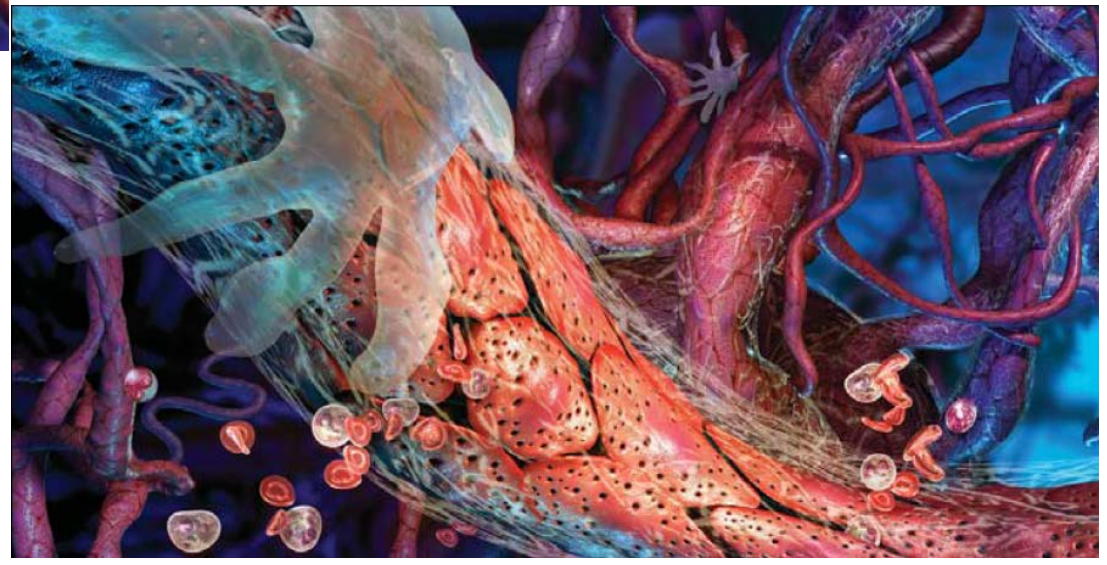


Leakiness of tumor vessels



Tumor vessels can be leaky (hyper-permeable) which is the basis of the EPR effect and the rational for the use of nanotechnology to treat cancer.

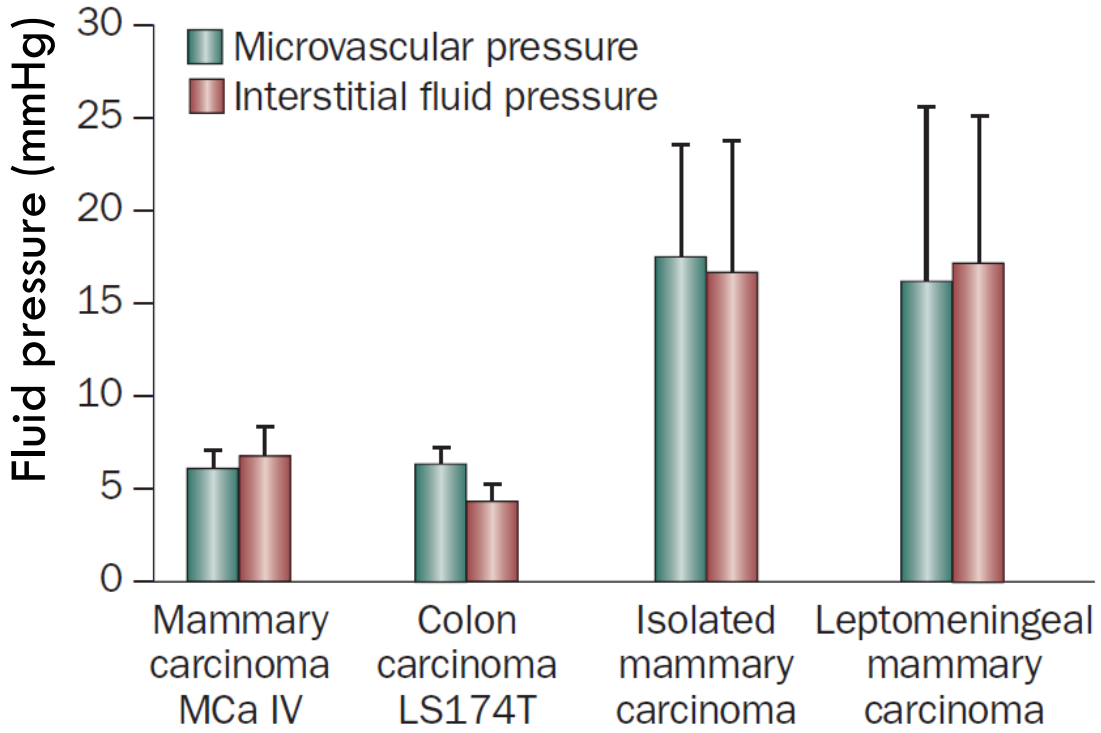
Normal vessels
(pore size: 7-12 nm)

