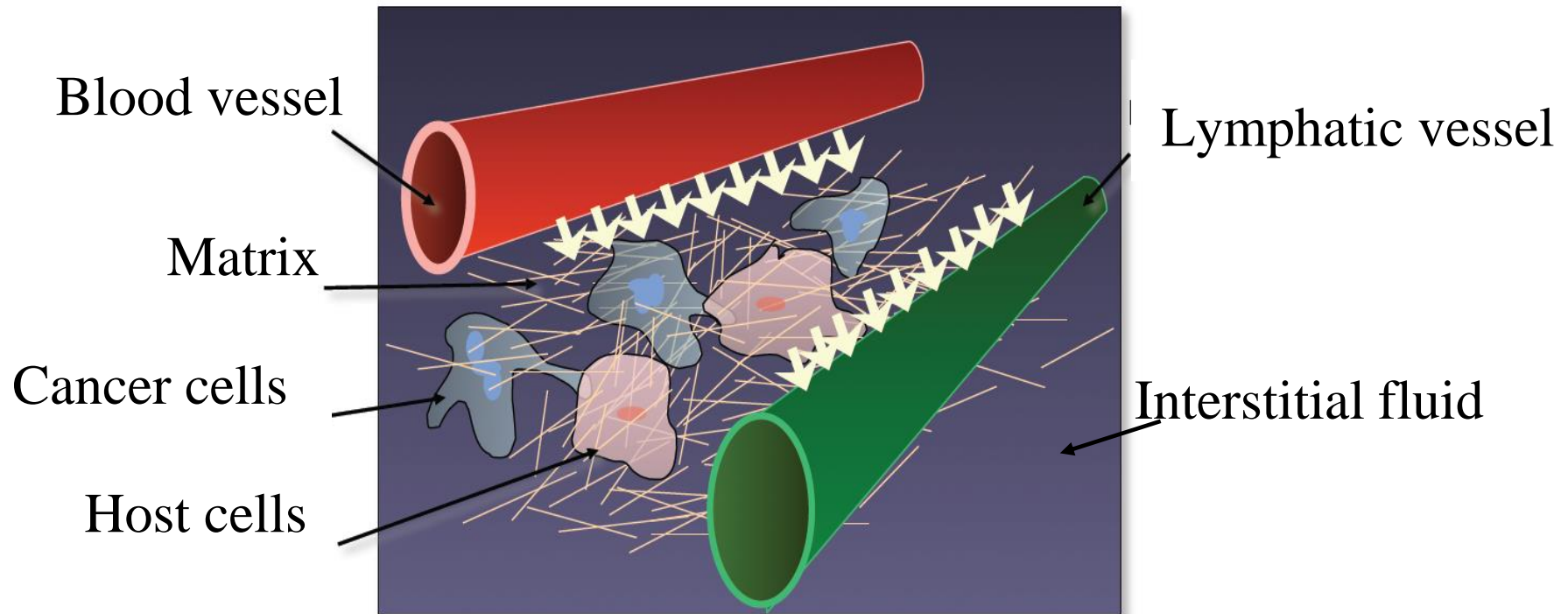


REPURPOSING COMMON ANTI-FIBROTIC DRUGS TO IMPROVE EFFICACY OF CANCER NANOMEDICINES

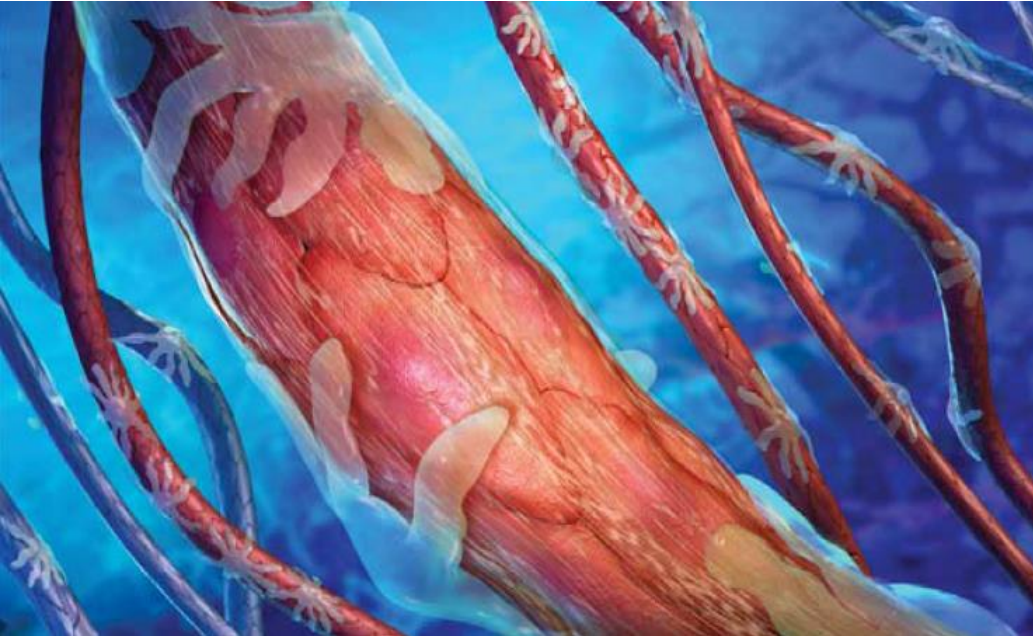
Triantafyllos Stylianopoulos, Ph.D.



