Image-guided Ultrasound Facilitated Drug Delivery into Tumors *In Vivo*

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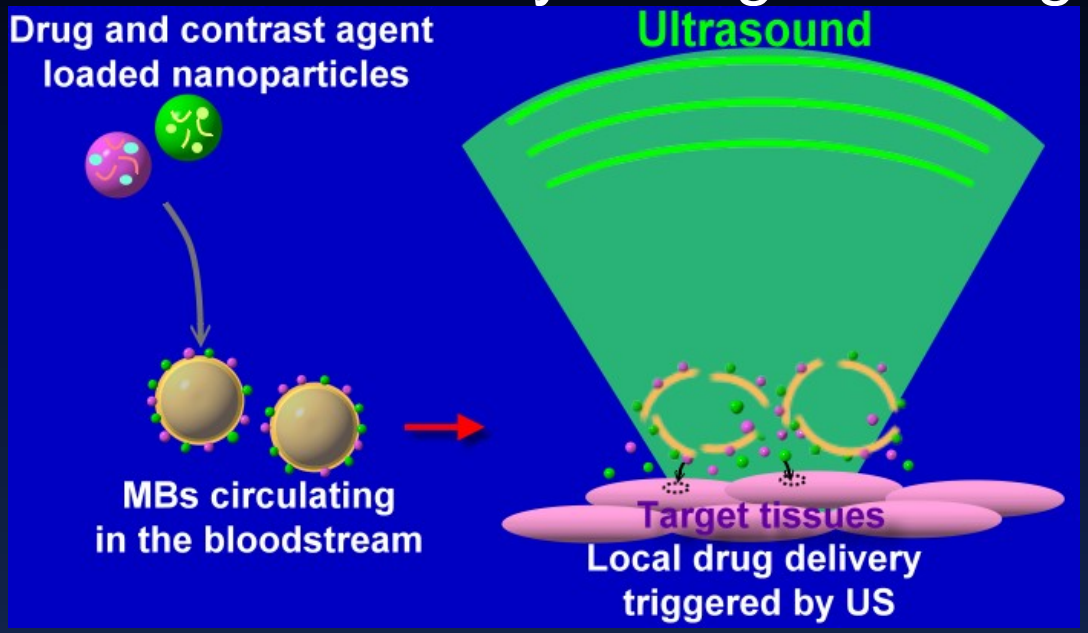
Drug Delivery for Cancer Therapy

- **Delivery of nanometer-sized drugs or carrier system into tumors relies on passive accumulation via *enhanced permeability and retention (EPR) effect*.**
- **EPR is inefficient, non-targeted delivery approach.**
  - Only <5% of administered drug is deposited in tumors.
  - EPR varies between tumors and even within a tumor
  - Ineffective for large (>100nm) therapeutic agents
- **An *active, targeted delivery* approach is beneficial for cancer therapy.**

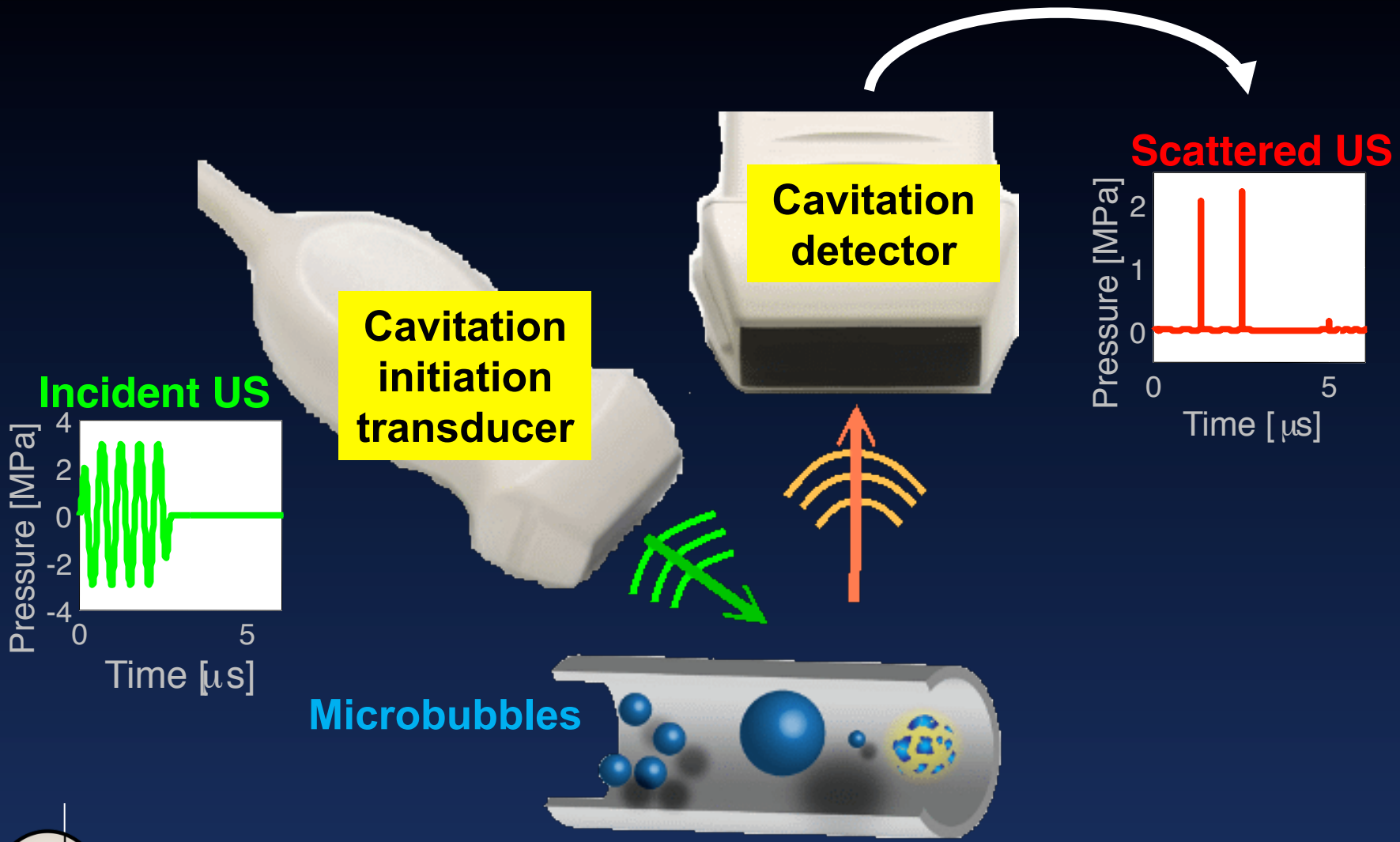
Ultrasound and Microbubble facilitated Drug Delivery

