

Tech Session 3: Immuno Delivery

TRIANTAFYLLOS STYLIANOPOULOS

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METRONOMIC ADMINISTRATION OF NANOMEDICINE INDUCES TUMOR MICROENVIRONMENT NORMALIZATION AND IMPROVES IMMUNOTHERAPY



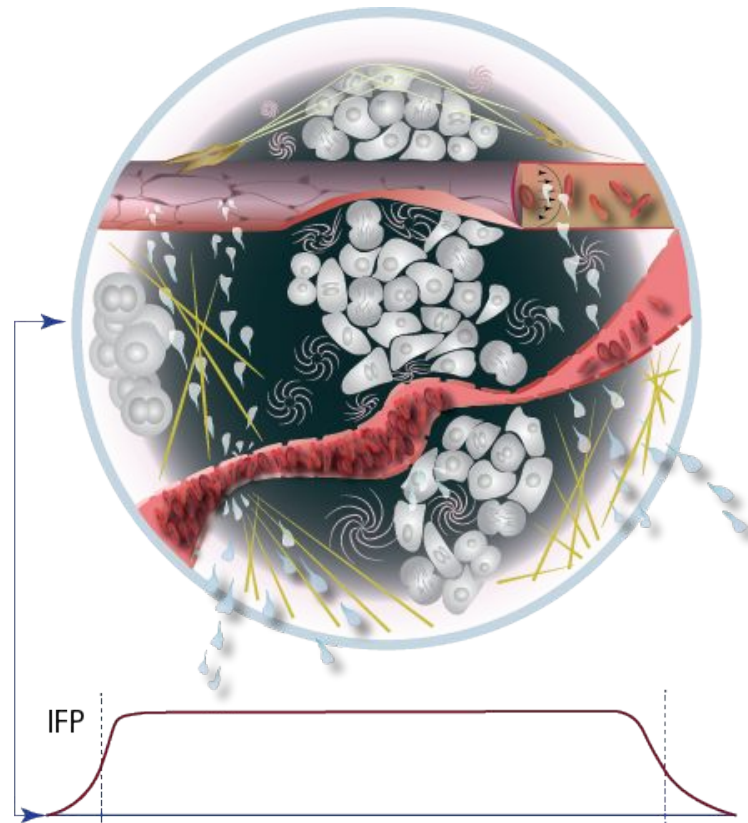
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The tumor mechanical micro-environment