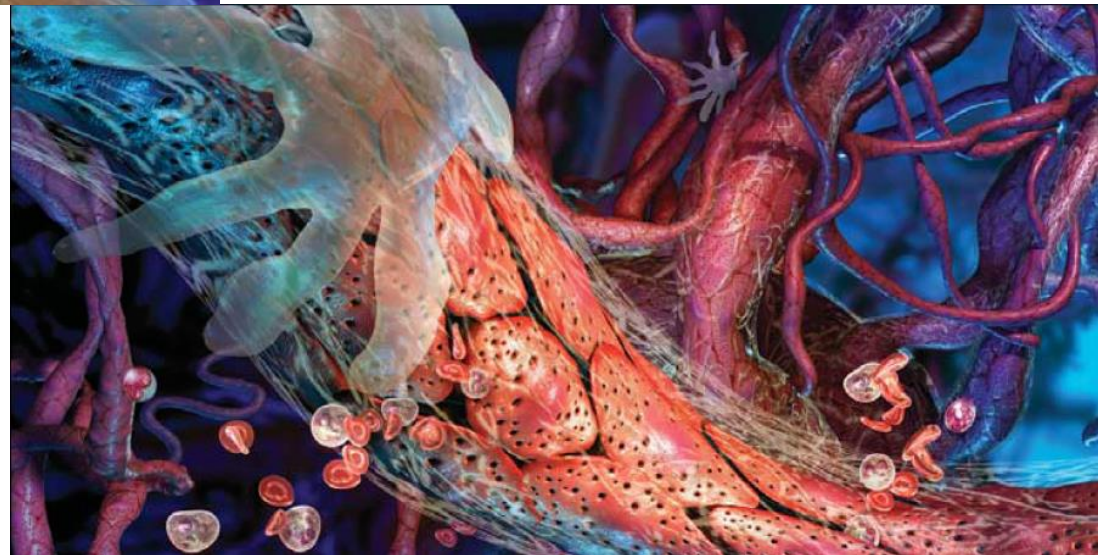
The tumor micro-environment



Leakiness of tumor vessels

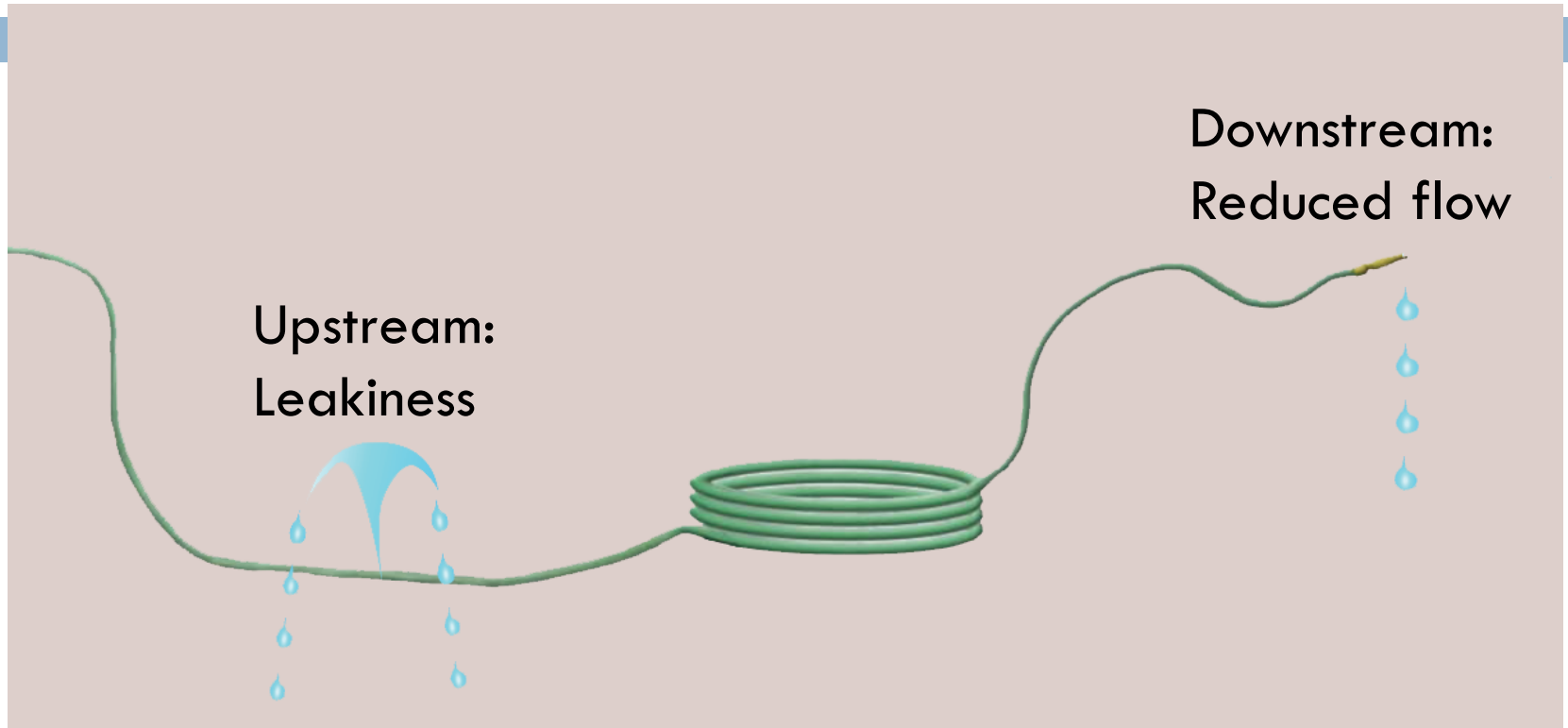


Normal vessels
(pore size: 7-12 nm)



Tumor vessels
(pore size: 10 nm – 2 μ m)

Hypo-perfusion



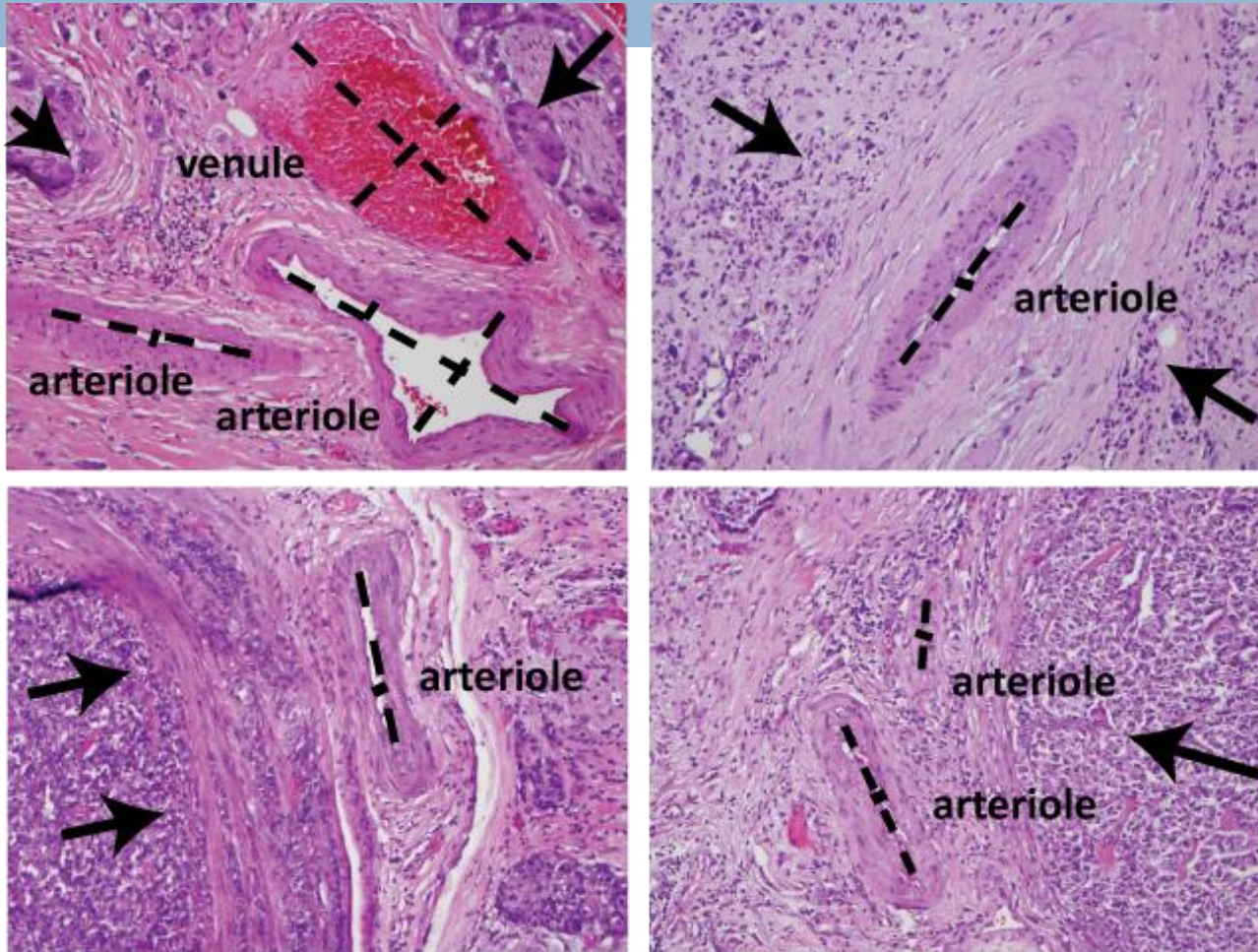
➤ Excessive fluid loss from the vascular to the interstitial space reduces blood velocity: Hypo-perfusion.

➤ Hypo-perfusion compromises drug delivery.

