

# Tech Session 3: Immuno Delivery

TRIANTAFYLLOS STYLIANOPOULOS

**CRS 2022 Annual Meeting & Expo**

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

***Advanced Delivery Science***

# METRONOMIC ADMINISTRATION OF NANOMEDICINE INDUCES TUMOR MICROENVIRONMENT NORMALIZATION AND IMPROVES IMMUNOTHERAPY



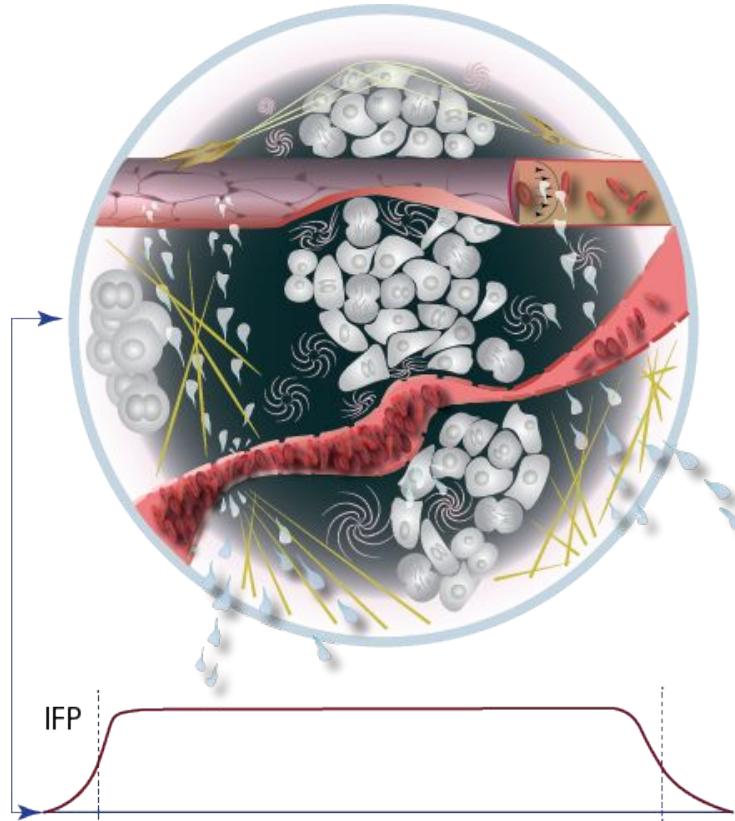
**CRS 2022 Annual Meeting & Expo**

*Advanced Delivery Science*

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



# The tumor mechanical micro-environment

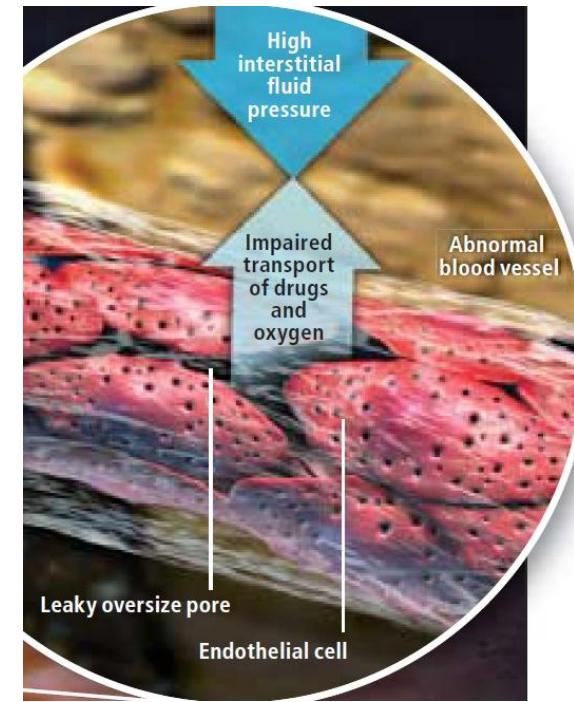


- Cancer cell
- Fibroblast
- Hyaluronan-HA