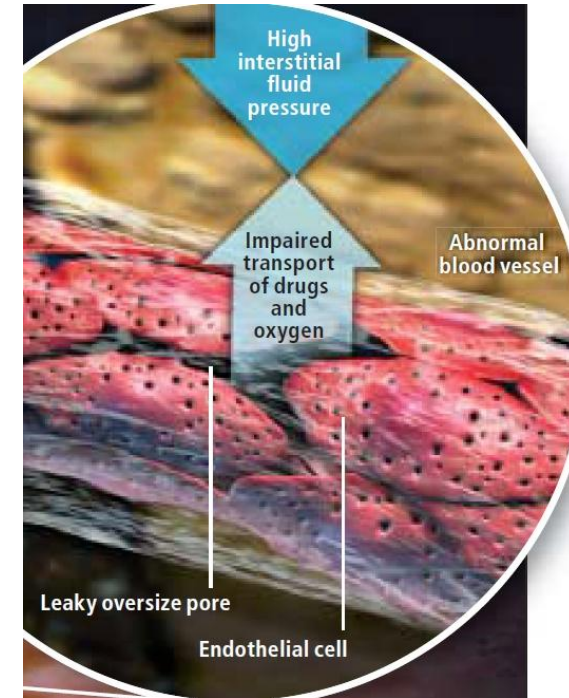


- Cancer cell
- Fibroblast
- Hyaluronan-HA
- Hydrated HA
- Collagen

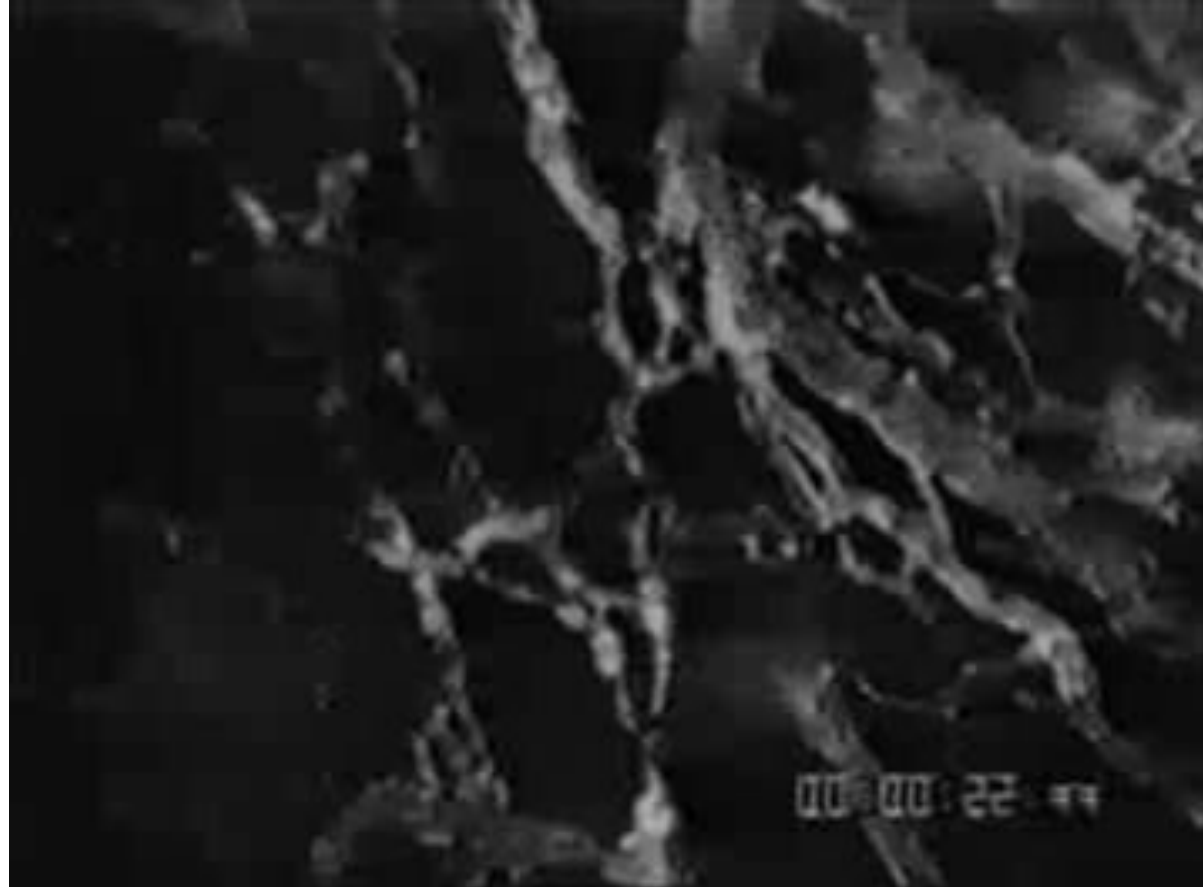
Mechanical Abnormalities

- Tumor stiffening
- Mechanical stress elevation
- Interstitial hypertension

(Stylianopoulos et al., Trends in Cancer, 2018)