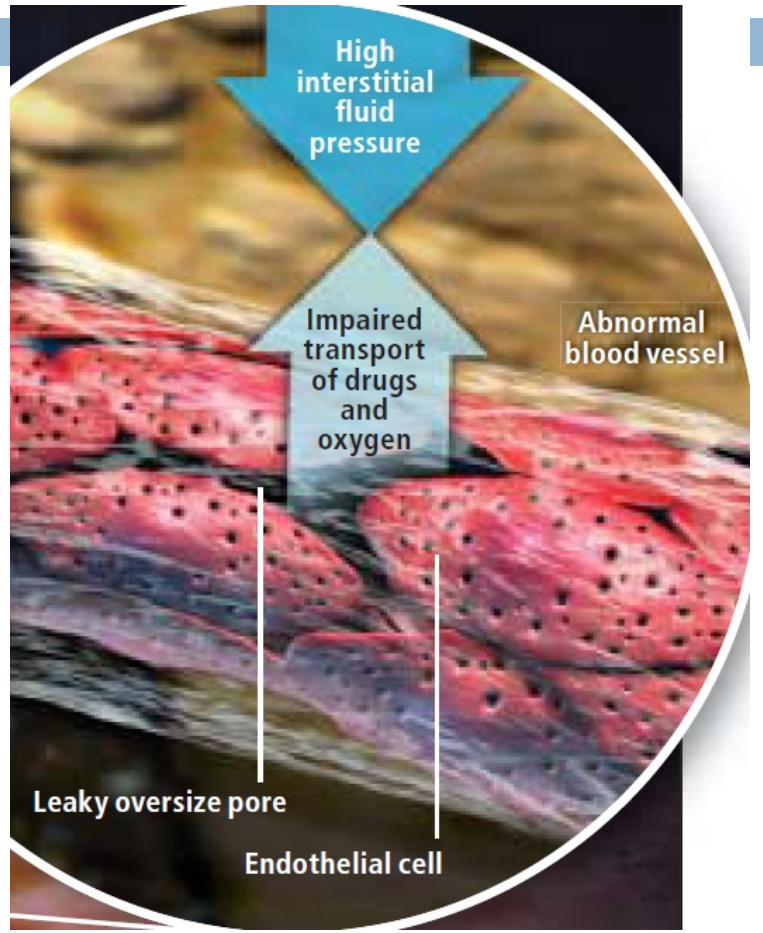


Tumor vessels
(pore size: 10 nm – 2 μm)

(Jain R. K., Scientific American, 2008)