- **Sonoporation:** Ultrasound-induced microbubble cavitation ➔ Permeability change ➔ Drug delivery



- ***Goal:*** Investigate effects of ultrasound and microbubble parameters on cavitation for effective delivery of 100-200nm therapeutics/nanocarriers *in vivo*

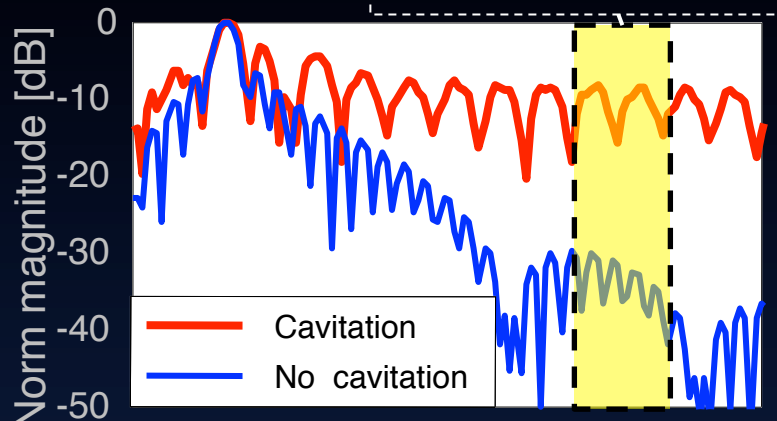
Experimental Setup



Cavitation Detection

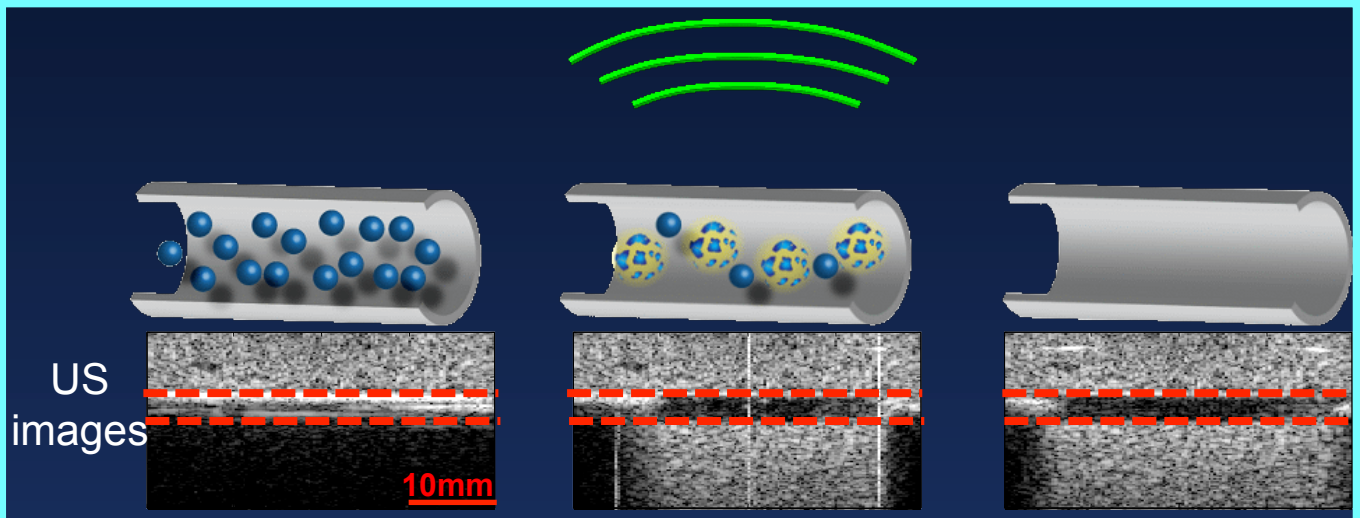
Passive

Active

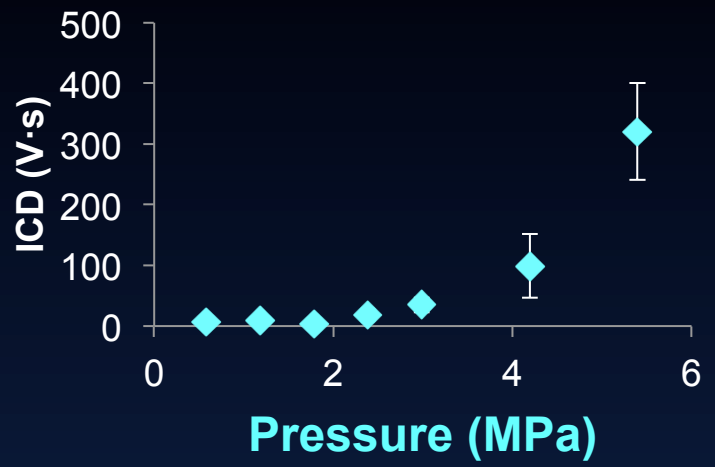


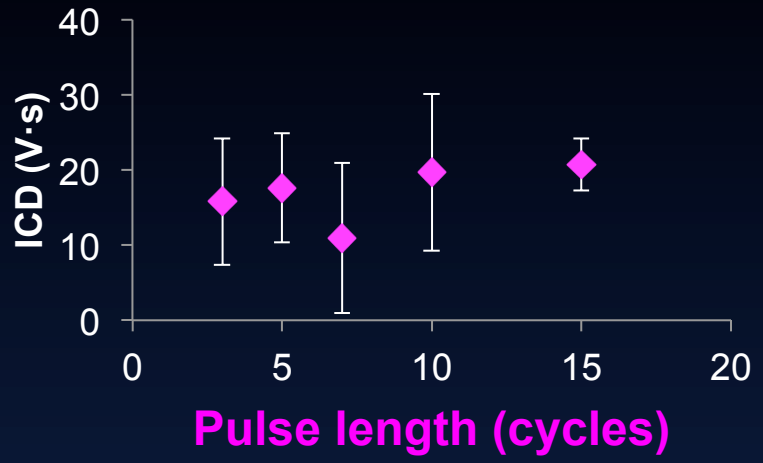
Time integral

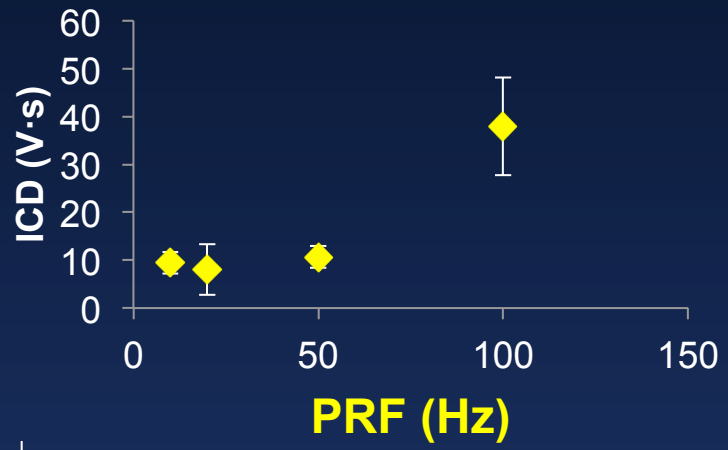
Inertial cavitation dose (ICD)