Heterogeneous Perfusion



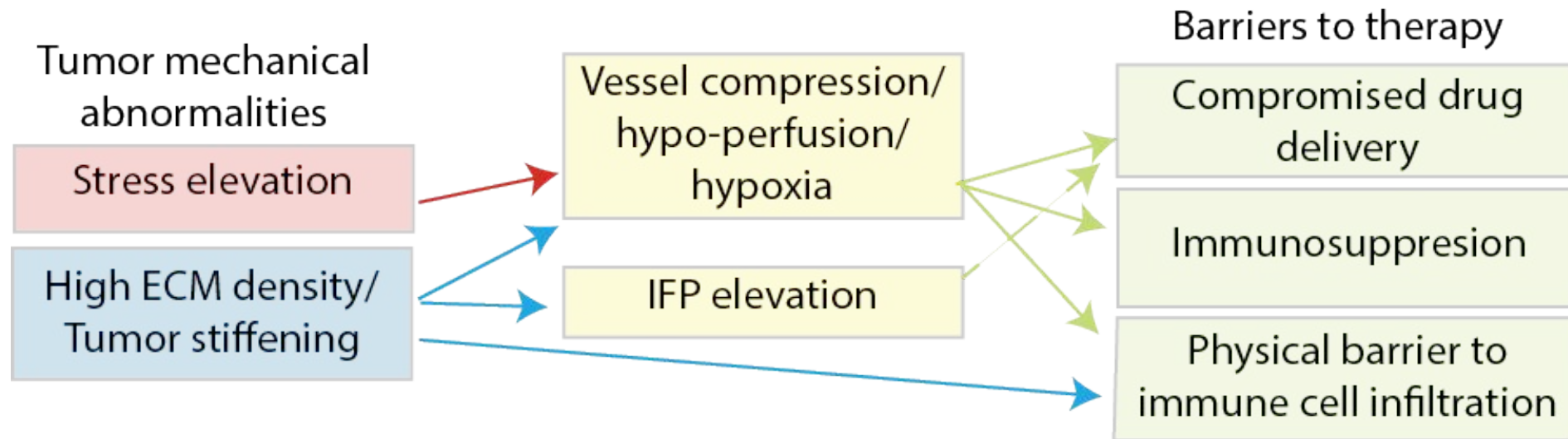
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Cancer MechanoPathology



(Stylianopoulos T, Munn LL, Jain RK et al., Trends in Cancer, 2018)



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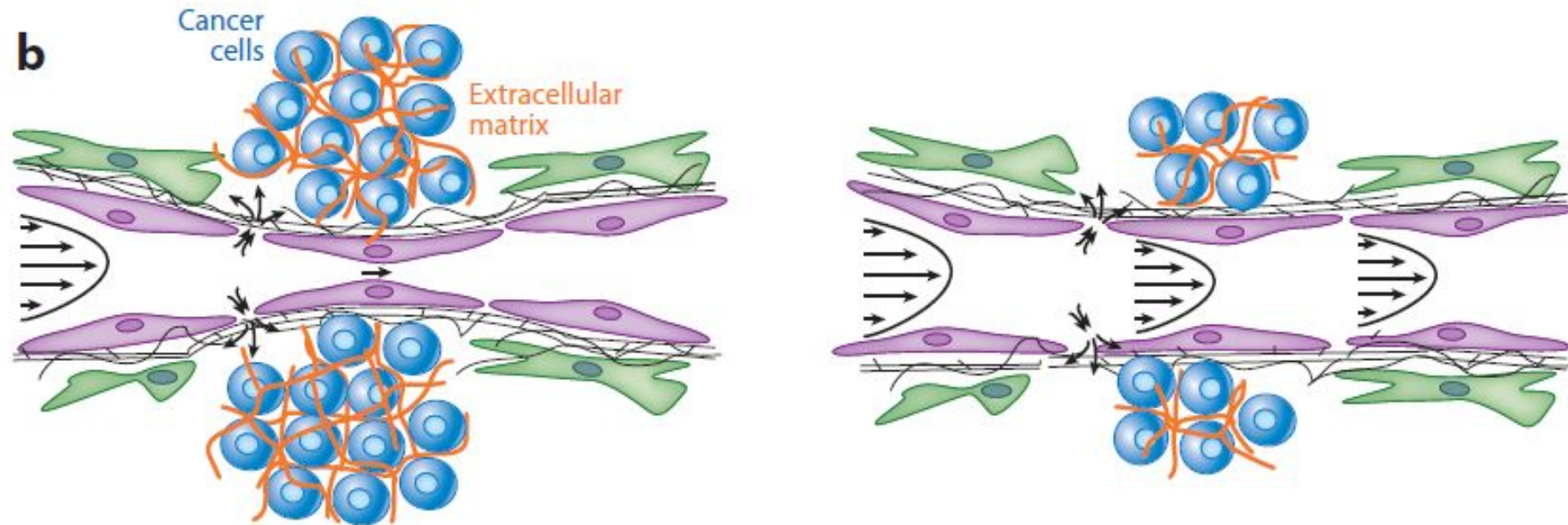
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Re-engineering Cancer