Generation of solid stresses/vessel compression



Compression of tumor vessels



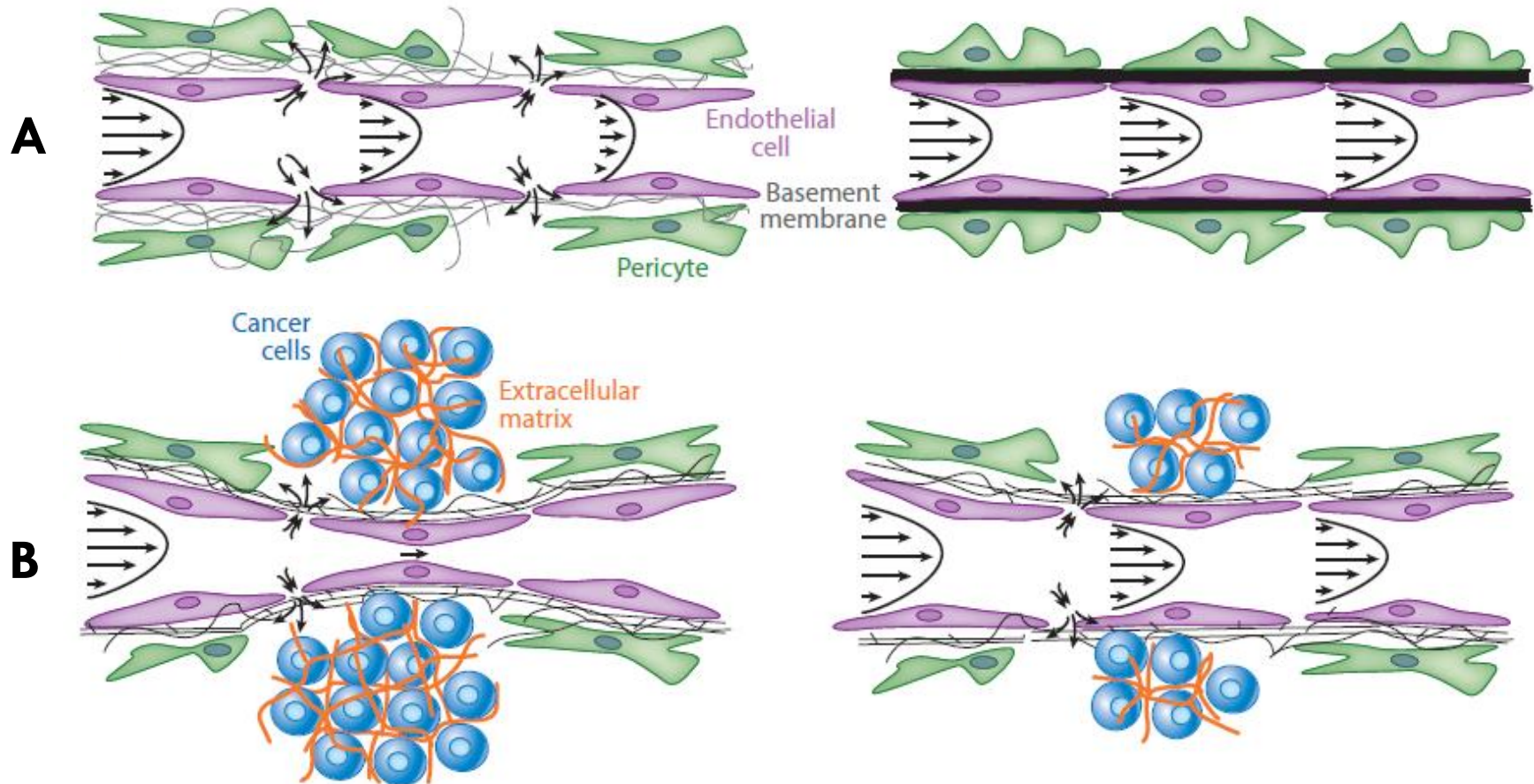
compression reduces perfusion

Heterogeneous Perfusion

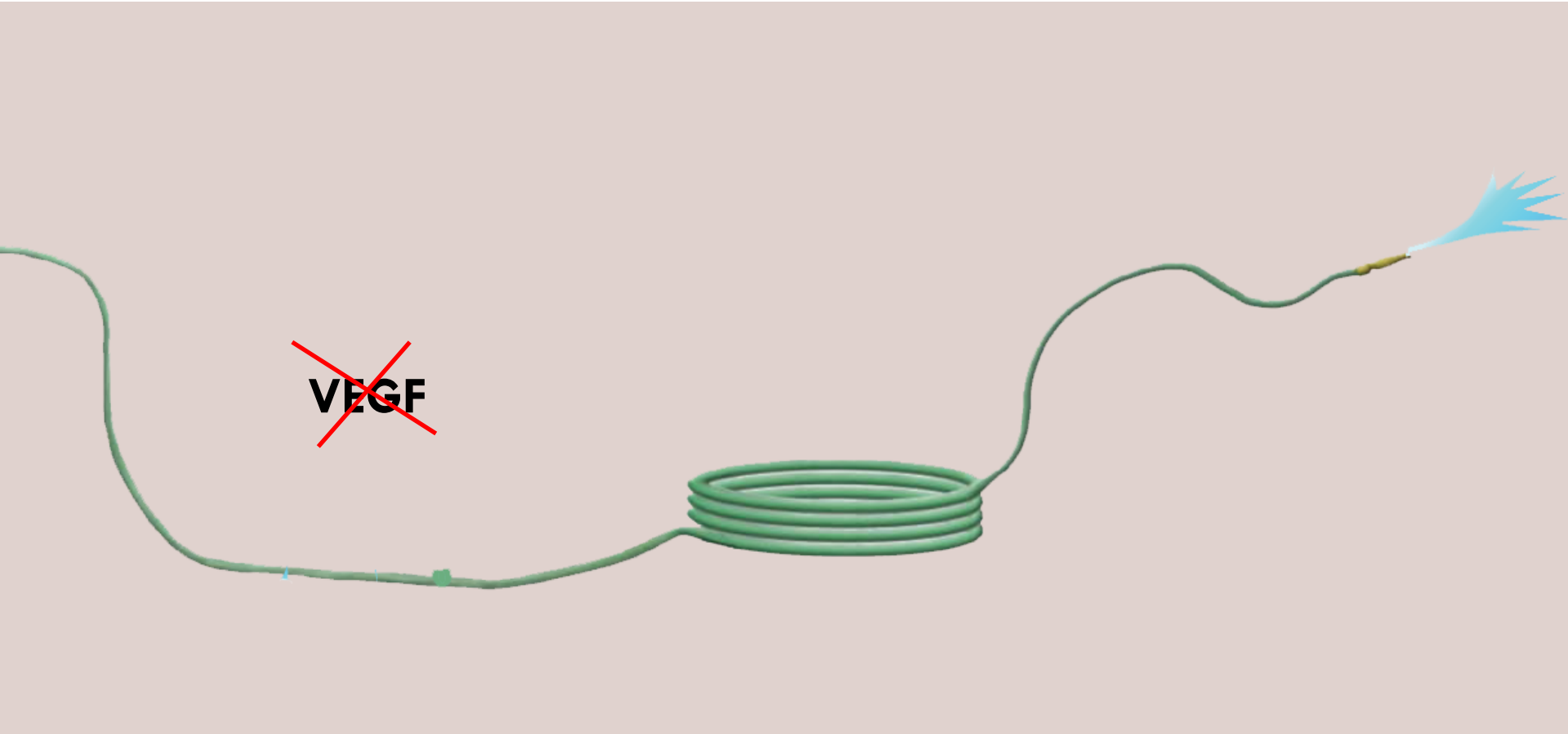


Strategies to enhance therapy

- 'Vascular normalization' – decrease vessel leakiness
- 'Stress Alleviation' – decompress tumor vessels



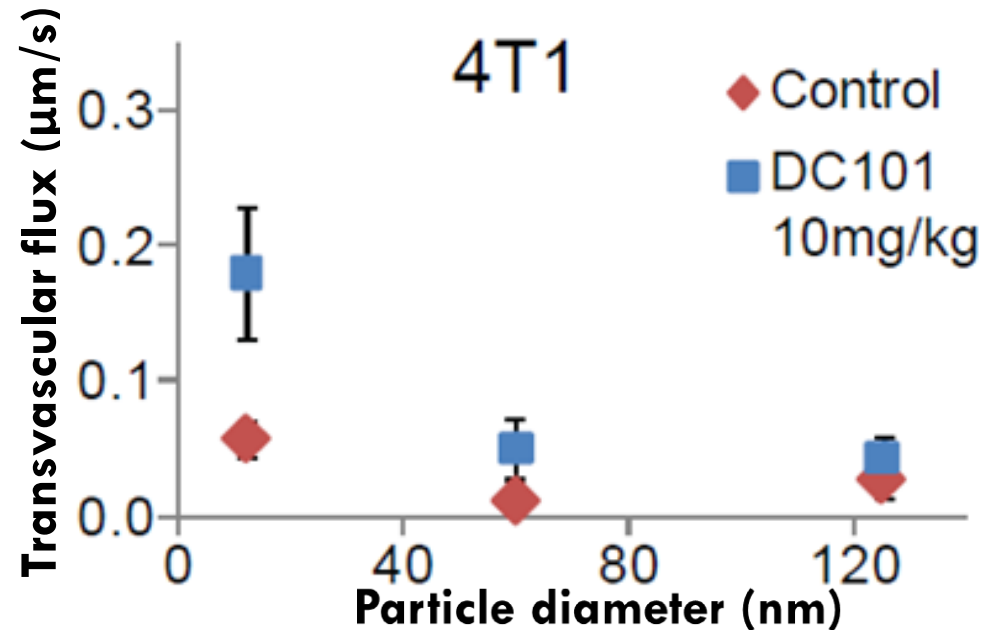
Vascular normalization



Vascular normalization and nanomedicine



- 4T1 mammary adenocarcinoma cells were implanted in the mammary fat of SCID mice.
- A solution of quantum dots (12, 60, 125 nm) was injected i.v. and their trans-vascular transport was measured with multi-photon microscopy.
- DC101 normalizes the tumor vessels.