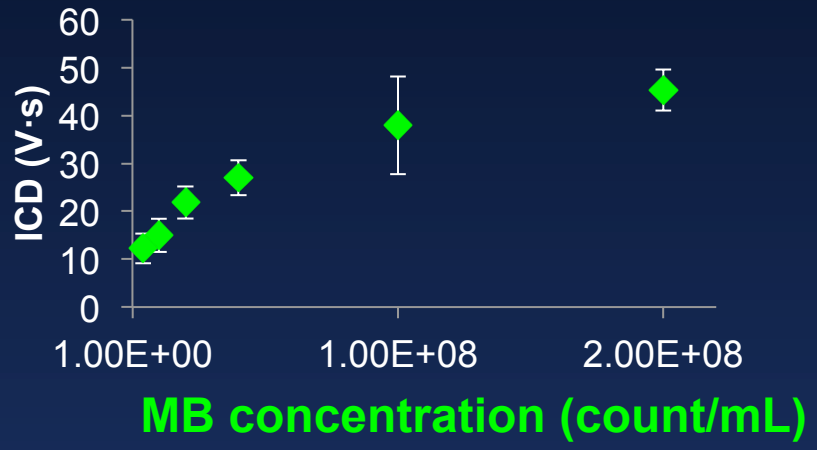


Passive Cavitation Detection in Tissue Phantoms

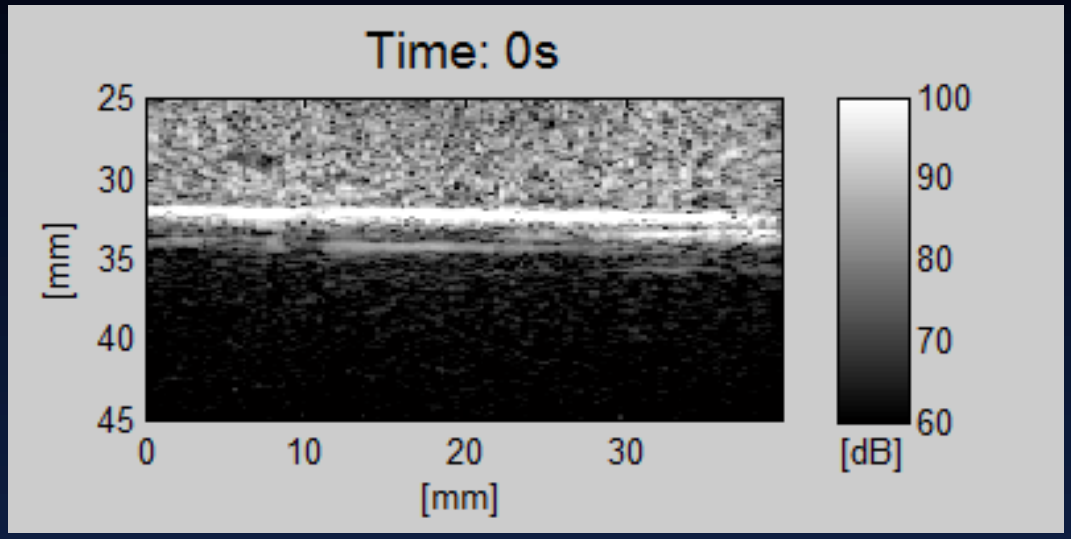




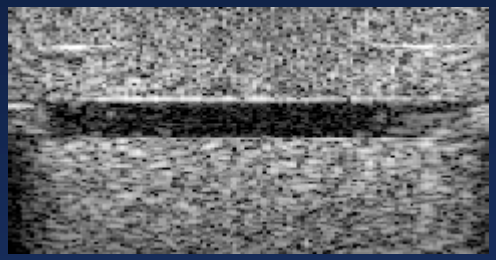




Active Cavitation Detection in Tissue Phantoms



5.4 MPa

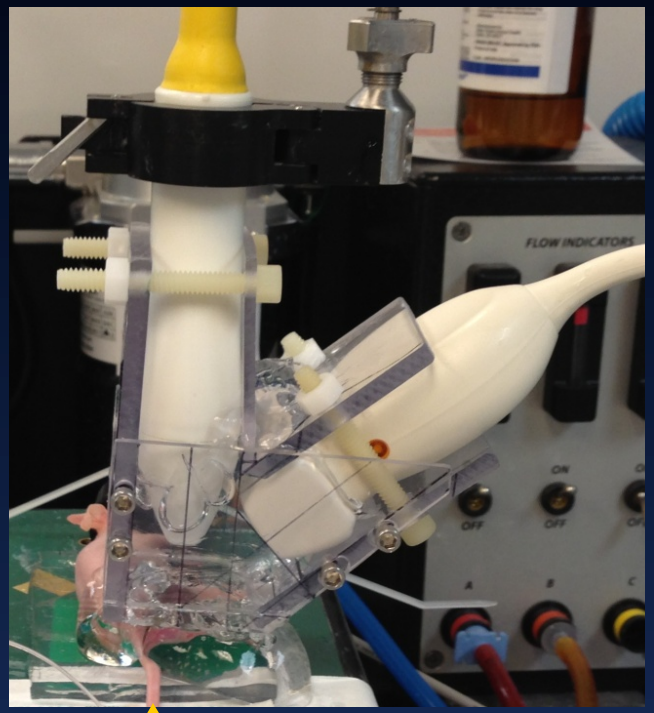


1.8 MPa

Ultrasound Image-guided Drug Delivery *In Vivo*

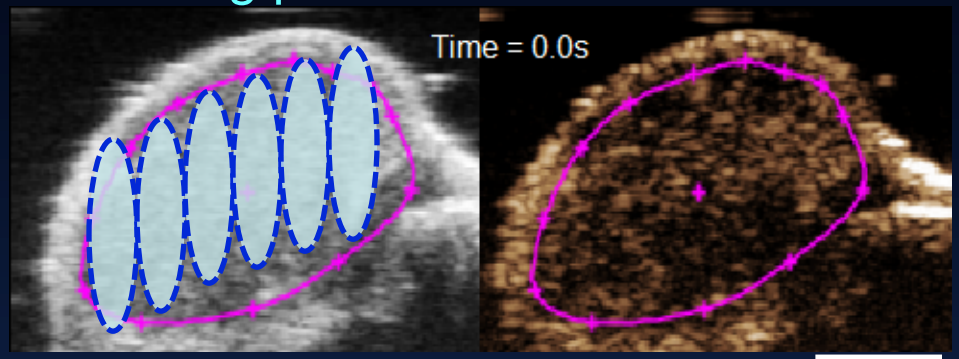