- Hydrated HA
- ▽ Collagen

## Mechanical Abnormalities

- Tumor stiffening
- Mechanical stress elevation
- Interstitial hypertension

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

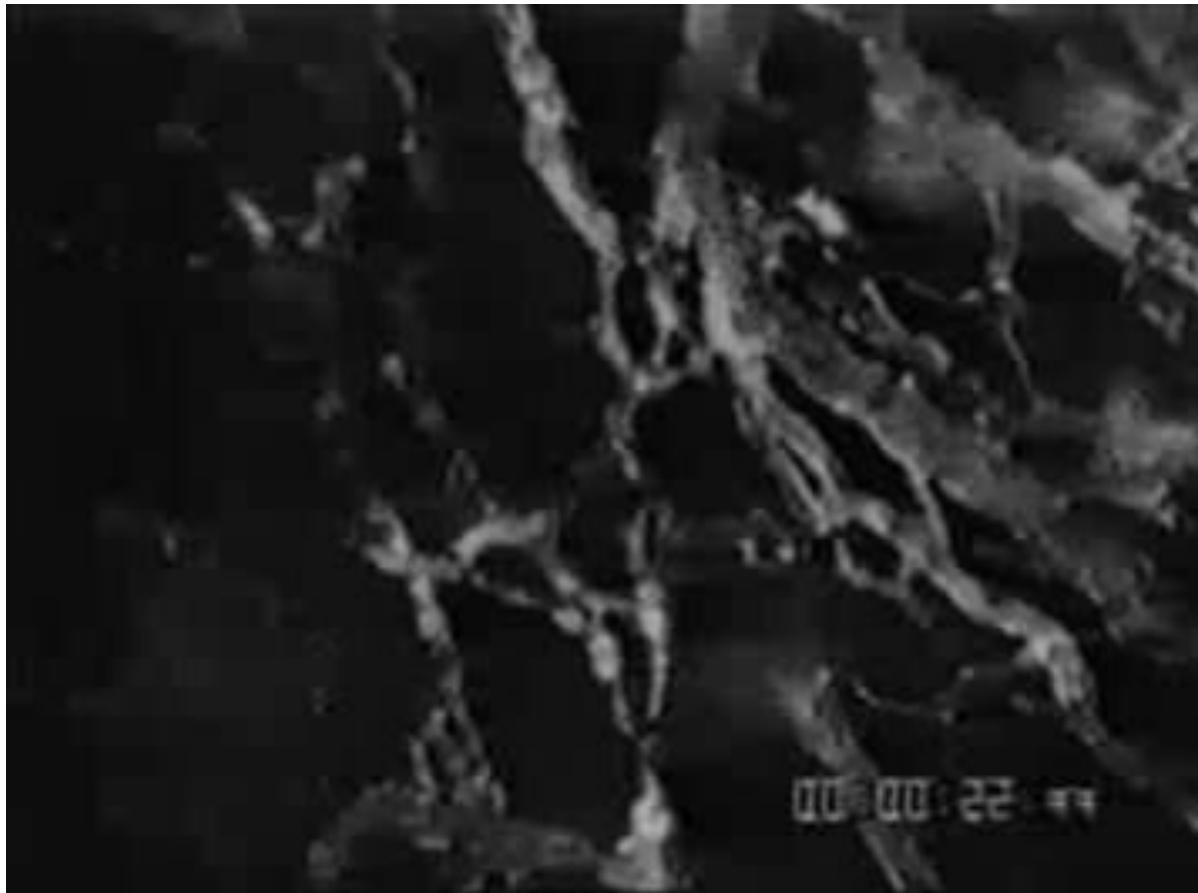


**CRS 2022 Annual Meeting & Expo**

***Advanced Delivery Science***

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

# Heterogeneous Perfusion



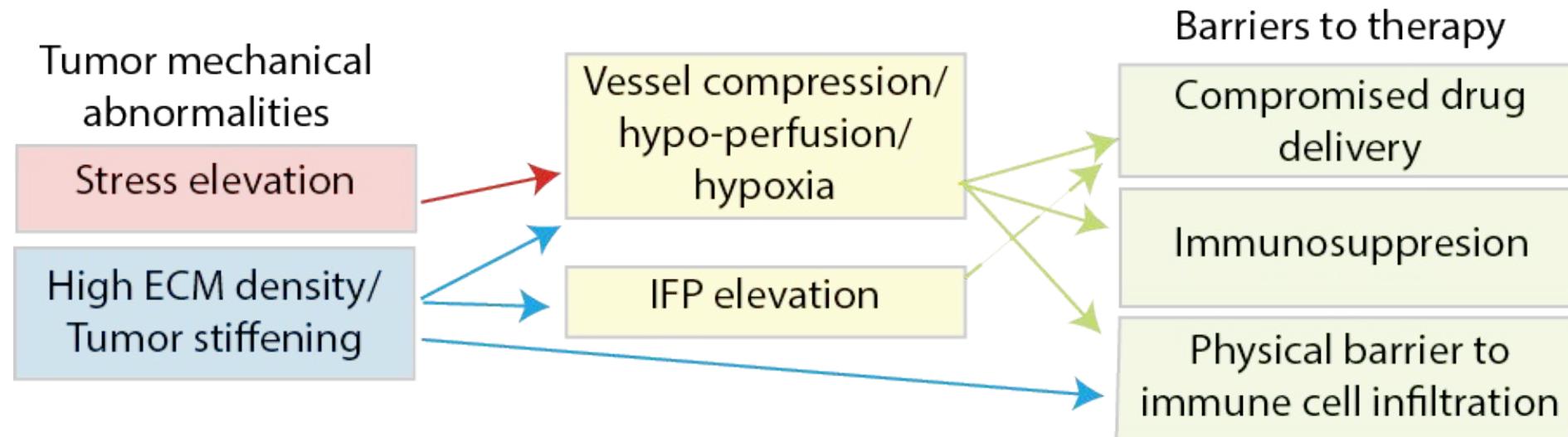
**CRS 2022 Annual Meeting & Expo**

*Advanced Delivery Science*

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



