Image-guided ultrasound facilitated drug delivery into tumors: optimization of treatment strategy based on quantitative measurement of cavitation

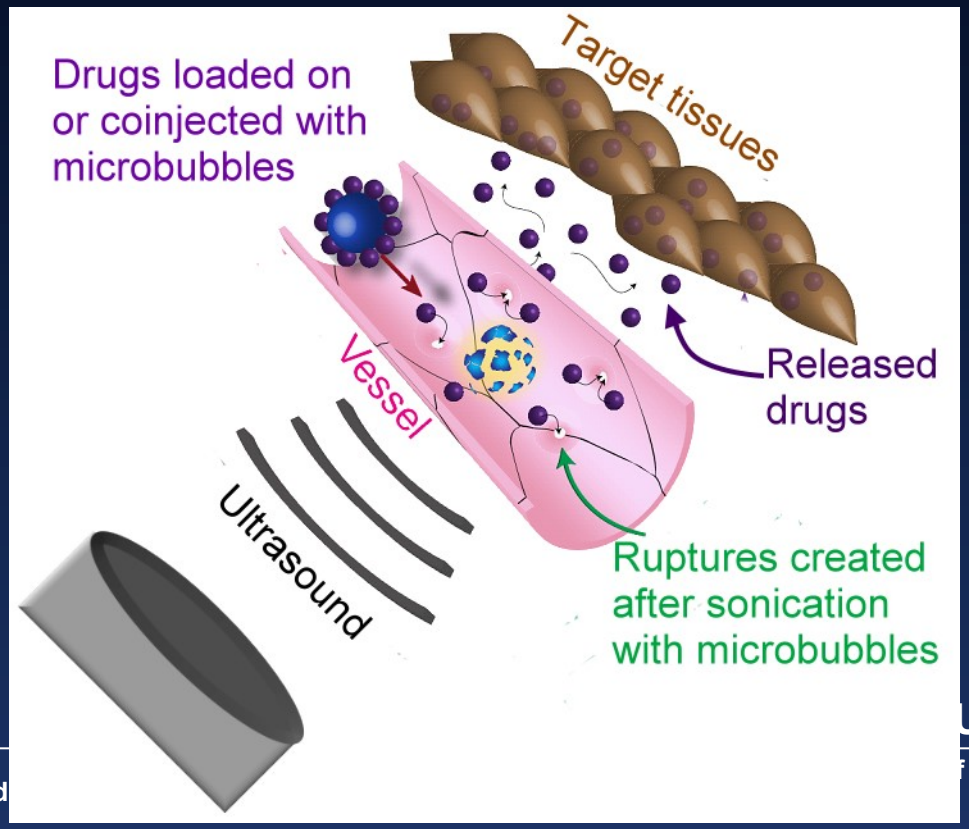
Presenter: Tzu-Yin Wang

Mentors: Juergen Willmann
Kim Butts-Pauly

Department of Radiology
Molecular Imaging Program at Stanford
School of Medicine, Stanford University

Background

- **Cavitation**: expansion, contraction, collapse of air encapsulated microbubbles
- **Sonoporation**: cavitation ➔ cell/vessel disruption ➔ delivery of therapeutics into target cells/tissues