Interstitial hypertension

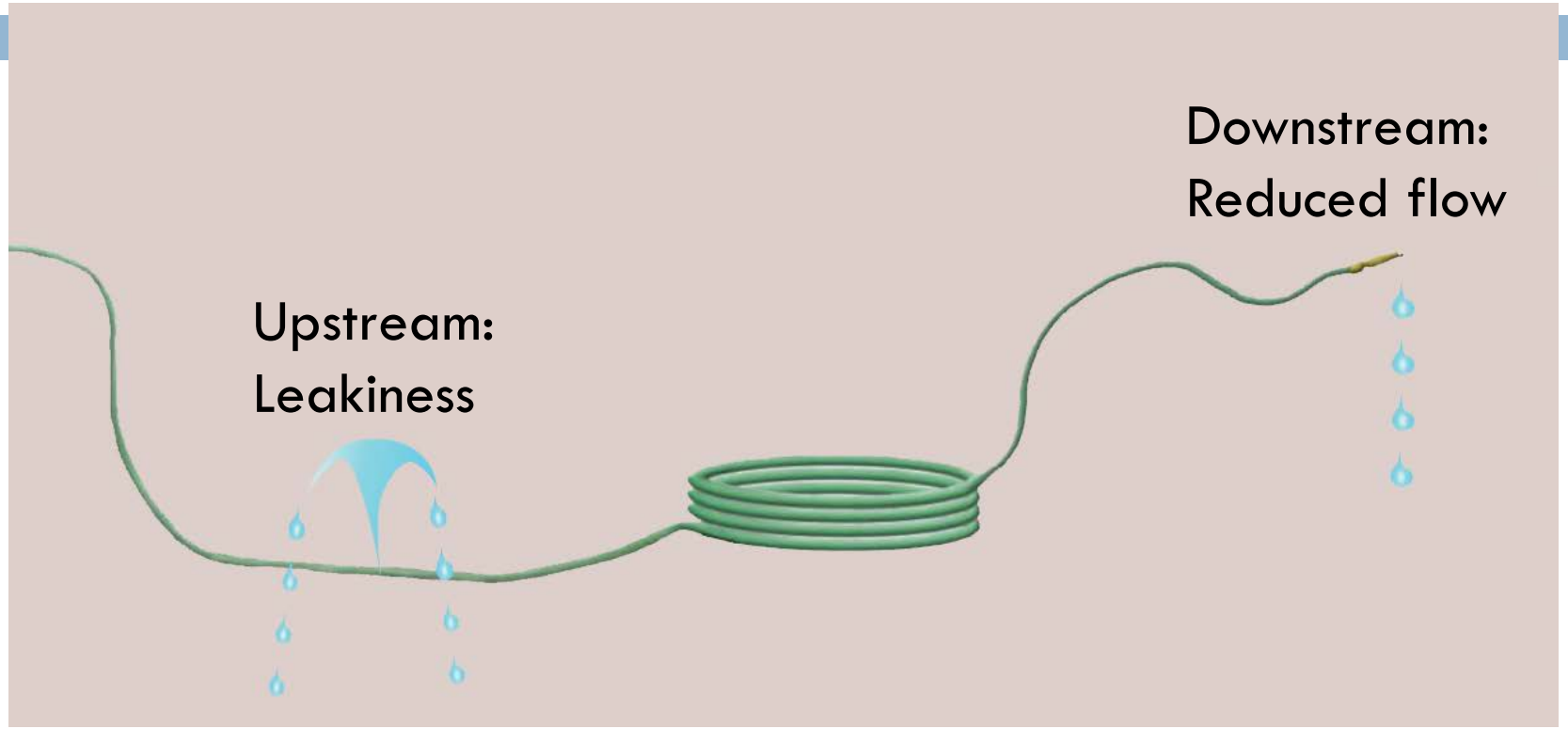




- Leakiness of tumor vessels, however, increases fluid flux to the tumor interstitial space causing alleviation of the Interstitial Fluid Pressure that resist nanoparticle transport across the vessel wall.

(Jain R. K. and Stylianopoulos T, Nature Reviews Clinical Oncology, 2010)