# Cancer MechanoPathology



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



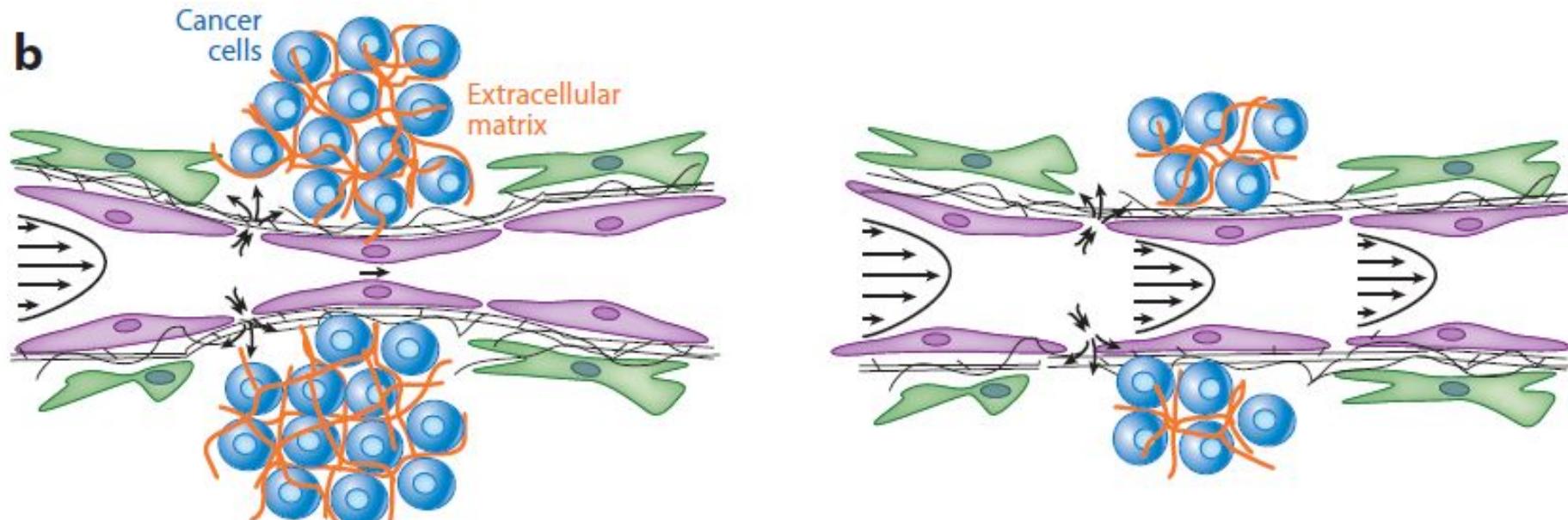
**CRS 2022 Annual Meeting & Expo**

*Advanced Delivery Science*

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

# 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)



**CRS 2022 Annual Meeting & Expo**

*Advanced Delivery Science*

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



# 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



## CRS 2022 Annual Meeting & Expo

*Advanced Delivery Science*

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