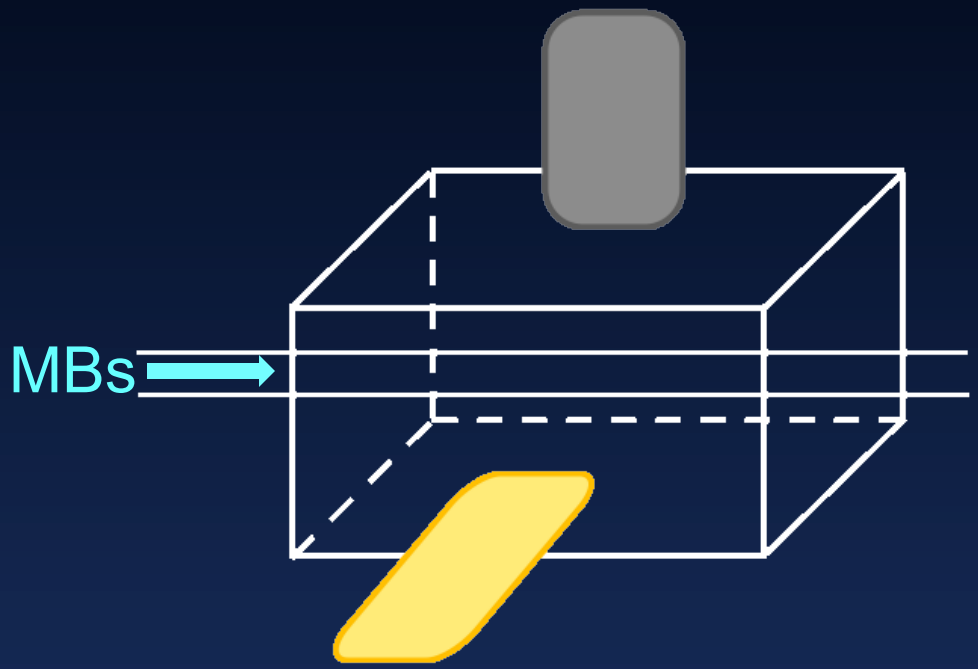


Goal

- Optimize treatment strategies for US-assisted delivery into tumor
  - Effects of acoustic and microbubble parameters
  - *In vivo* treatment platform
  - Image guidance of treatment