➤ Vascular normalization improves the delivery of drugs in a size-dependent manner

Strategies to enhance therapy

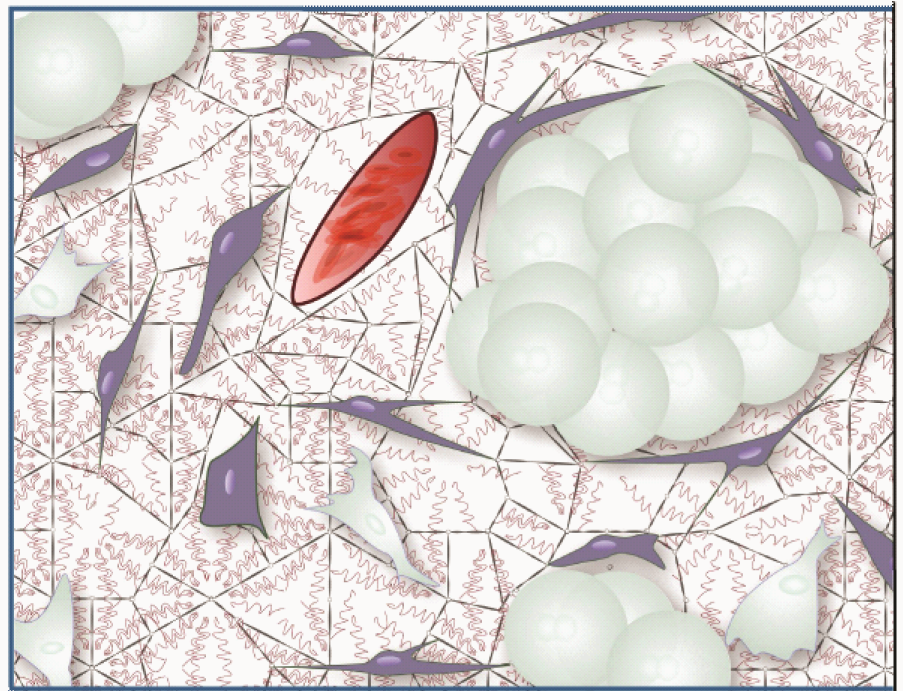
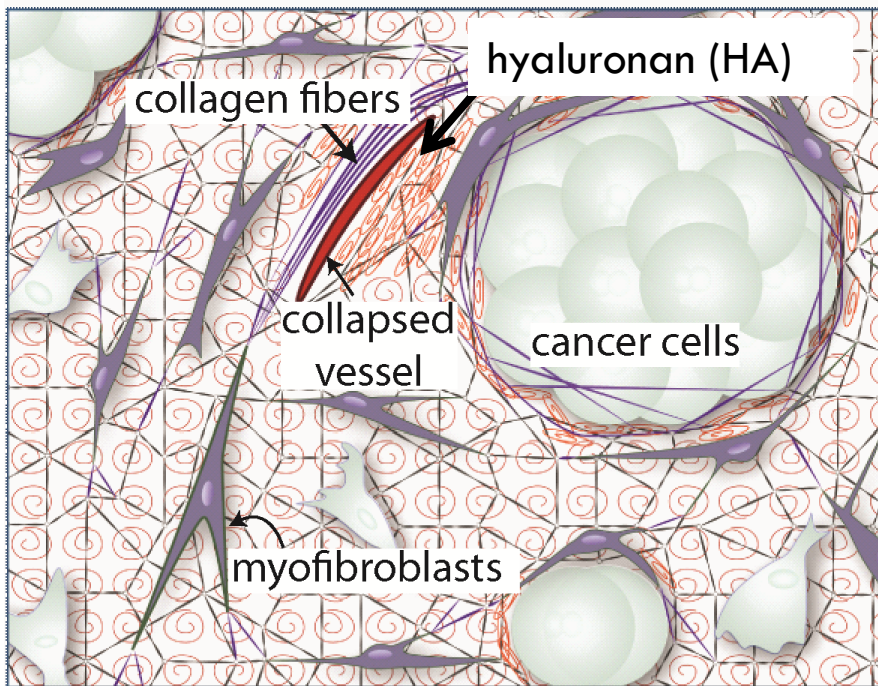
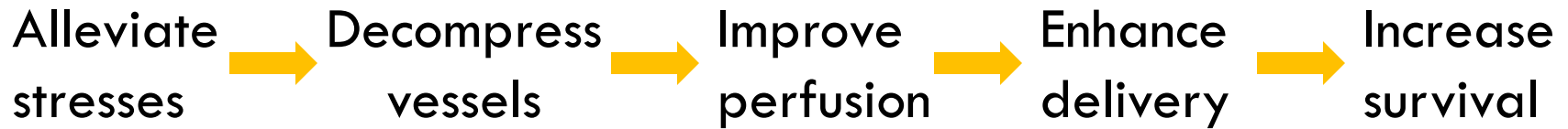


- 'Vascular normalization' – decrease in vessel leakiness

- **'Stress Alleviation' – decompression of tumor vessels**

Re-Engineering cancer

□ Proposed mechanism to optimize therapy:



Repurposing common anti-fibrotic drugs to alleviate intratumoral stresses



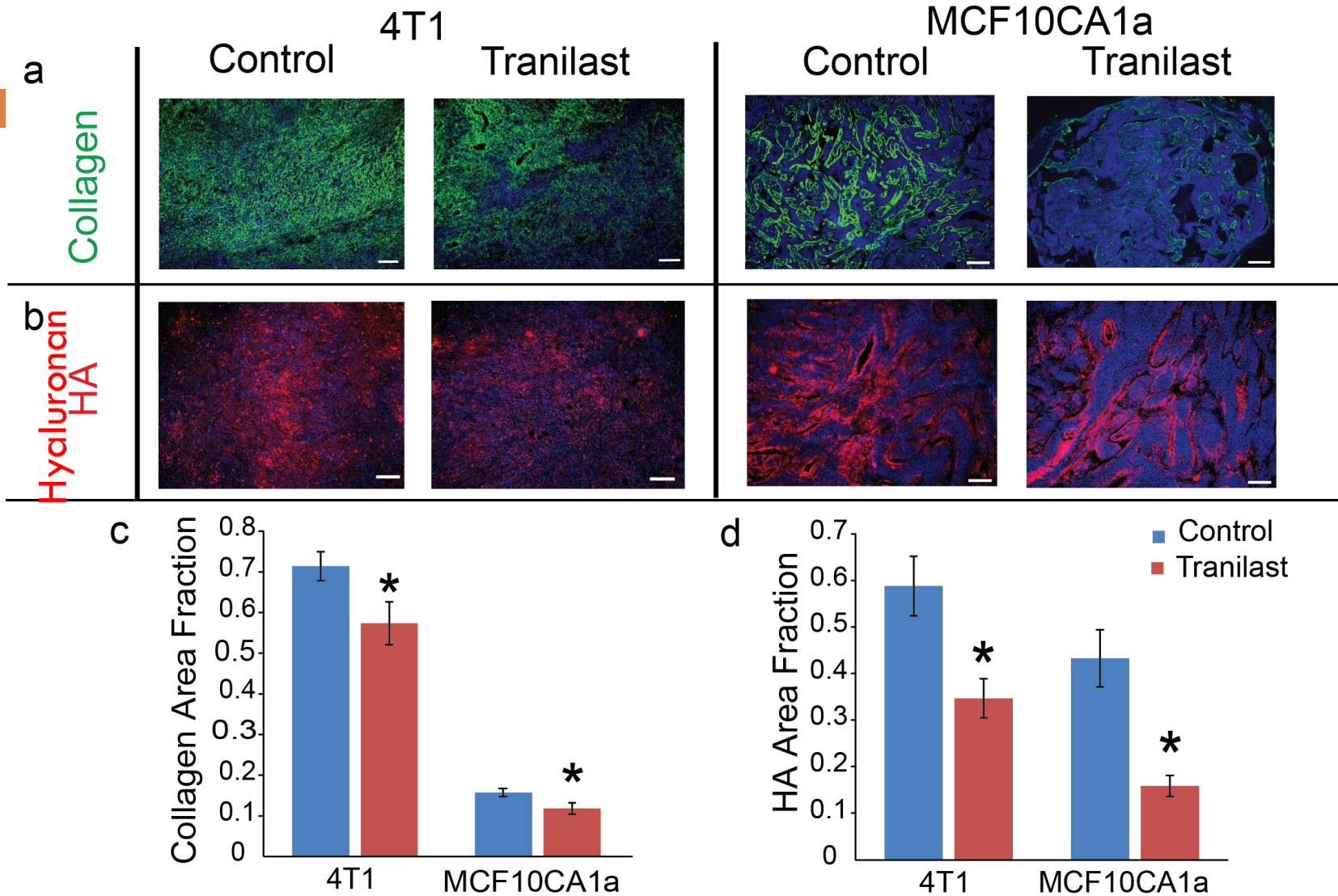
- Tranilast (Rizaben, Kissei Pharmaceuticals)
- Approved in Japan and S. Korea as an anti-fibrotic and anti-allergic drug.