- 'Tumor Normalization' to decompress tumor vessels



(Stylianopoulos T, RK Jain, PNAS, 2013; Stylianopoulos T, Munn LL, Jain RK, Trends in Cancer, 2018; Martin JD, Cabral H, Stylianopoulos T, Jain RK, Nature Reviews Clinical Oncology, 2020)



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Metronomic Therapy

- ❑ **Maximum tolerated dose (MTD):** large dose of chemotherapy every 2-3 weeks. These long breaks give time to cancer cells to recover.
- ❑ **Metronomic chemotherapy:** more frequent administration of chemotherapeutic drugs at lower doses than MTD and with minimal drug-free breaks. There is evidence that can induce normalization and improve tumor perfusion. It does not always work in preclinical/clinical trials.
- ❑ **Hypothesis:** Nanomedicine can induce metronomic effects when administer at proper dose schedules



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Doxil induced normalization

- Doxil can reduce collagen and hyaluronan levels in murine breast tumors and breast cancer lung metastasis.



Research Paper

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

FULL PAPER



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



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Normalizing the Microenvironment Overcomes Vessel Compression and Resistance to Nano-immunotherapy in Breast Cancer Lung Metastasis



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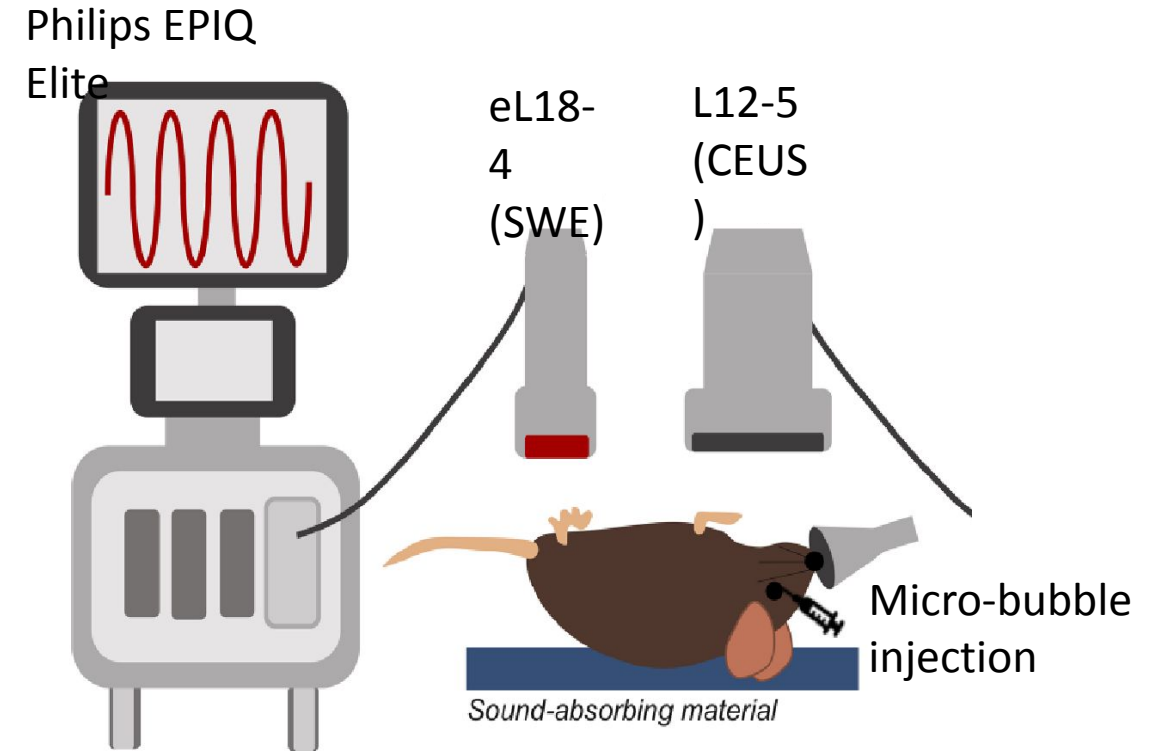
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Monitoring normalization effects with US