- Effects of ***pressure*** on delivery outcomes
- Model drug carrier system: **120nm** semiconducting polymer nanoparticles (SPNs).
- Evaluation:
  - Drug delivery profile examined on immunohistochemical staining.
  - Histological/morphological examination

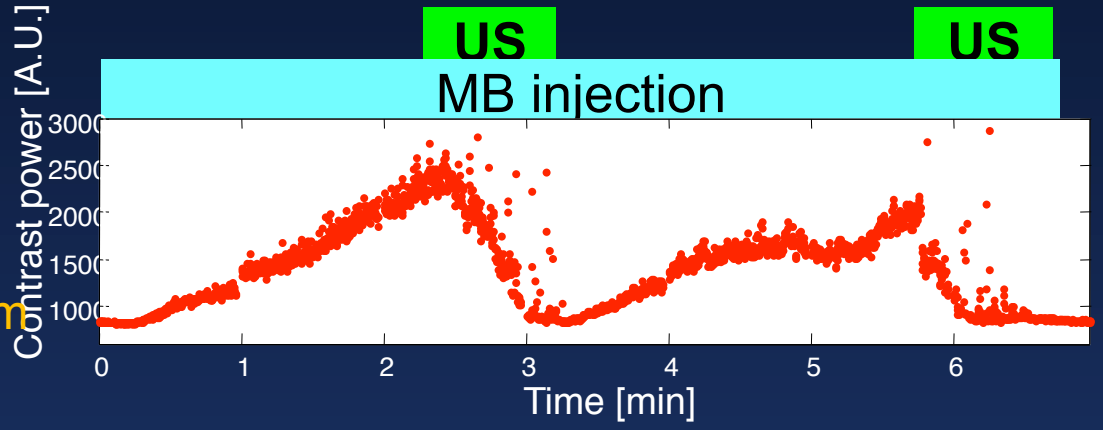
Ultrasound Image-guided Drug Delivery *In Vivo*



MBs + model drug system
(120nm SPNs)