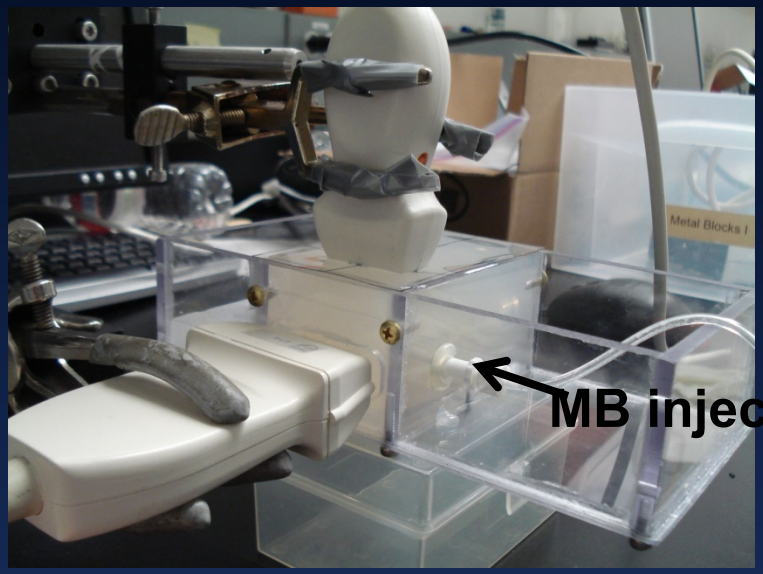
Phantom study:
Experimental setup

Cavitation generation



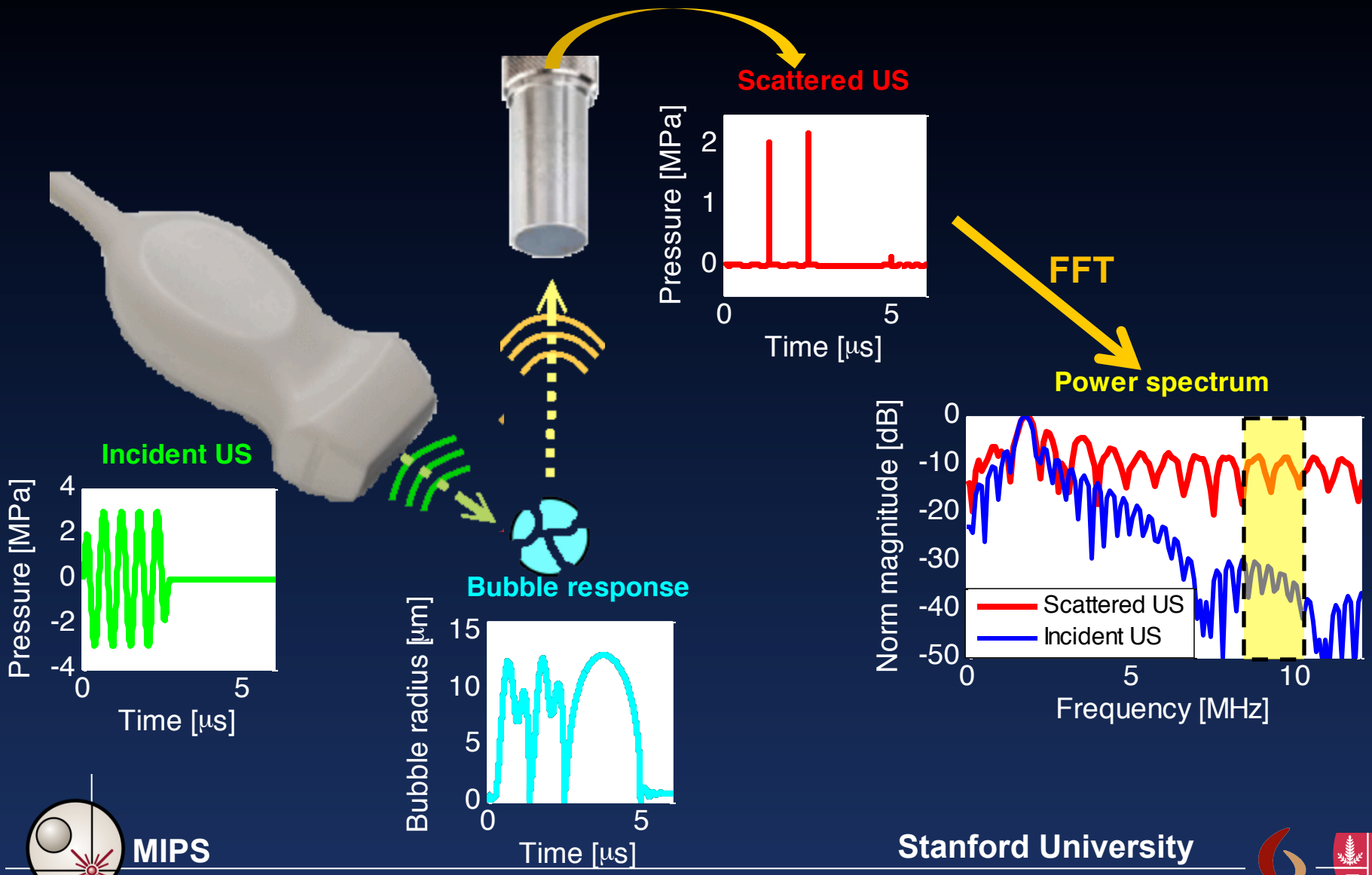
Active/passive cavitation detector