4T1 murine mammary tumors and MCA205 fibrosarcoma treated with Doxil

- 1mg/kg daily
- 2mg/kg other day,
- 6 mg/kg once per week
- a-PDL1 was added at a second phase.



SWE: shear wave elastography
CEUS: contrast-enhanced ultrasound

(Mpekris F. et al., JCR, 2022)

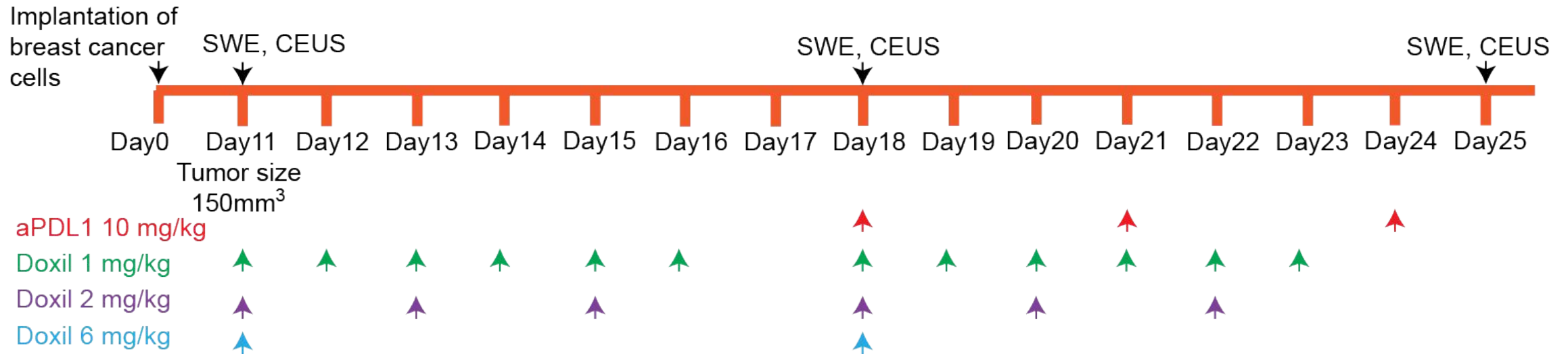


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Treatment Protocol



(Mpekris F. et al., JCR, 2022)