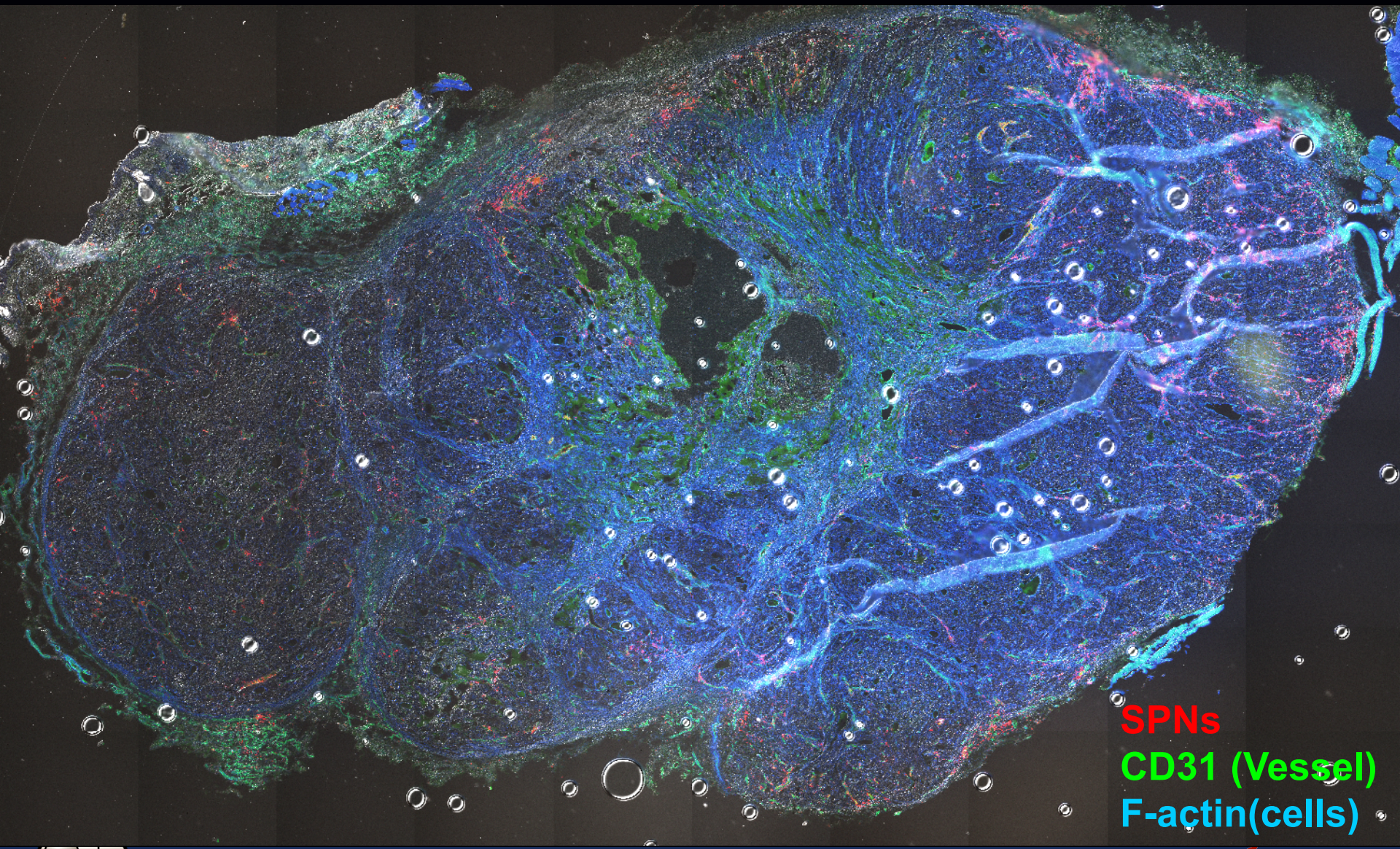
Ultrasound
scanning pattern

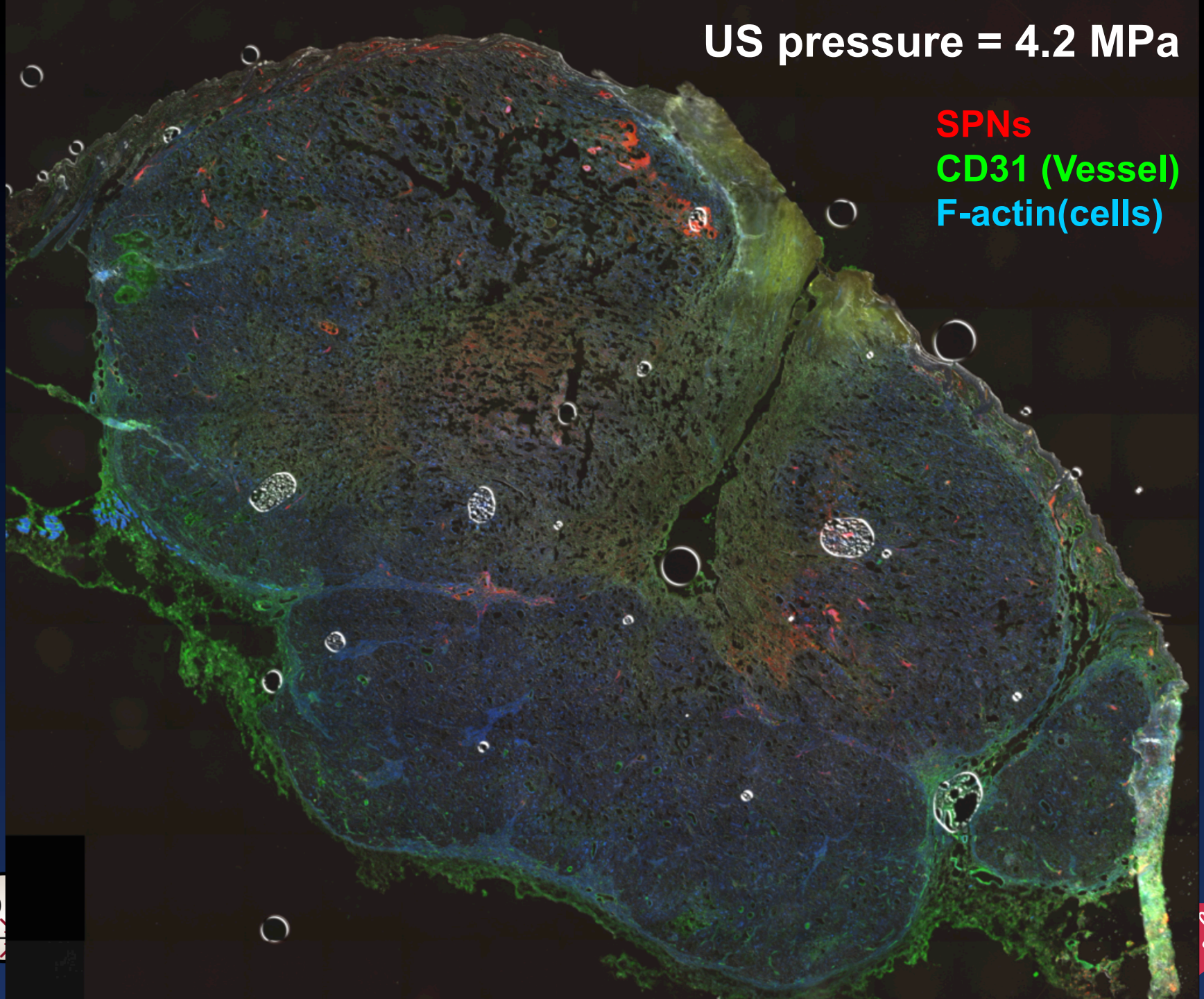




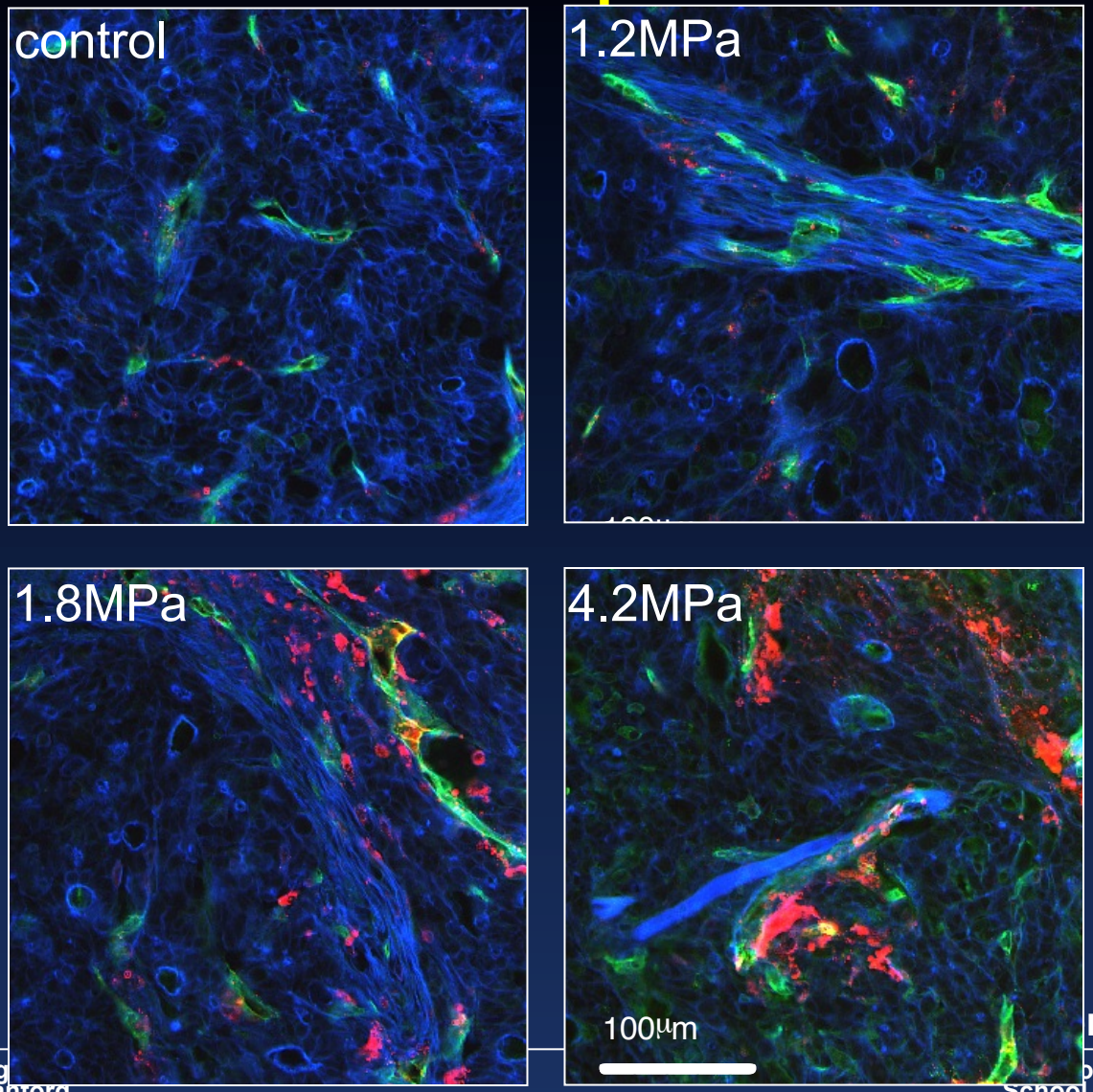
Ex Vivo Immunohistochemical Staining

US pressure = 1.8 MPa



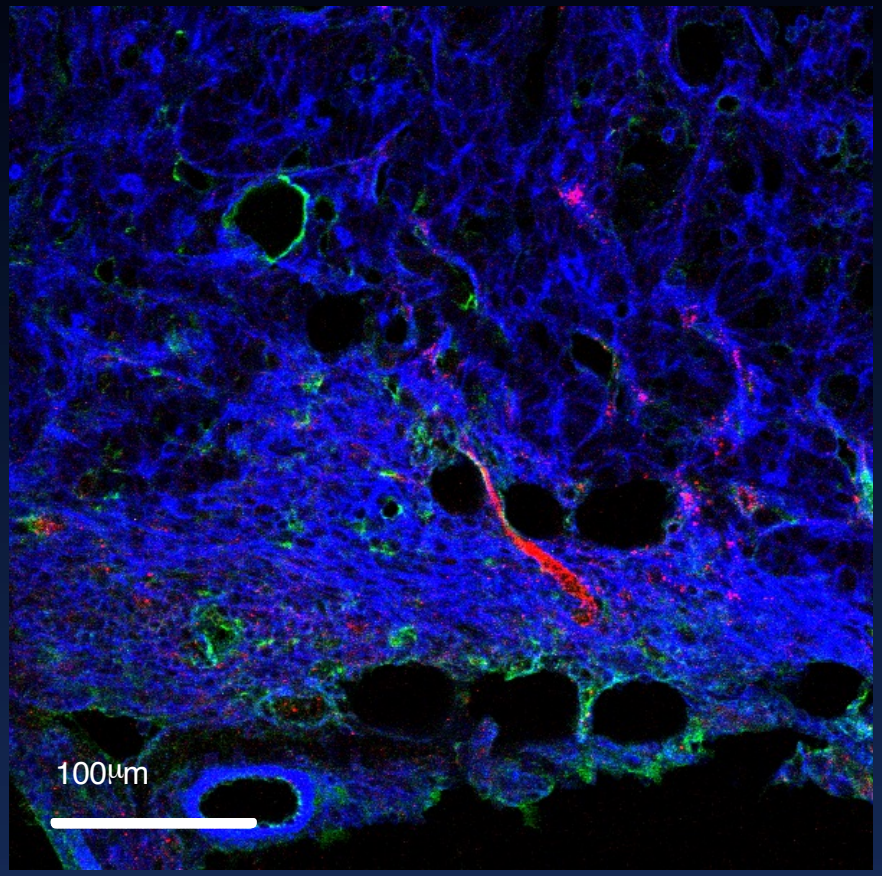