# Doxil induced normalization

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



Research Paper



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

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

**FULL PAPER**



[www.advancedscience.com](http://www.advancedscience.com)

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



**CRS 2022 Annual Meeting & Expo**

***Advanced Delivery Science***

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

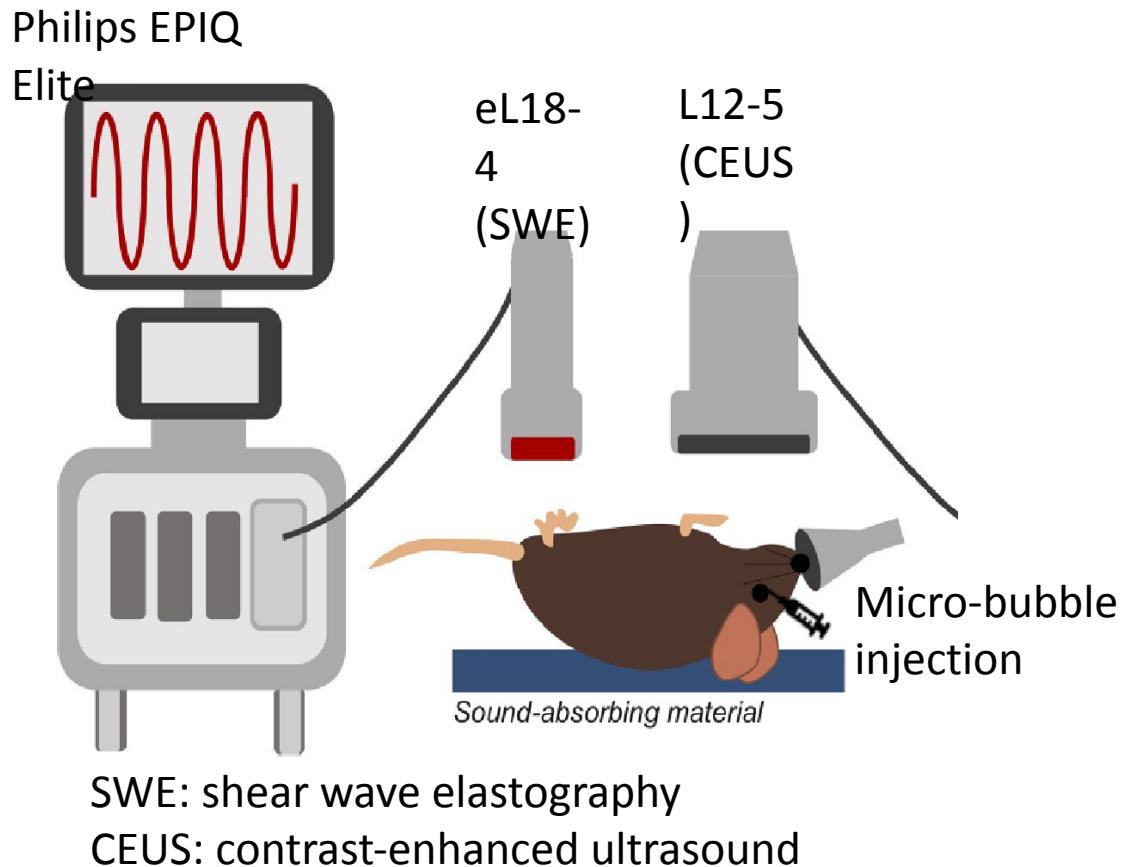


# Monitoring normalization effects with US

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.