Hypo-perfusion



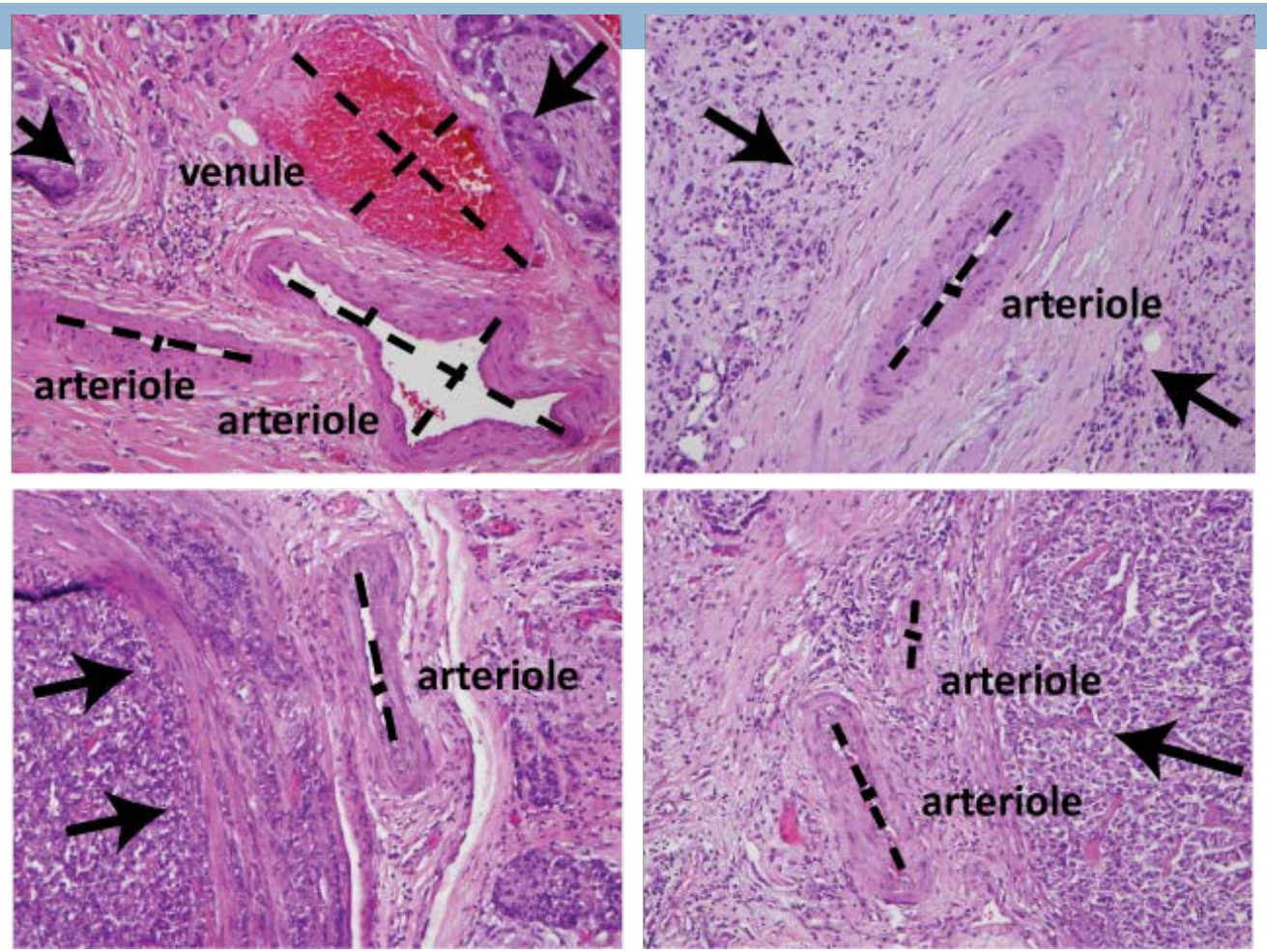
➢Excessive fluid loss from the vascular to the interstitial space also reduces blood velocity: Hypo-perfusion.

➢ Hypo-perfusion creates hypoxia and compromises immune response, drug delivery and radio-therapy.

Compression of tumor vessels

- Rapid tumor growth within the confined space of the host tissue results in the accumulation of mechanical forces that compress intratumoral blood vessels. In the picture arrows show the position of cancer cells that compress the vessels.

- Vessel leakiness and compression are two abnormalities of the tumor micro-environment that reduce drastically perfusion.