P4-1 probe → cavitation

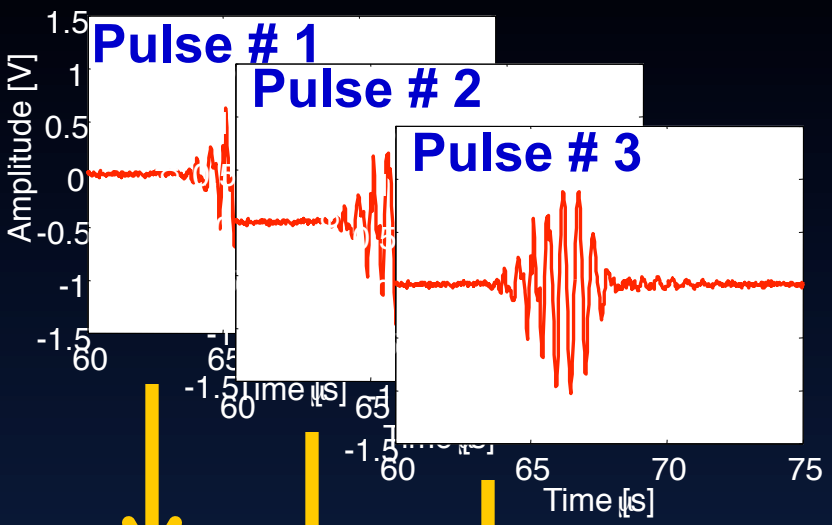


L7-4 probe → ACTIVE cavitation monitoring

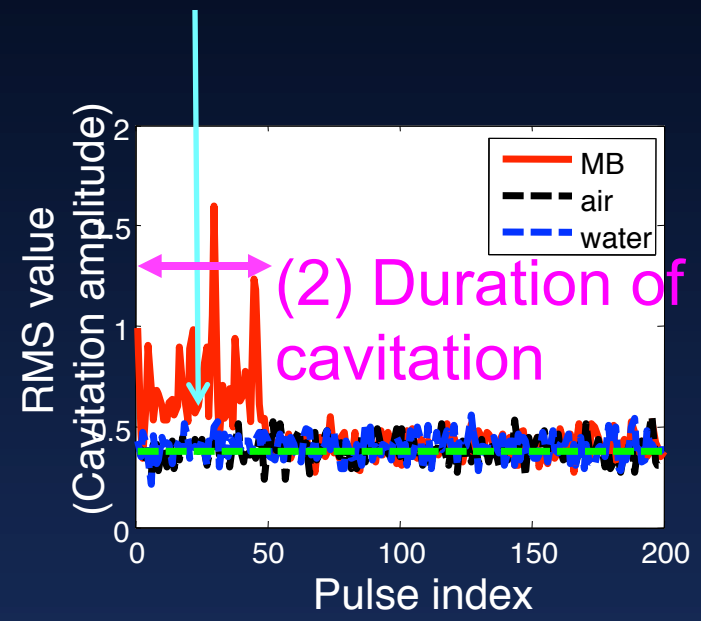
Passive cavitation detection (PCD)