(P. Papageorgis et al., Scientific Reports, 2017)

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

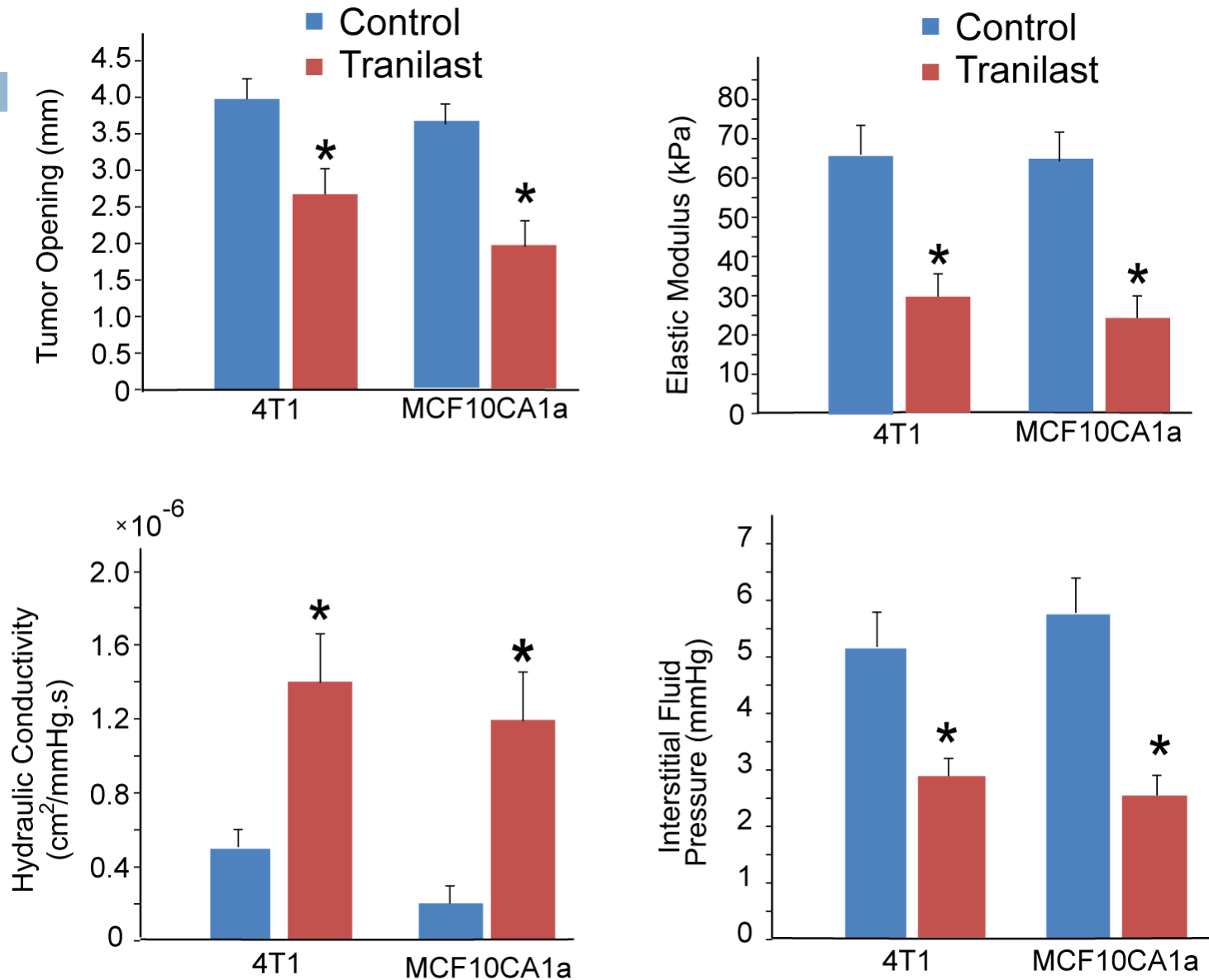
(C. Polydorou et al., Oncotarget, 2017)

Repurposing Tranilast (Rizaben, Kissei)

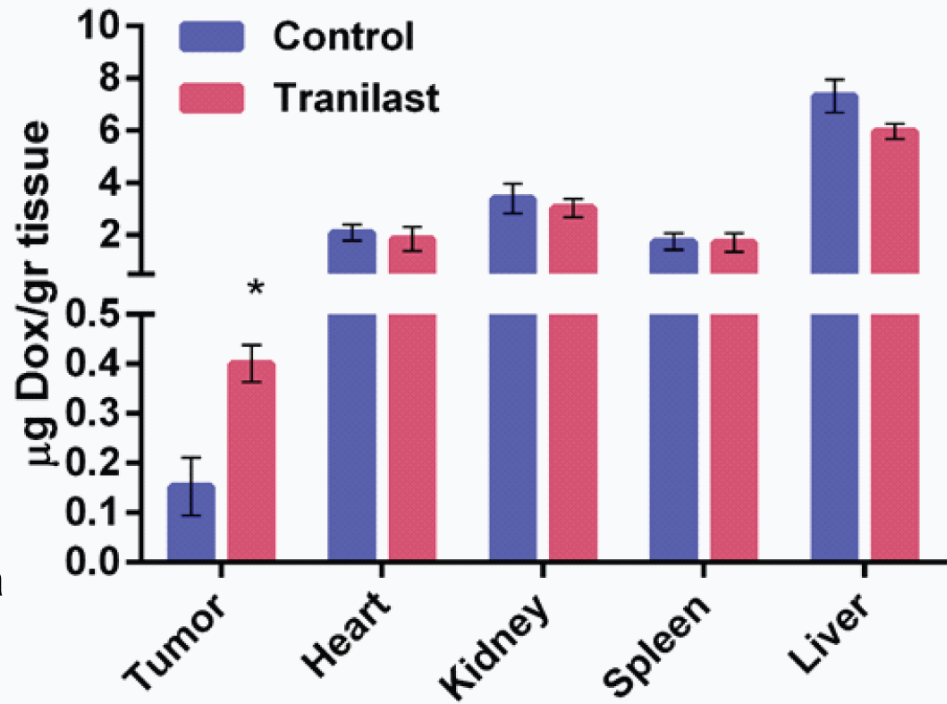
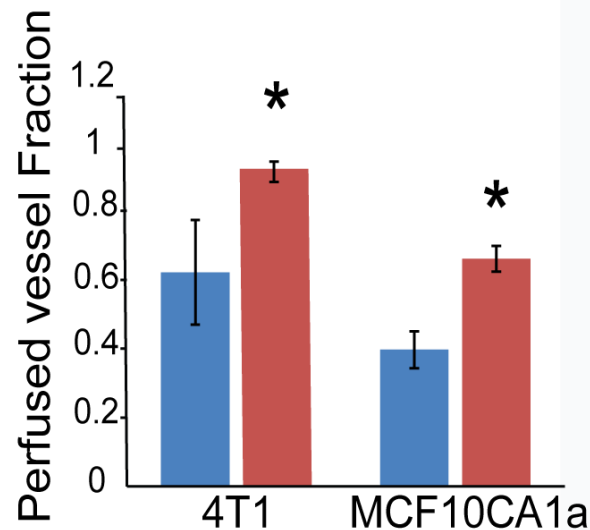