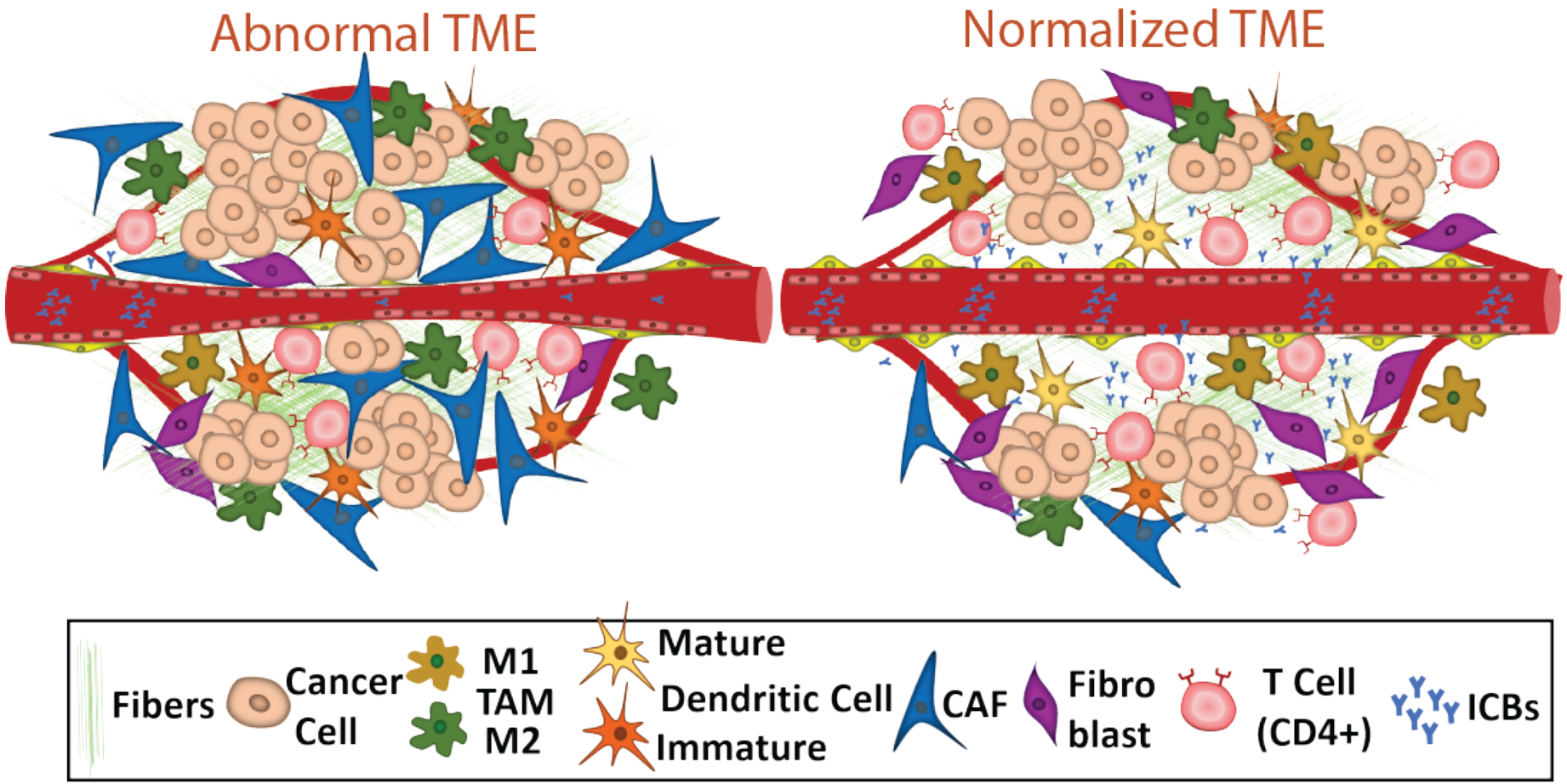


Vessel compression reduces perfusion

(Stylianopoulos T et al., Cancer Research, 2013)

Re-engineering Cancer

ReEngineeringCancer



- Re-engineering the tumor microenvironment (TME) to reduce vessel leaking and open compressed vessels has the potential to improve perfusion, oxygenation and drug delivery.

(Stylianopoulos et. al., Nature Reviews Clinical Oncology, 2020)

Mechano-Therapeutics

ReEngineeringCancer

European Research Council
Established by the European Commission

- Tranilast (Rizaben, Kissei Pharmaceuticals)
- Approved in Japan and S. Korea as an anti-fibrotic and anti-allergic drug.

(P. Papageorgis et al., Scientific Reports, 2017, Panagi M. et al., Theranostics, 2020)

- Pirfenidone (Esbriet, Roche Pharmaceuticals)
- Approved worldwide for idiopathic pulmonary fibrosis

(C. Polydorou et al., Oncotarget, 2017)

- Dexamethasone
- Common corticosteroid drug with anti-allergic, anti-inflammatory properties

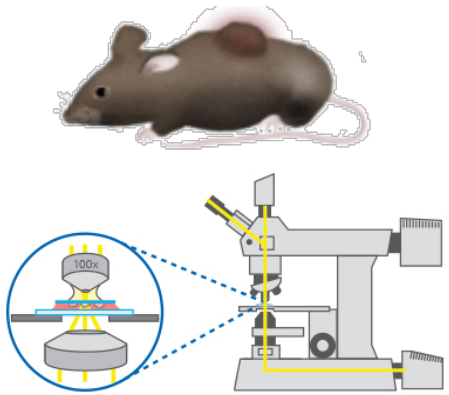
(J.D. Martin et al., ACS Nano, 2019)