Quantification of cavitation

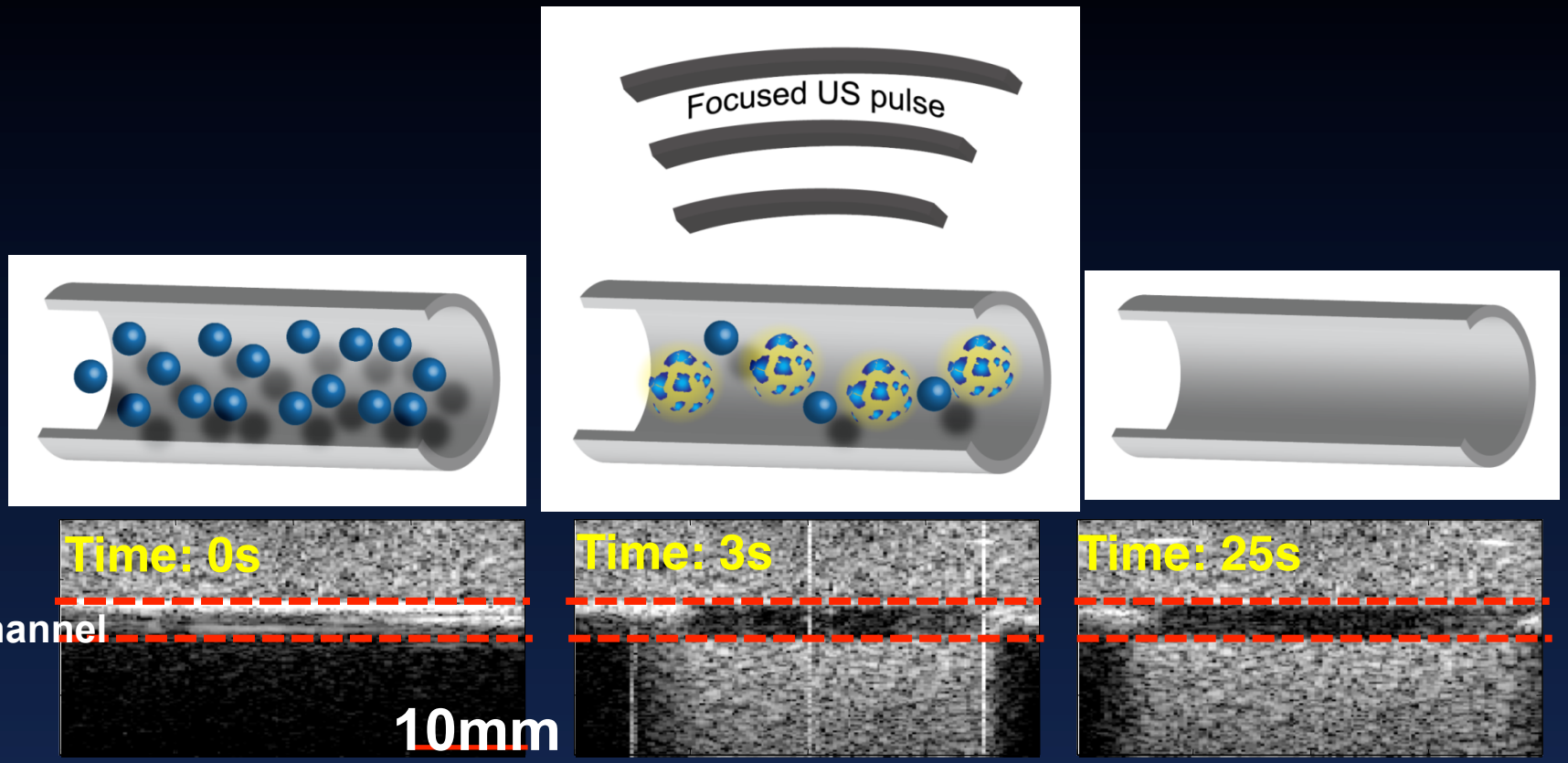


Temporal integral ➔ inertial cavitation dose (ICD)



(3) Mean RMS value during onset of cavitation

Active cavitation detection



Presence of MBs ➔ high image intensity and acoustic shadowing

US➔ destruction of MBs

Destruction of MBs ➔ reduced image intensity

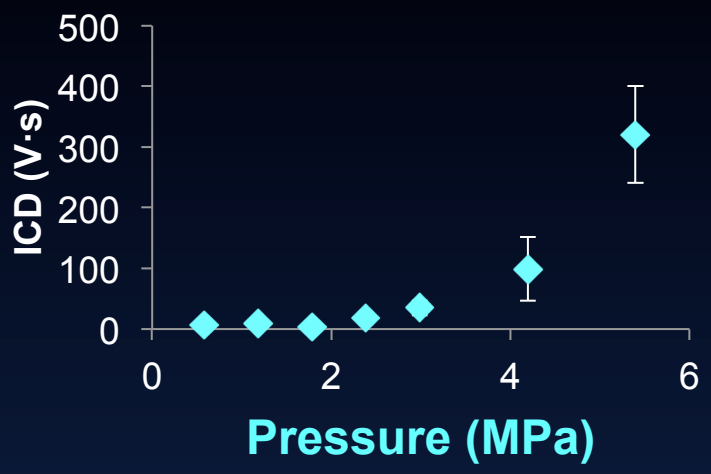
B-mode image intensity ⬇ ➔MB destruction