US pressure = 4.2 MPa
SPNs
CD31 (Vessel)
F-actin(cells)

Ex Vivo Immunohistochemical Staining: Close-up view



SPNs
CD31 (Vessel)
F-actin(cells)

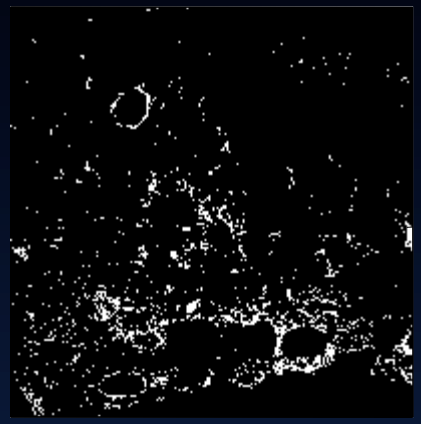
Quantitative analysis of NP distribution



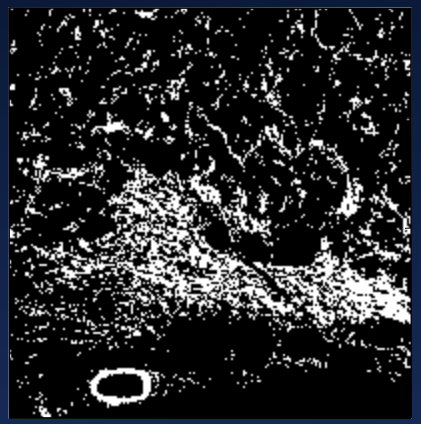
Threshold:
average + 5*STD
background pixel
value

NPs

CD31



F-actin

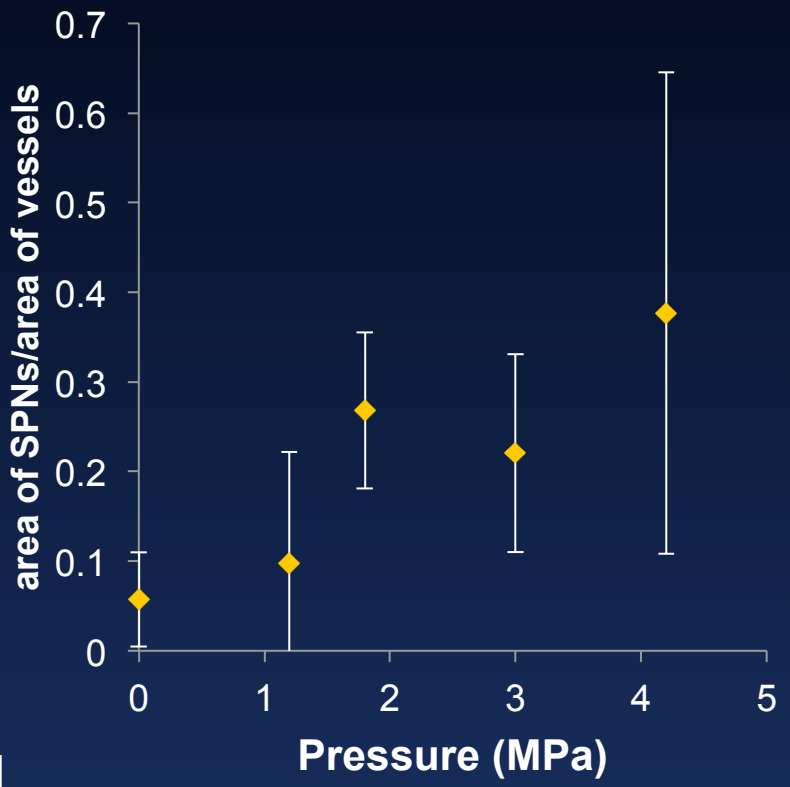


NP/vessel ratio = area of NPs / area of vessels
NP/Factin ratio = area of NPs / area of Factin