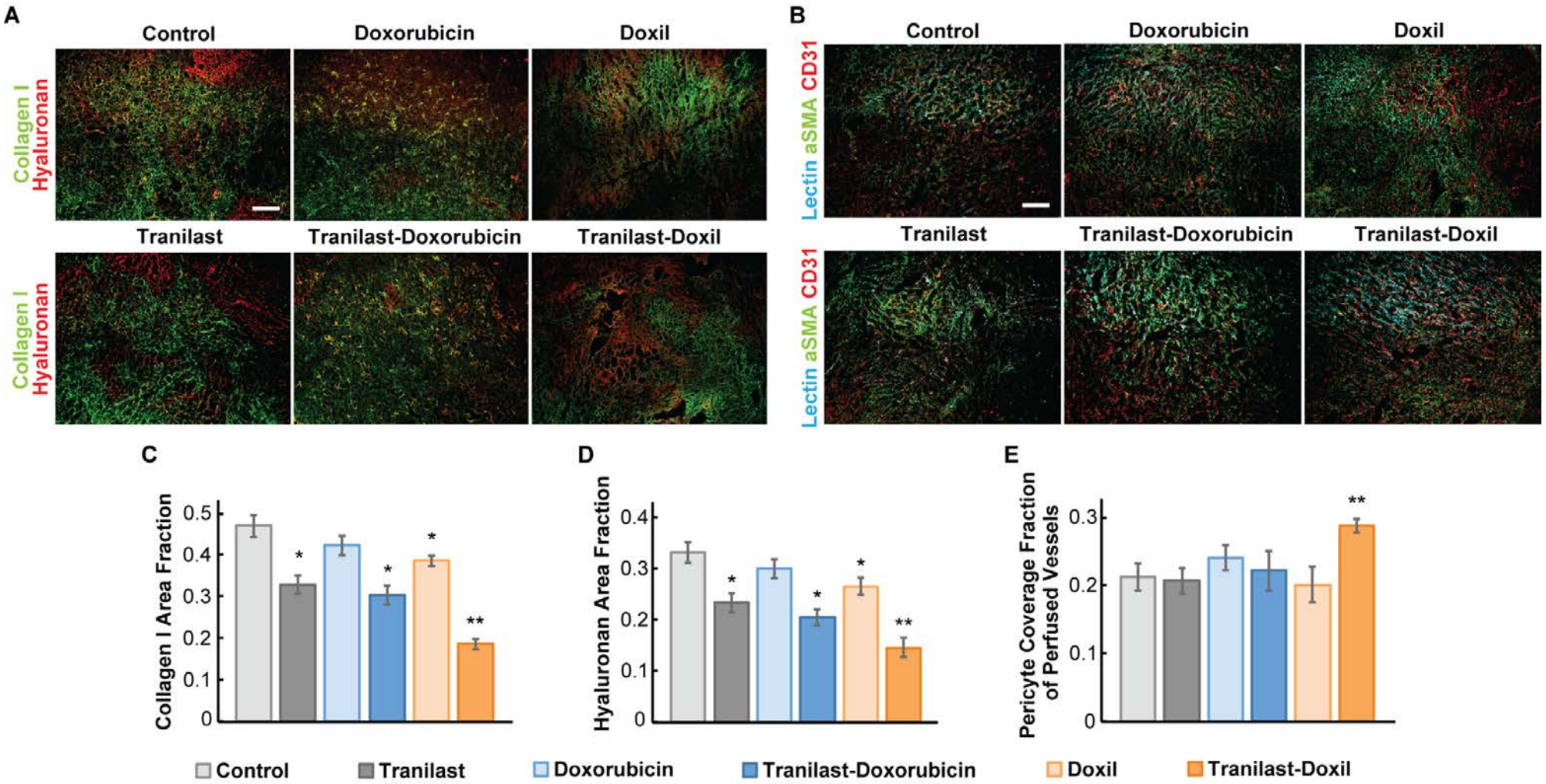
- Vismodegib (Erivedge, Genetech)
- Approved sonic hedgehog pathway inhibitor targeting tumor fibroblasts

(F. Mpekris et al., J. Controlled Release, 2017)

- Mechano-therapeutics are common drugs that we have re-purposed to target components of the tumor in order to re-engineer the tumor micro-environment.

In vivo studies: Tranilast+Doxil combination reduces extracellular fiber levels and increases pericyte coverage of the vessel wall.