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

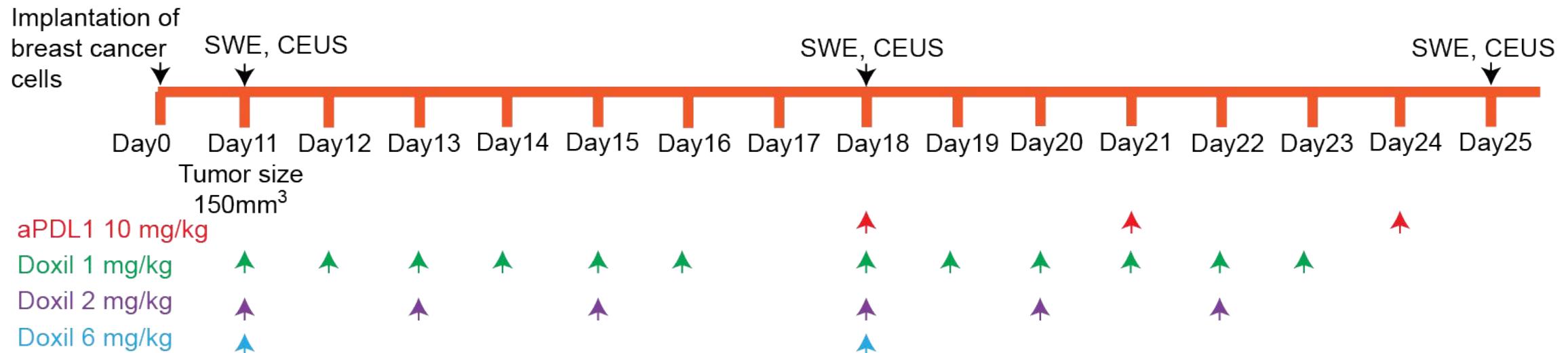


CRS 2022 Annual Meeting & Expo

*Advanced Delivery Science*

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

# Treatment Protocol



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

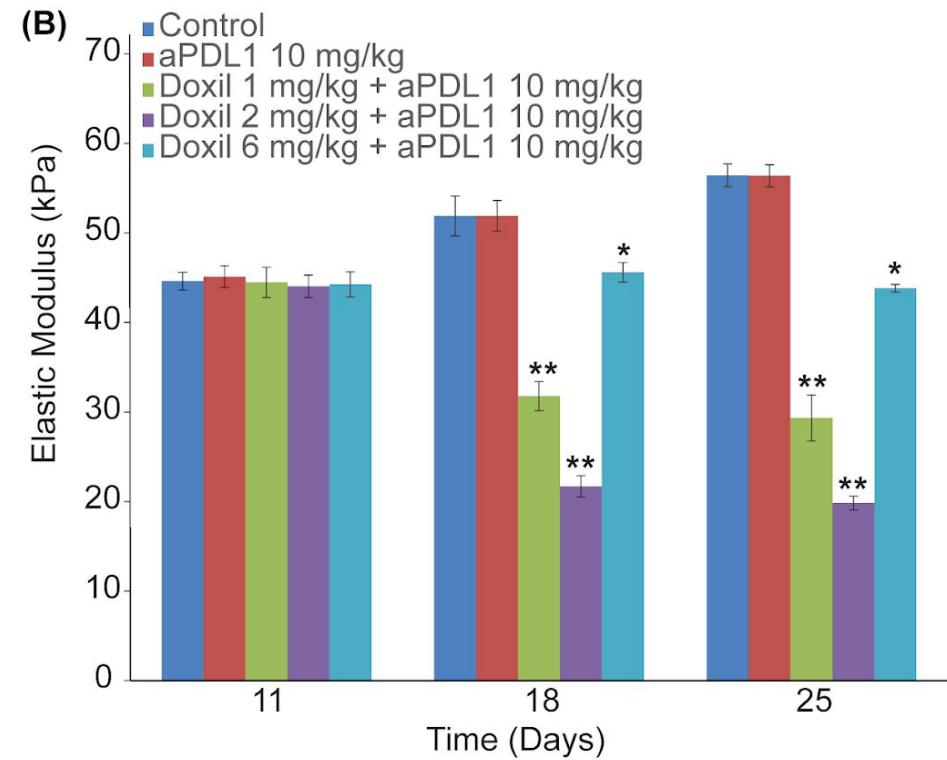
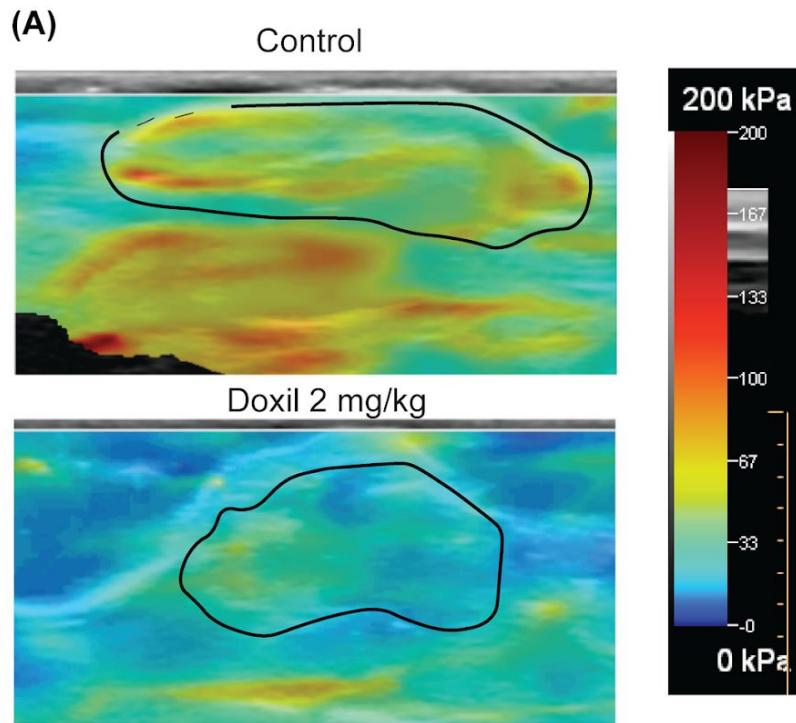