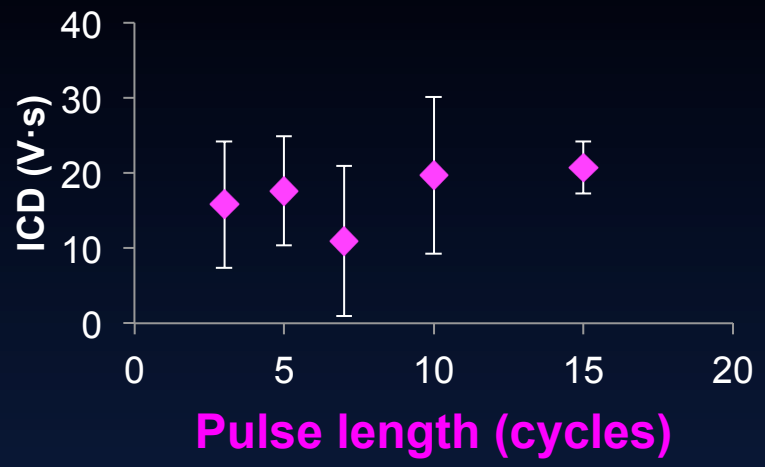
Experimental series

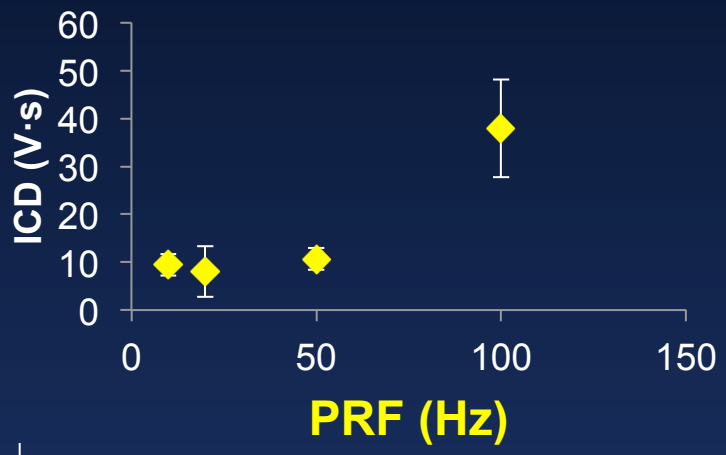
* Total treatment time = 2 sec (200 pulses).

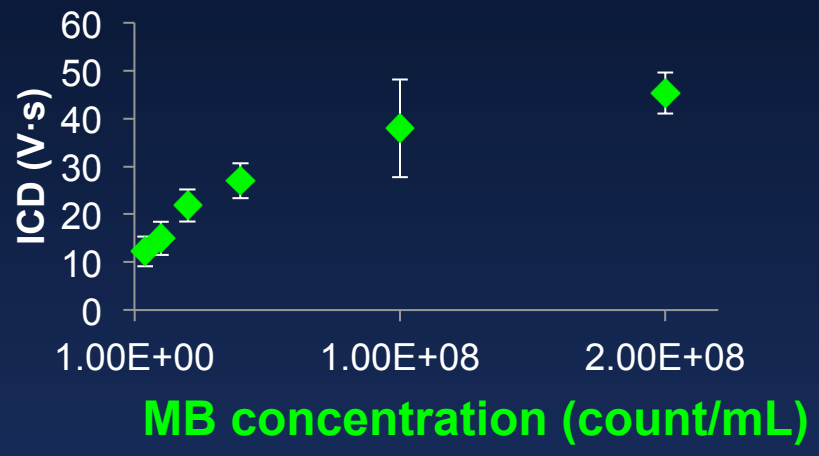
	Frequency (MHz)	P- Pressure (MPa)	PD (cycles)	PRF (Hz)	MB (BR38) (count/mL)
Series 1	1.8	**0.6 – 5.4**	5	100	1×10^8
Series 2	1.8	2.4	**3, 5, 7, 10, 15**	100	1×10^8
Series 3	1.8	3.0	5	**10, 20, 50, 100**	1×10^8
Series 4	1.8	3.0	5	100	**4×10^6 ~ 2×10^8**