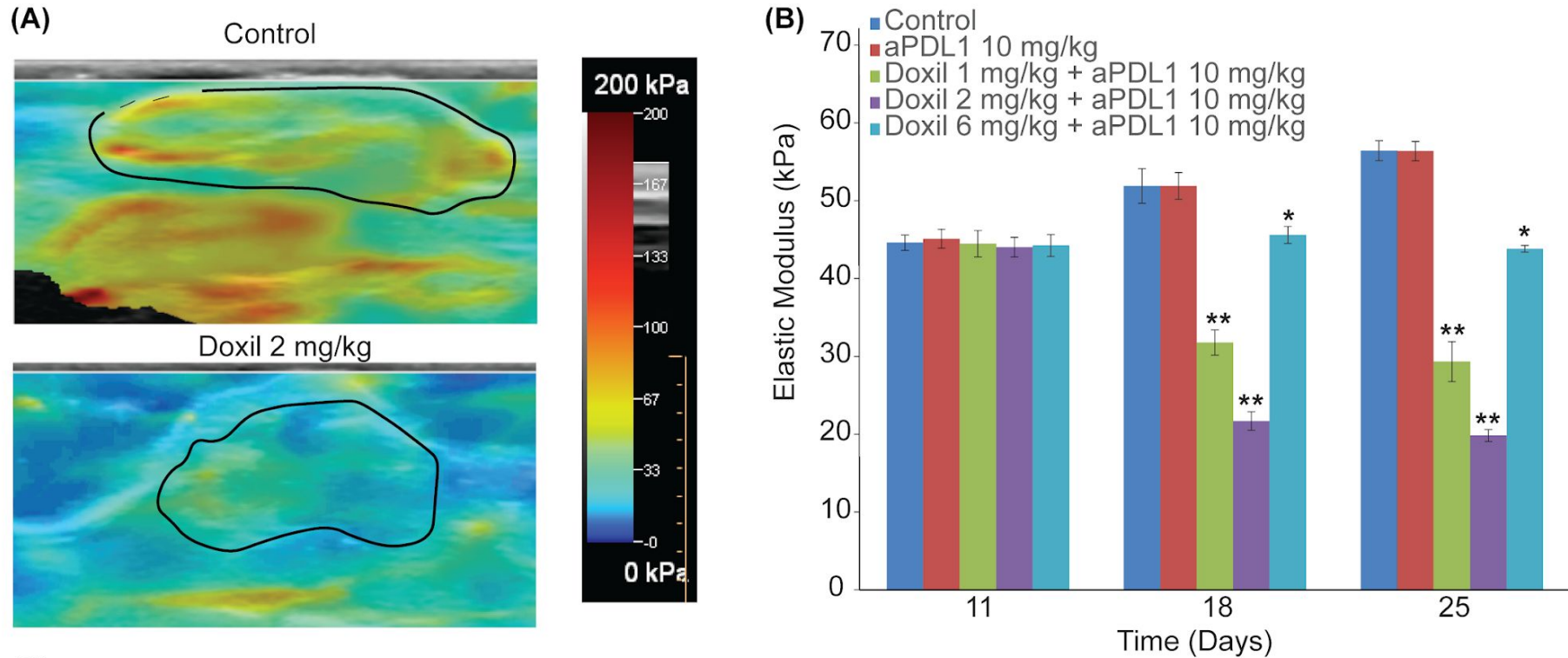


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Frequent doses of Doxil reduce stiffness



(Mpekris F. et al., JCR, 2022)