Tranilast reduces collagen and hyaluronan levels

Solid and fluid stress alleviation

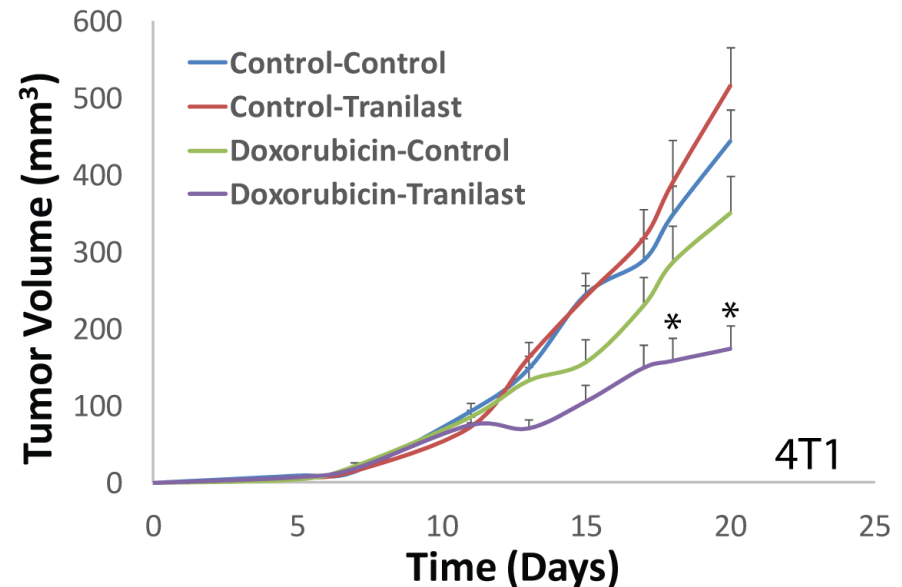
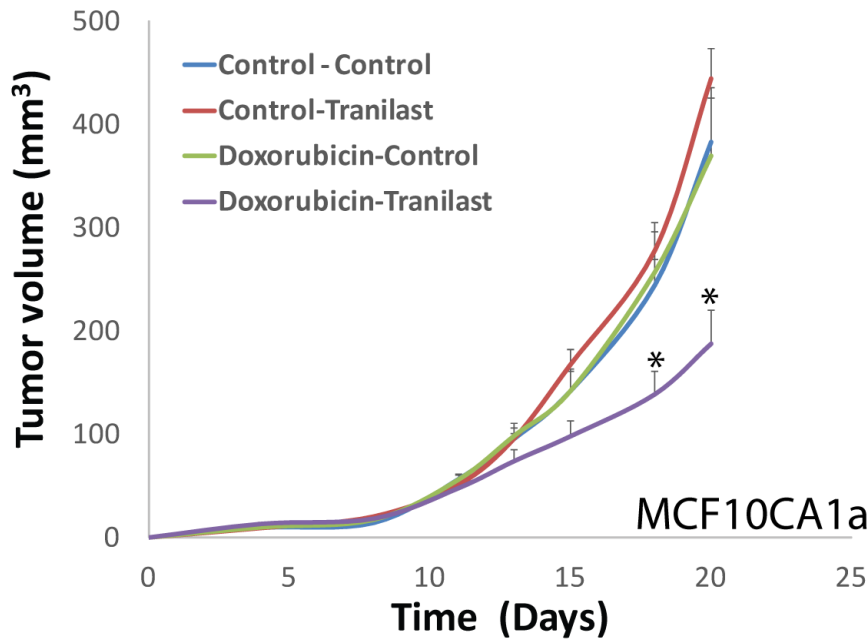


Improved perfusion and drug delivery



Stress alleviation improves tumor perfusion and delivery of doxorubicin in the tumor but not in other organs

Improved efficacy of chemotherapy



Doxorubicin (2 mg/kg)

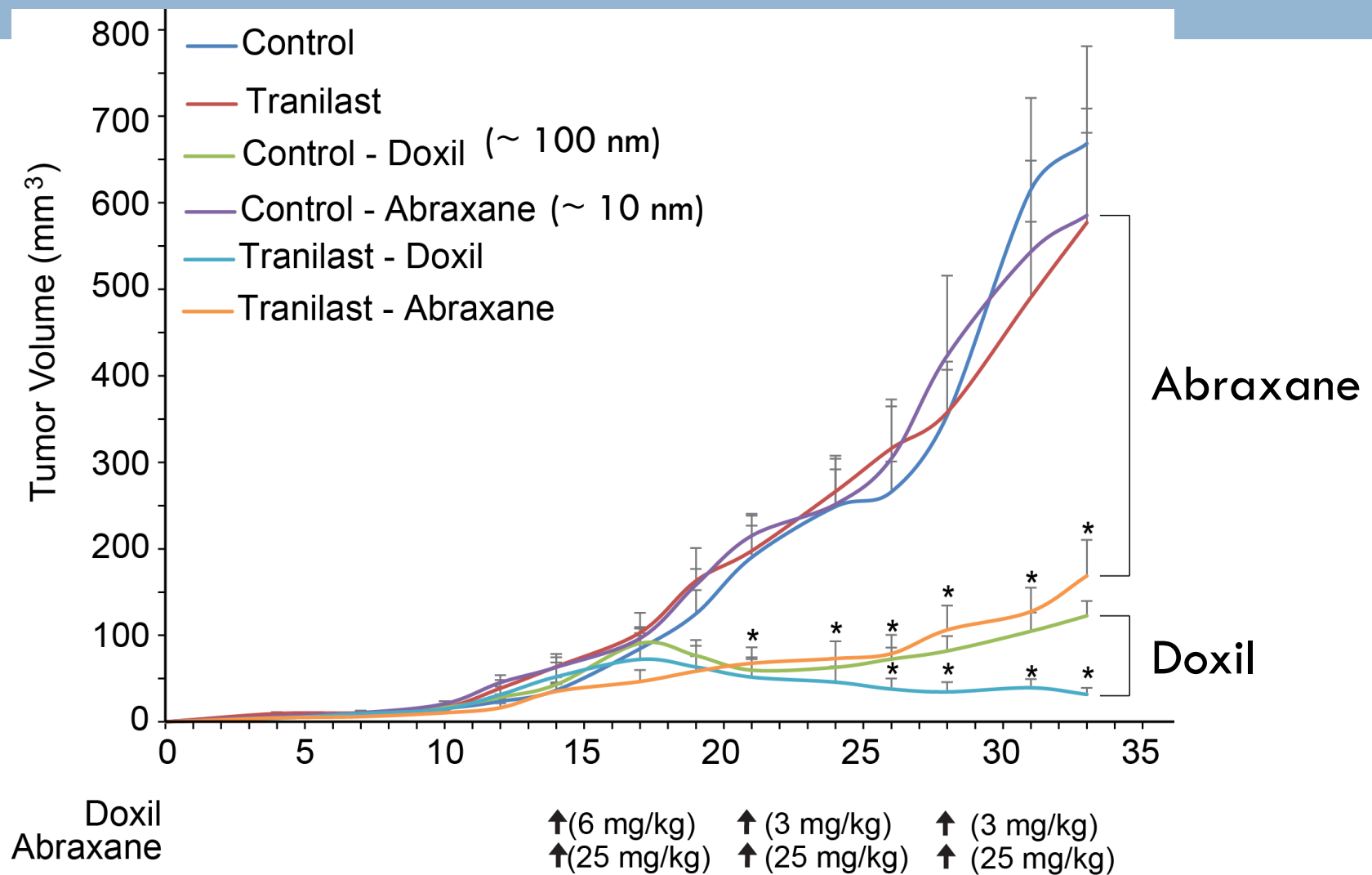
↑ ↑ ↑ ↑

Doxorubicin (5 mg/kg)

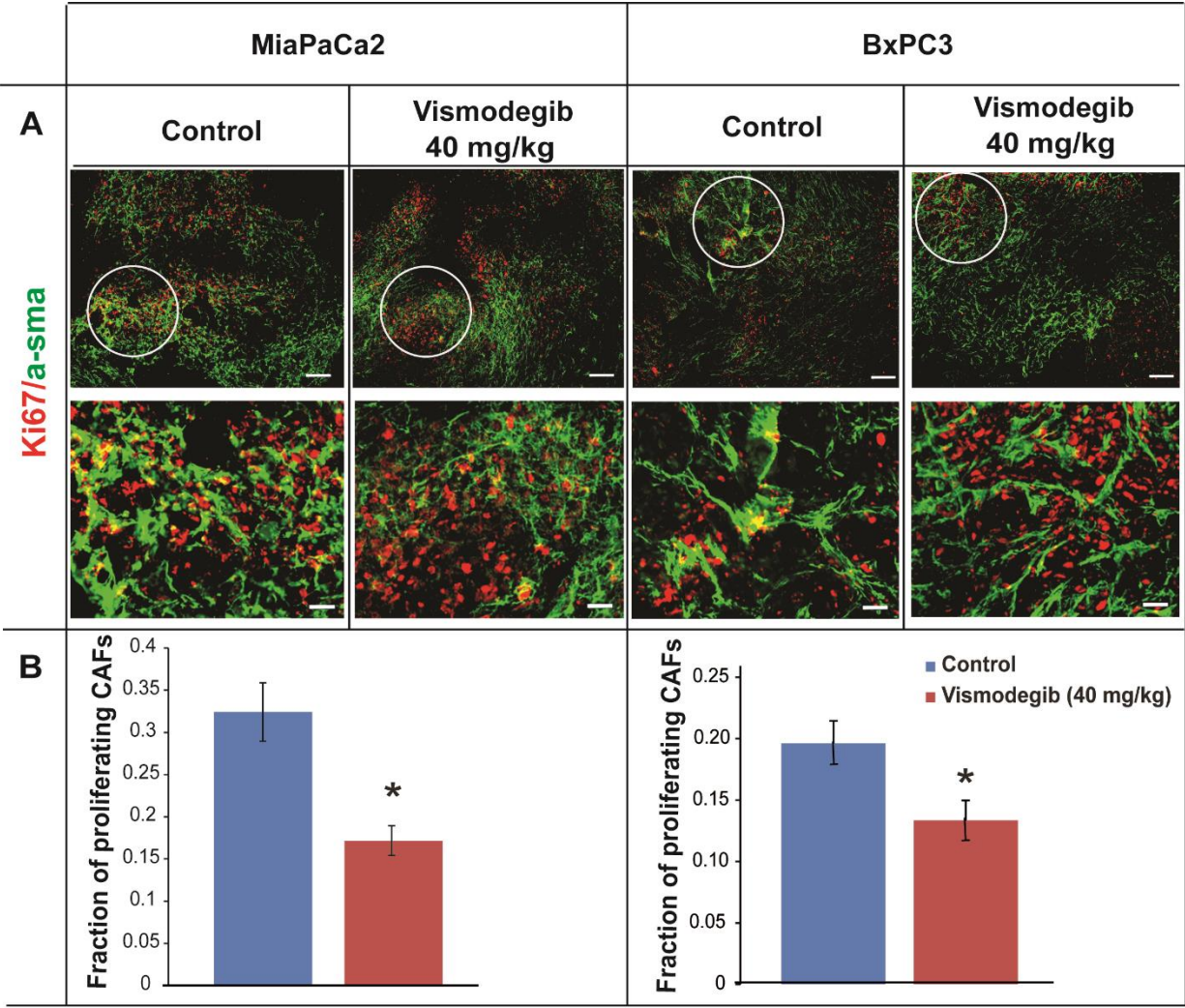
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Stress alleviation improves efficacy of doxorubicin in orthotopic breast tumor models