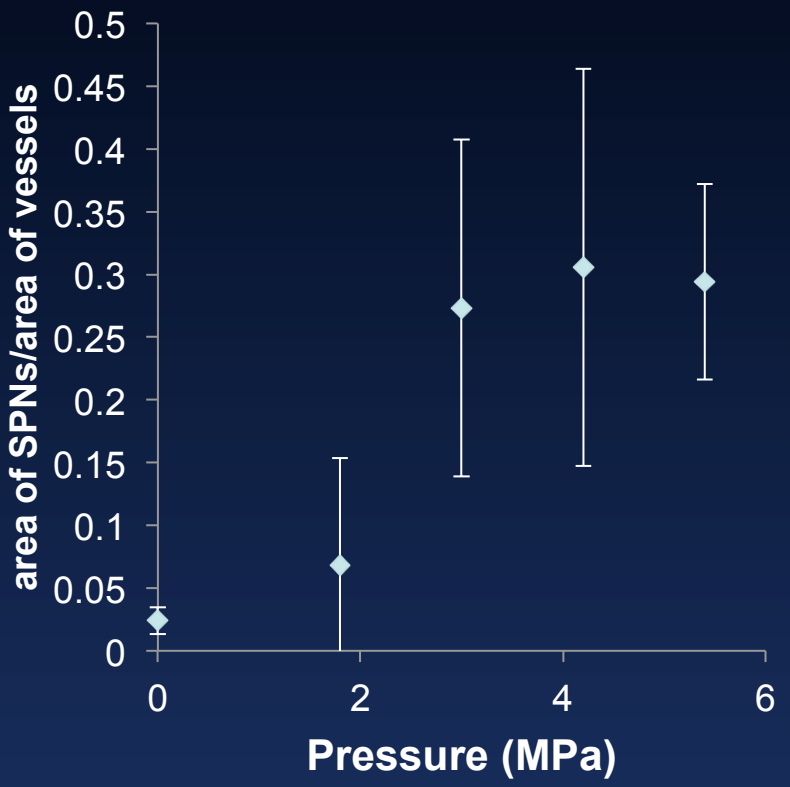
Delivery of 120nm SPNs into tumors

US ➔ 6 – 8X more nanoparticle delivery than control

NP/vessel



NP/F-actin

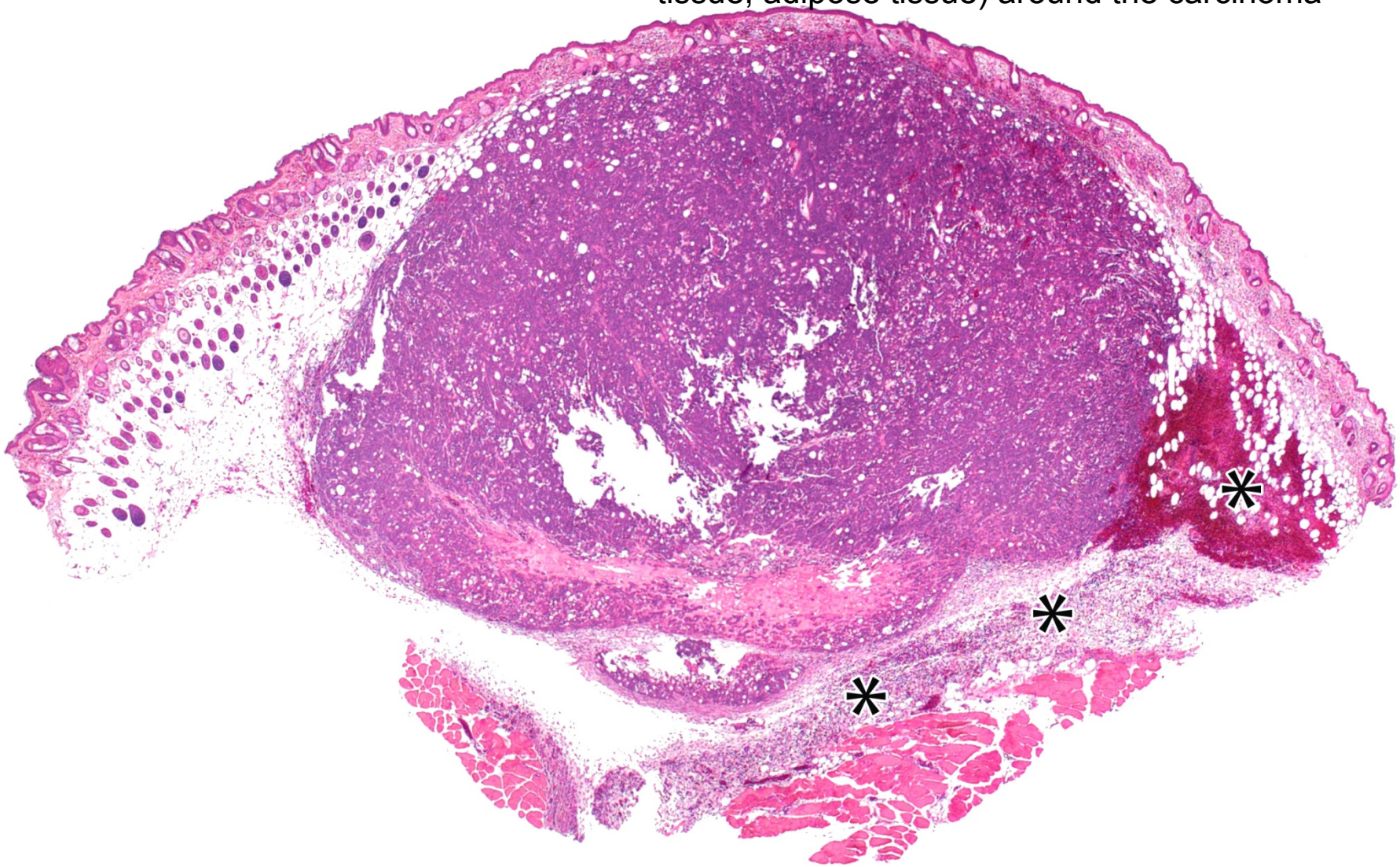


N=3-4 each

Histological/morphological examination

5MPa US

Extensive hemorrhage in connective tissue (fibrous tissue, adipose tissue) around the carcinoma



Histological/morphological examination

US pressure (MPa)	Morphology	H&E
-		Minimal peri-tumoral hemorrhage
1.2		
1.8		
3		Minimal to mild peri-tumoral hemorrhage
4.2		
5.4		Multifocal, moderate peri-tumoral hemorrhage.

Conclusions

- Acoustic pressure and microbubble concentration have the most significant effects on cavitation.
- Real-time US imaging allows for confirmation of successful cavitation *in vitro* and *in vivo*.
- *In vivo* results demonstrate feasibility of delivery of 120 nm model drug systems into tumor xenografts in mice.
- Higher pressure → more NP delivery in vivo. More hemorrhage. Mid pressure range (1.8 – 4.2 MPa) may result in enhanced delivery without significant damage.

Acknowledgement

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