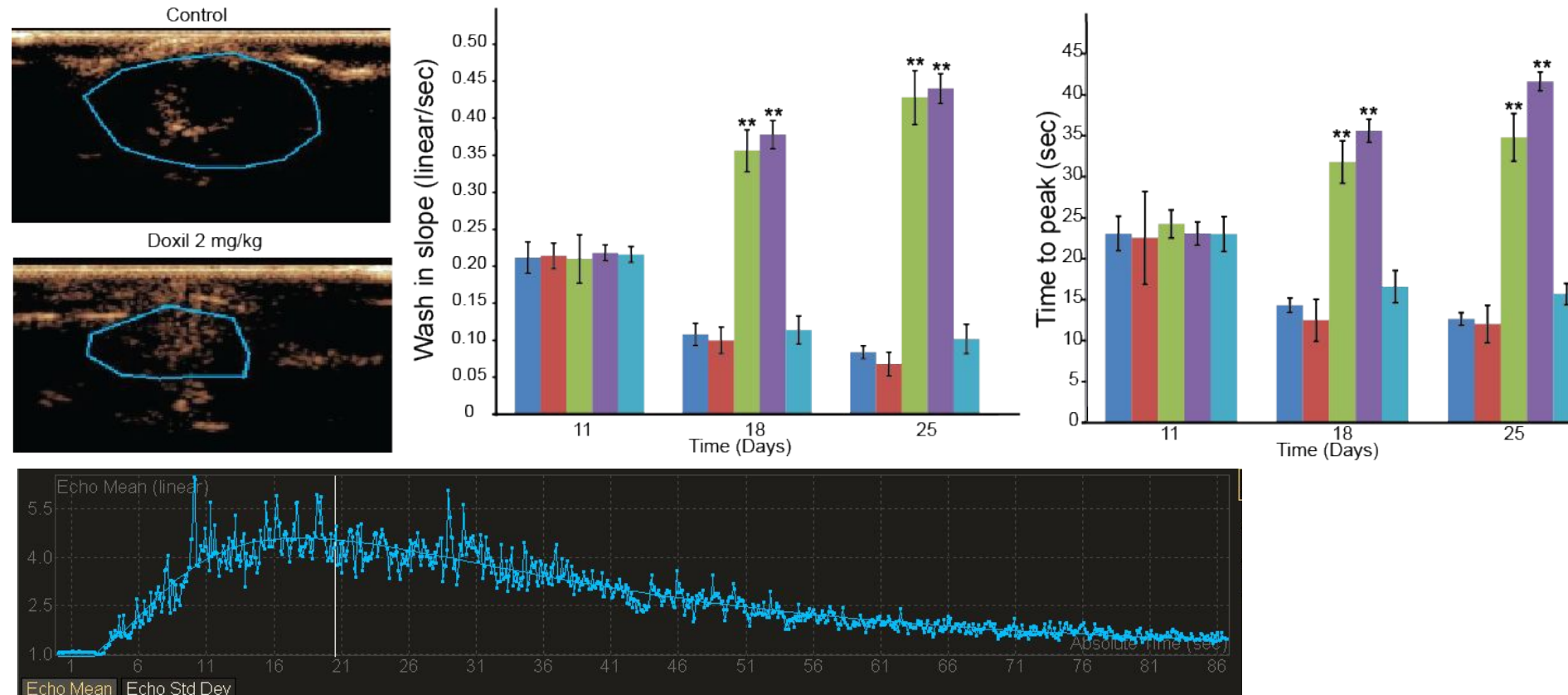


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Frequent doses of Doxil improve perfusion



(Mpekris F. et al., JCR, 2022)