Tranilast increases the efficacy of ABRAXANE[®] and DOXIL[®]



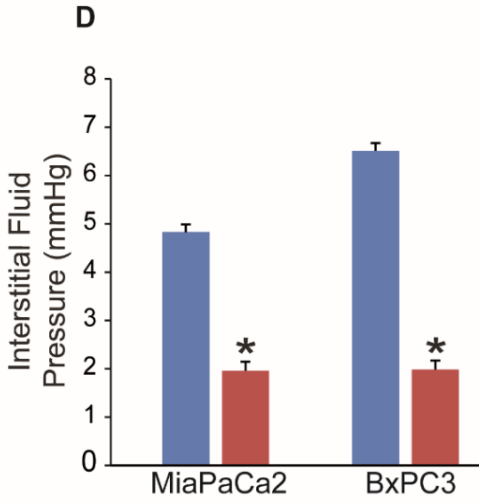
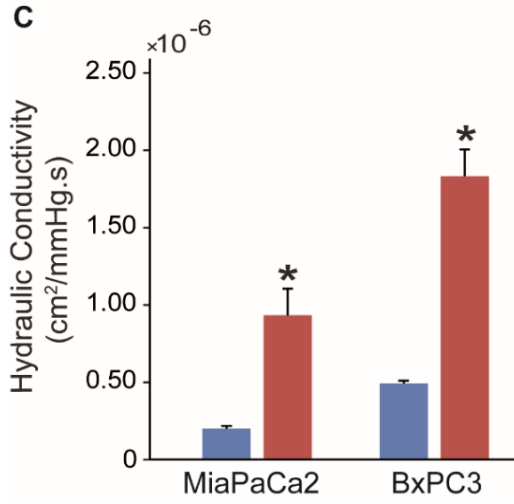
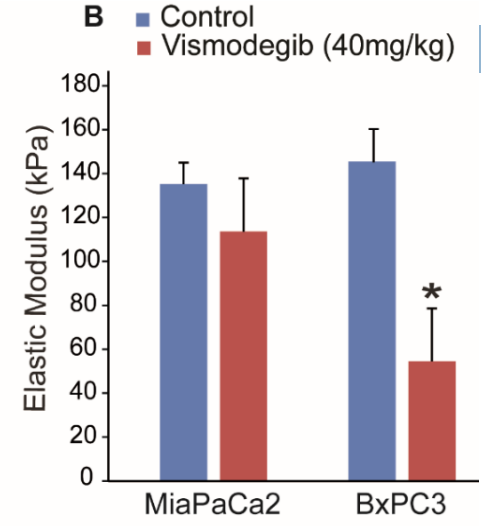
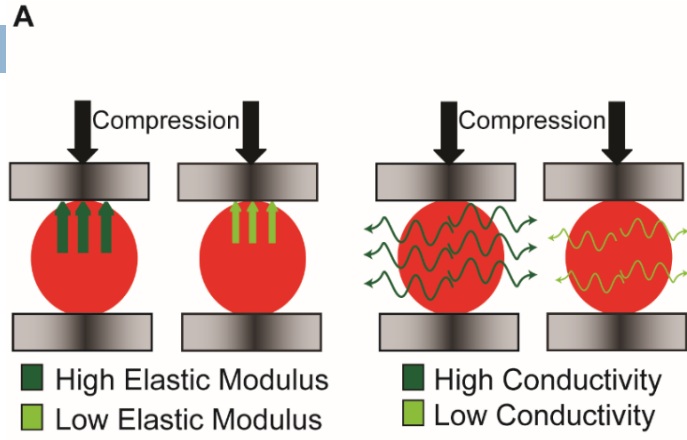
Repurposing Vismodegib to target CAFs



Vismodegib targets cancer-associated fibroblasts (CAFs)

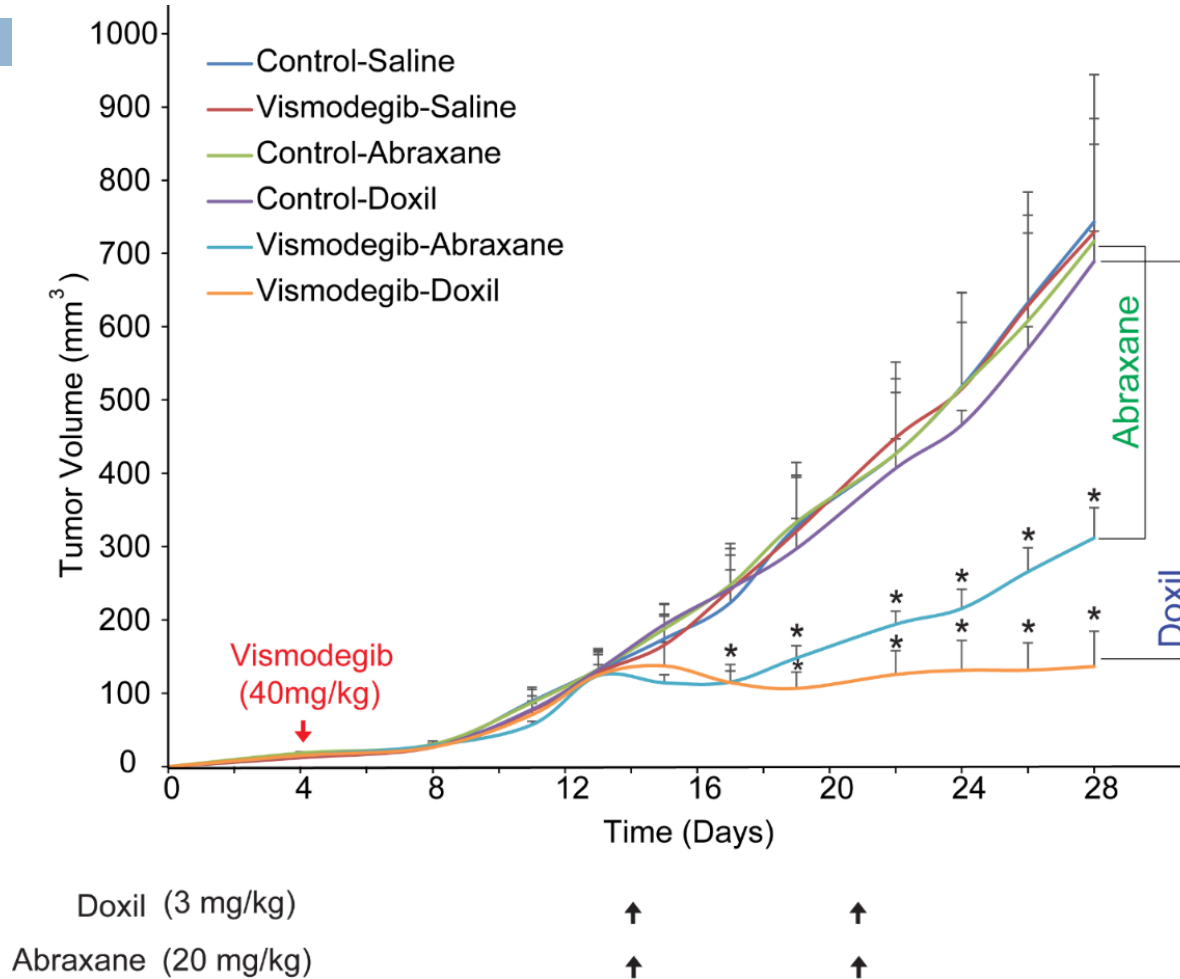
(F. Mpekris,, T. Stylianopoulos, J. Controlled Release, 2017)