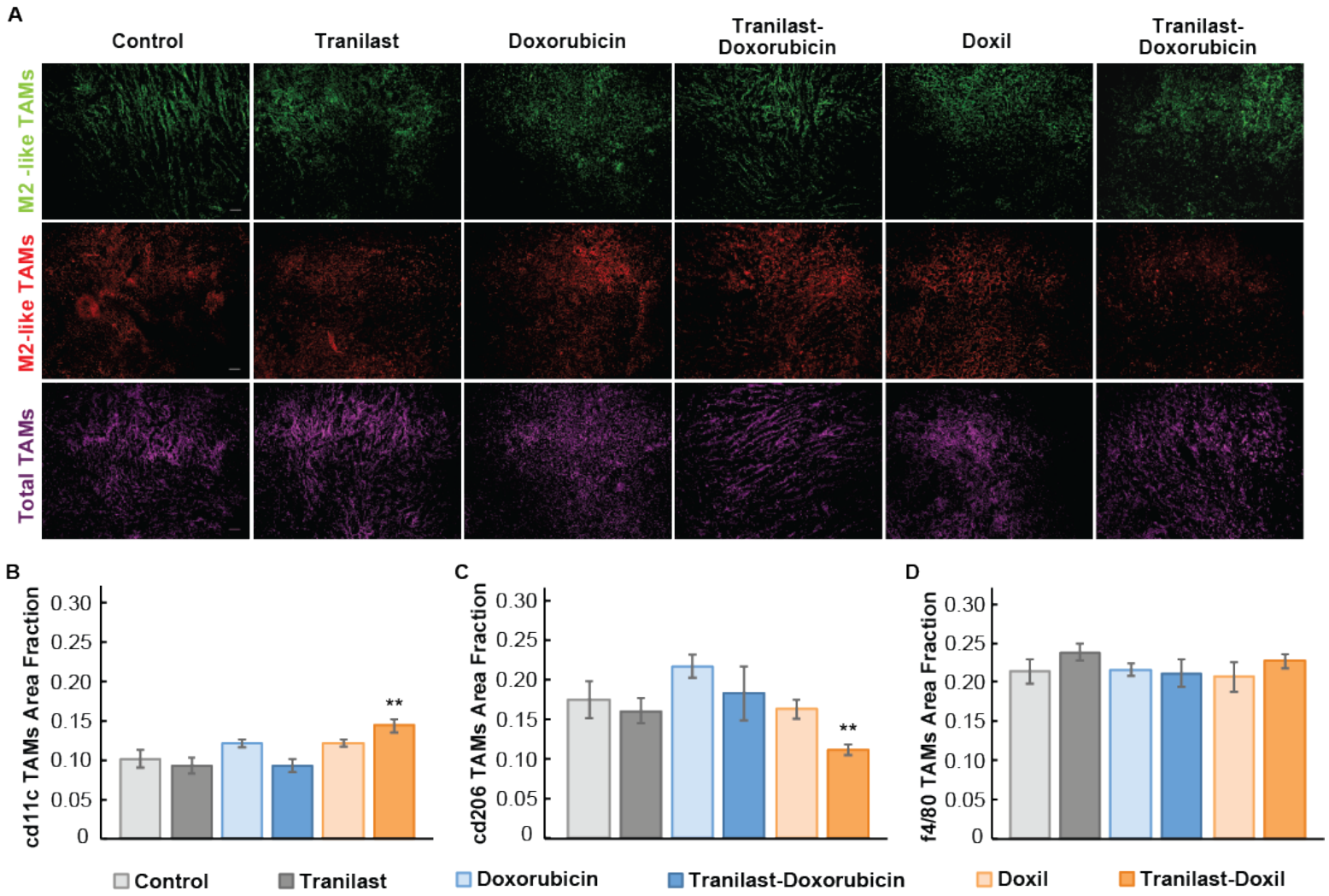


(P. Papageorgis, Scientific Reports, 2017)

Tranilast-Doxil enhanced macrophages polarization to M1 phenotype

Tumor Associated Macrophages (TAMs)