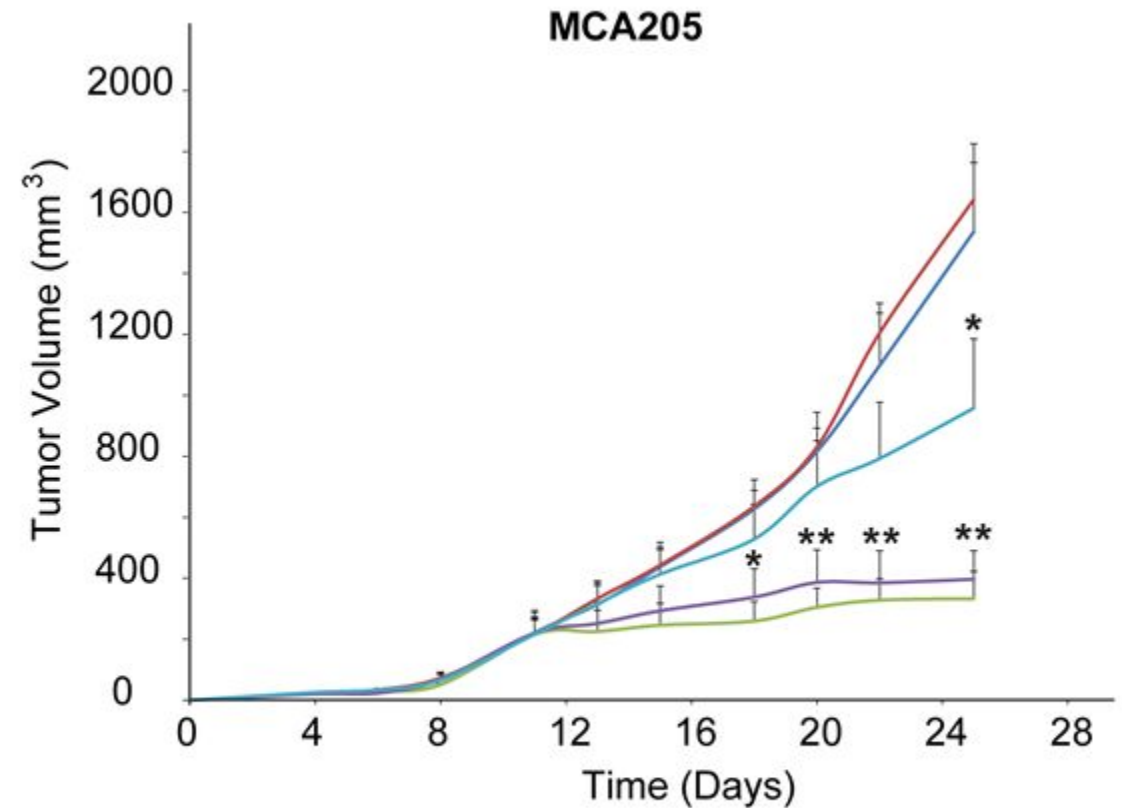
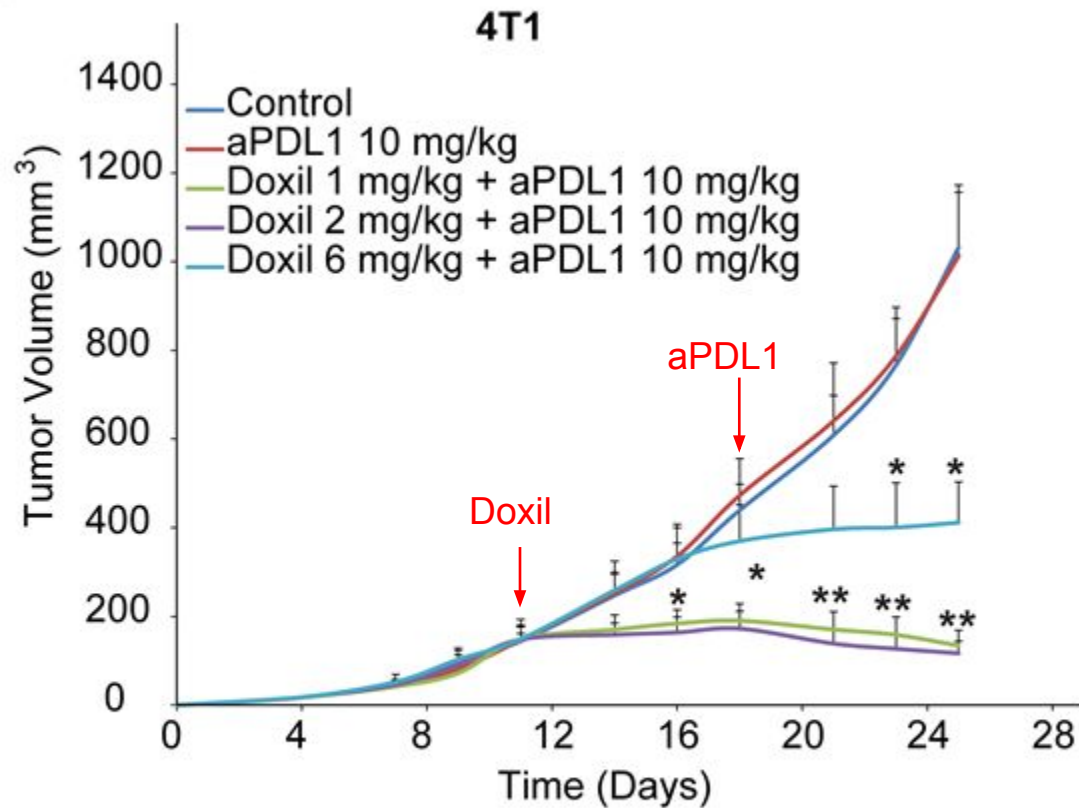
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Frequent doses of Doxil improve therapy



(Mpekris F. et al., JCR, 2022)



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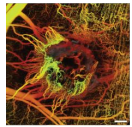
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