Solid and fluid stress alleviation



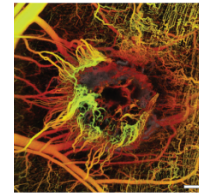
Vismodegib alleviates solid and fluid forces

Improved efficacy of ABRAXANE[®] and DOXIL[®]



Vismodegib improves efficacy of common nanomedicines

Acknowledgements



Cancer Biophysics Laboratory

Cancer Biophysics Lab members:

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PhD students: Valantis Voutouri, Stelios Angeli,
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657139 STROMAMECH)

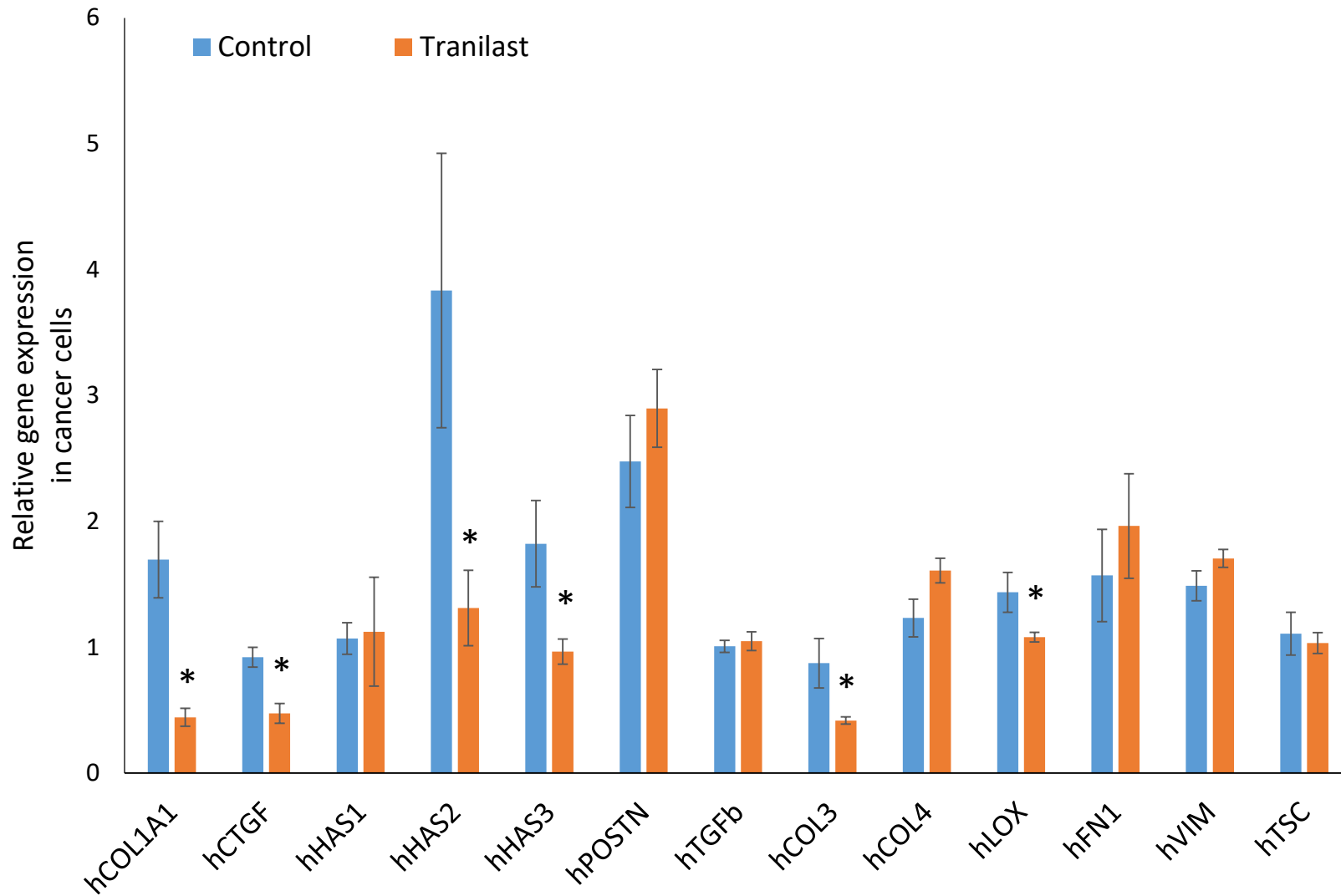
Funding from:



European Research Council
Established by the European Commission

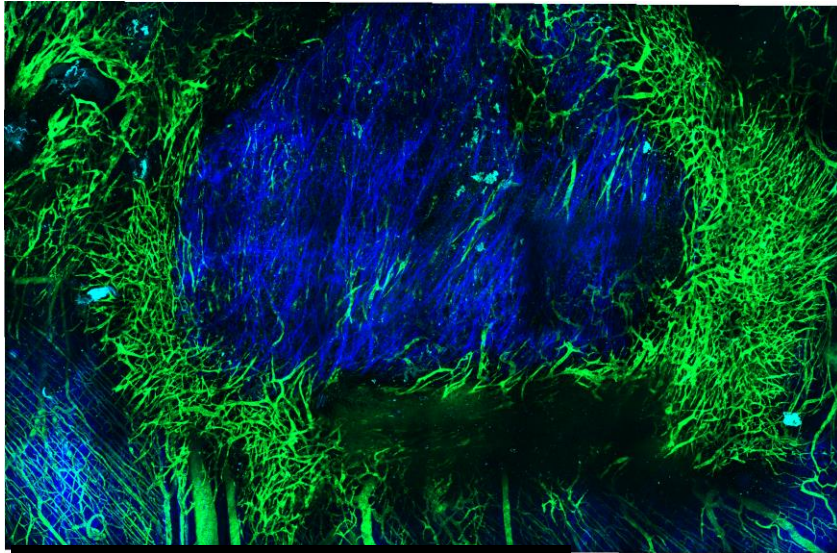


Figure 6B



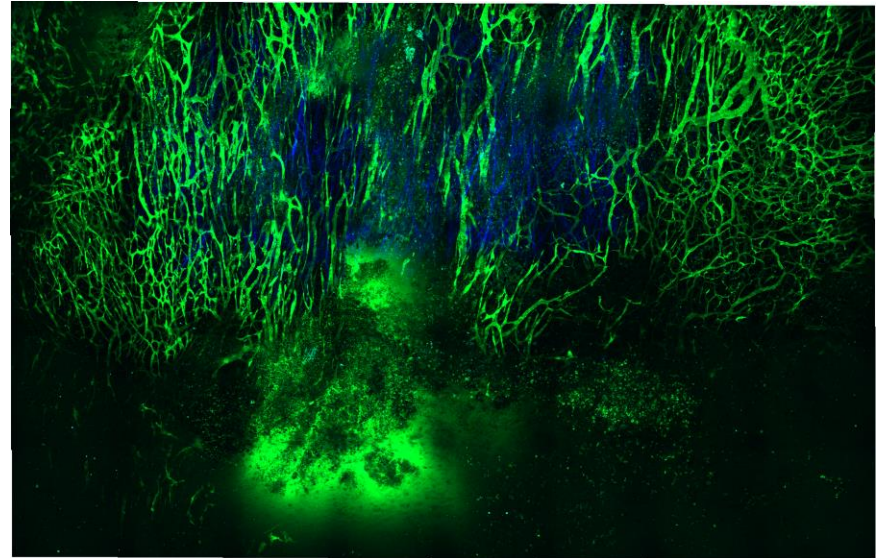
Re-purposing losartan (Cozaar, Merk)

Pre-losartan



Vessels, matrix

Post-losartan



Losartan treatment reduces collagen levels and improves vessel functionality in mice bearing breast tumors