**CRS 2022 Annual Meeting & Expo**

*Advanced Delivery Science*

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

# Frequent doses of Doxil reduce stiffness



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



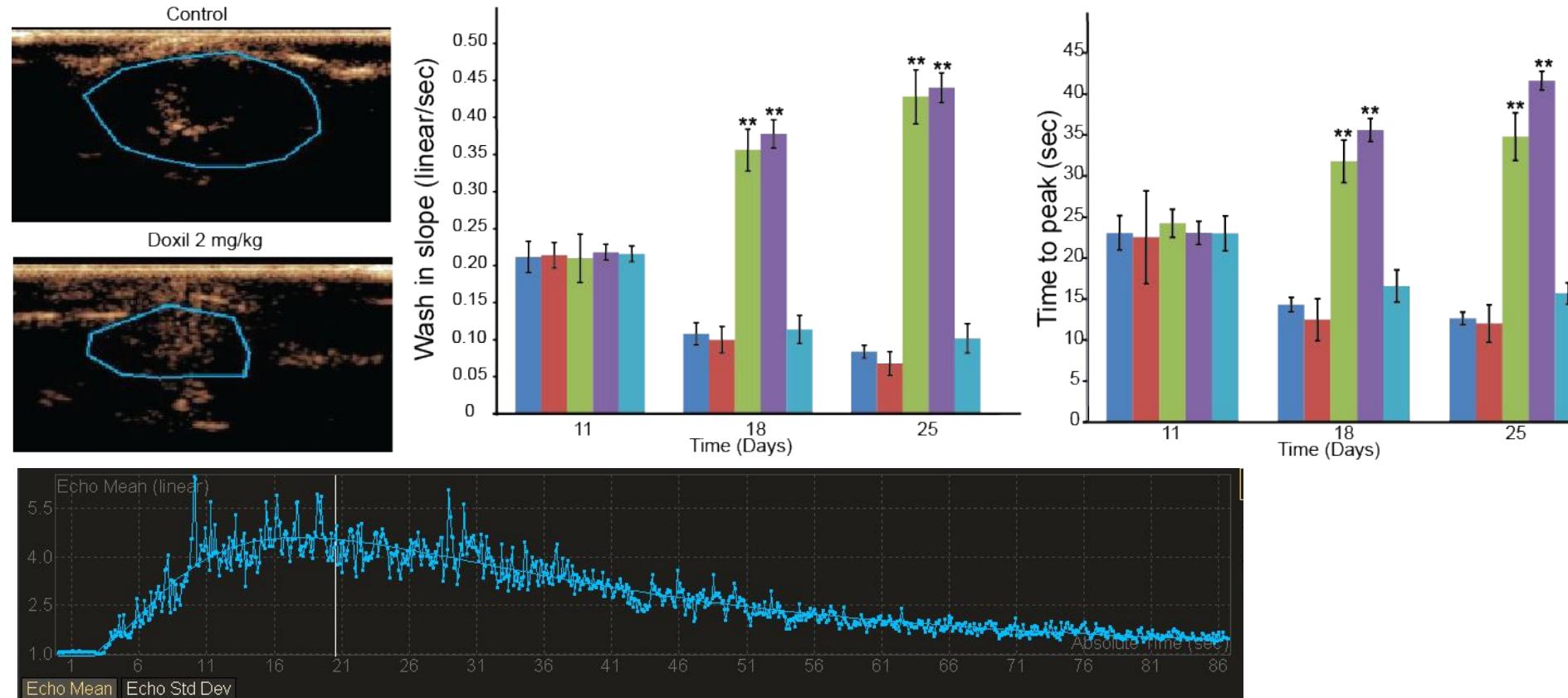
CRS 2022 Annual Meeting & Expo

*Advanced Delivery Science*

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



# Frequent doses of Doxil improve perfusion



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



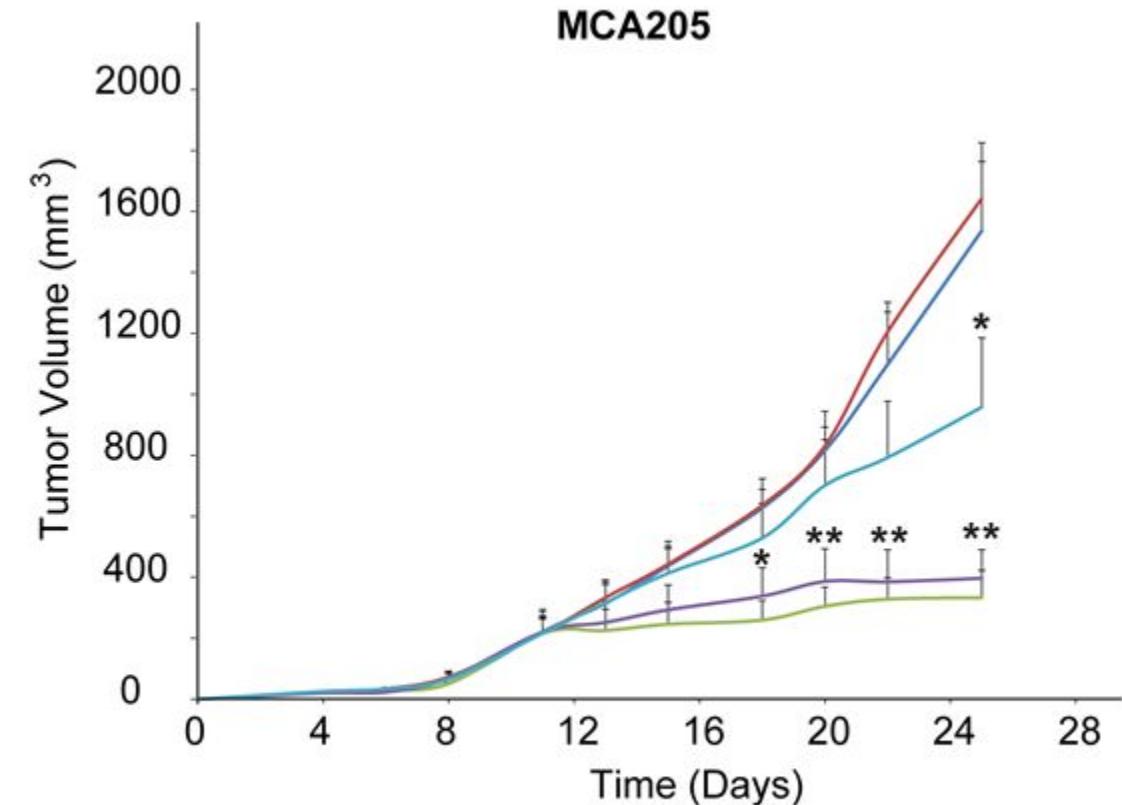
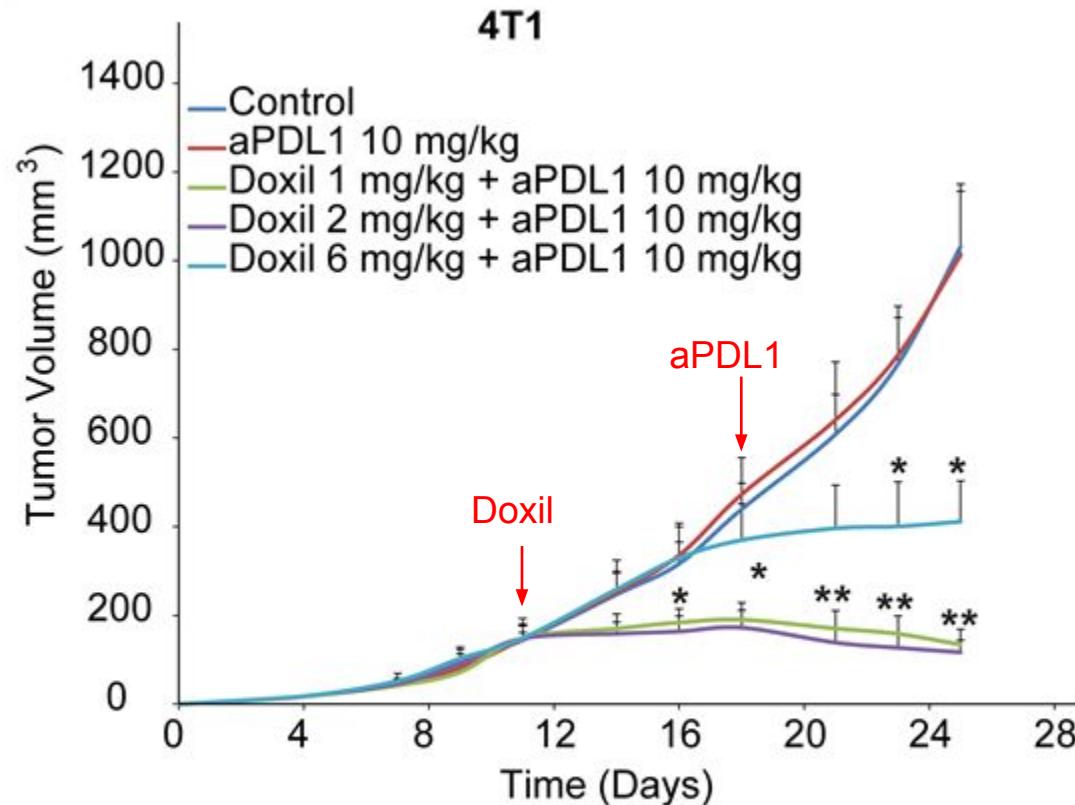
**CRS 2022 Annual Meeting & Expo**

***Advanced Delivery Science***

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



# Frequent doses of Doxil improve therapy



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



**CRS 2022 Annual Meeting & Expo**

*Advanced Delivery Science*

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



# Acknowledgements

## Cancer Biophysics Lab members:

- Dr. Fotios Mpekris,
- Dr. Valantis Voutouri,
- Dr. Miranda Panagi



Cancer Biophysics  
Laboratory



## Collaborators:

- Rakesh K. Jain, Harvard Medical School/Mass General Hospital
- James W. Baish, Bucknell University
- Mike Averkiou, University of Washington

## Funding from:



European Research Council  
Established by the European Commission



RESEARCH  
& INNOVATION  
FOUNDATION

ERC Consolidator Grant  
“Immuno-Predictor”

**CRS 2022 Annual Meeting & Expo**

***Advanced Delivery Science***

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



# Thank You to Our Session Sponsor

AstraZeneca

AstraZeneca 



**CRS 2022 Annual Meeting & Expo**

*Advanced Delivery Science*

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