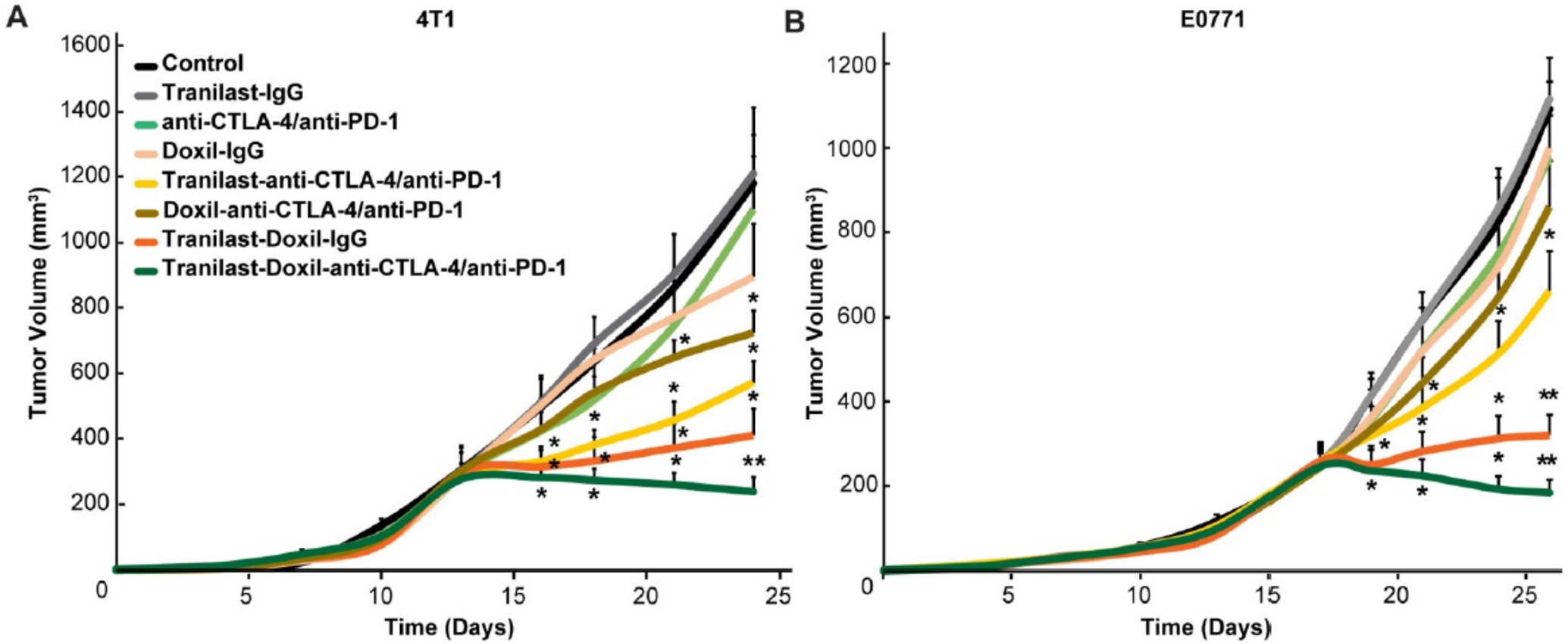
- Increase in immuno-supportive M1-like TAMs
- Decrease in immuno-suppressive M2-like TAMs
- Both in primary breast tumors and lung metastases



(Mpekris F. et al., *Advanced Science*, 2020, Panagi M. et al., Theranostics, 2020)

Mechano-therapeutics improve Nano-immunotherapy efficacy

Tumor growth delay study of tranilast combined with Doxil and Immune Checkpoint Blockade.



(Mpekris F. et al., *Advanced Science*, 2020, Panagi M. et al., Theranostics, 2020)

Pertinent Publications

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2020; 10(4): 1910-1922. doi: 10.7150/thno.36936

Research Paper

TGF-β inhibition combined with cytotoxic nanomedicine normalizes triple negative breast cancer microenvironment towards anti-tumor immunity

"Normalizing the Microenvironment Overcomes Vessel Compression and Resistance to Nano-immunotherapy in Breast Cancer Lung Metastasis" *Advanced Science*, In press.

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Tranilast-induced stress alleviation in solid tumors improves the efficacy of chemo- and nanotherapeutics in a size-independent manner

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2017

Pirfenidone normalizes the tumor microenvironment to improve chemotherapy

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Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Sonic-hedgehog pathway inhibition normalizes desmoplastic tumor microenvironment to improve chemo- and nanotherapy

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ΔΙΑΡΘΡΩΤΙΚΑ ΤΑΜΕΙΑ
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