Passive cavitation detection in tissue phantoms

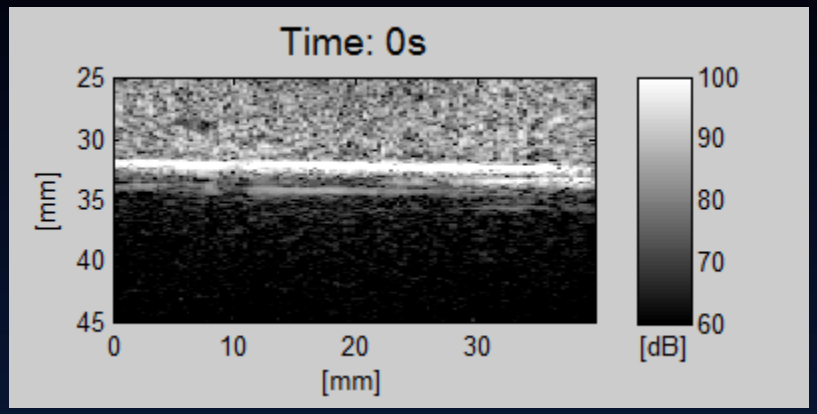




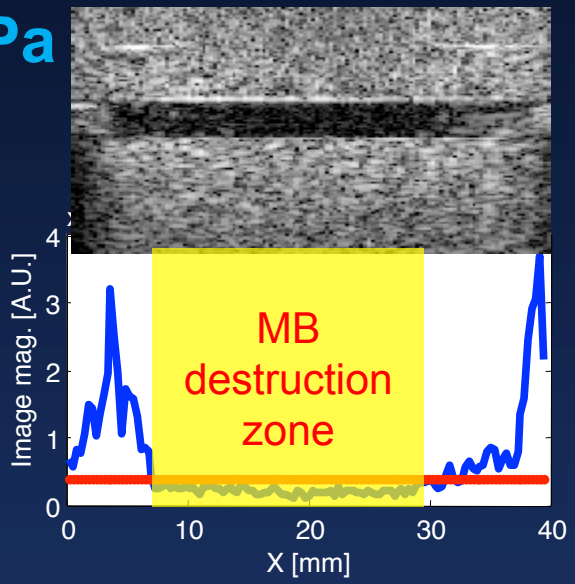




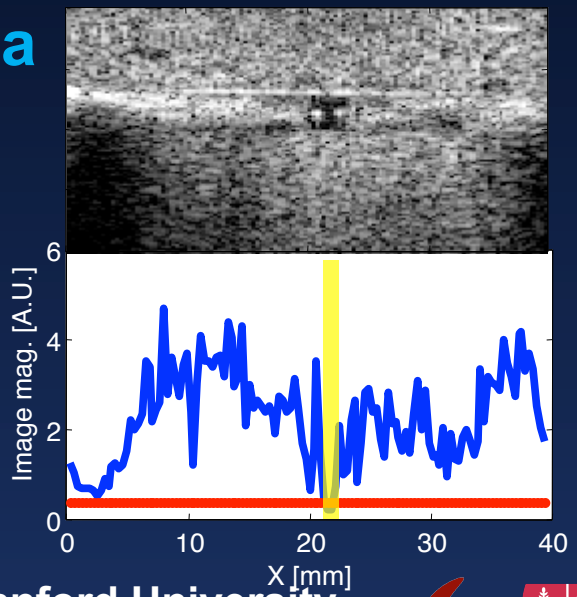
Active cavitation detection in tissue phantoms



5.4 MPa

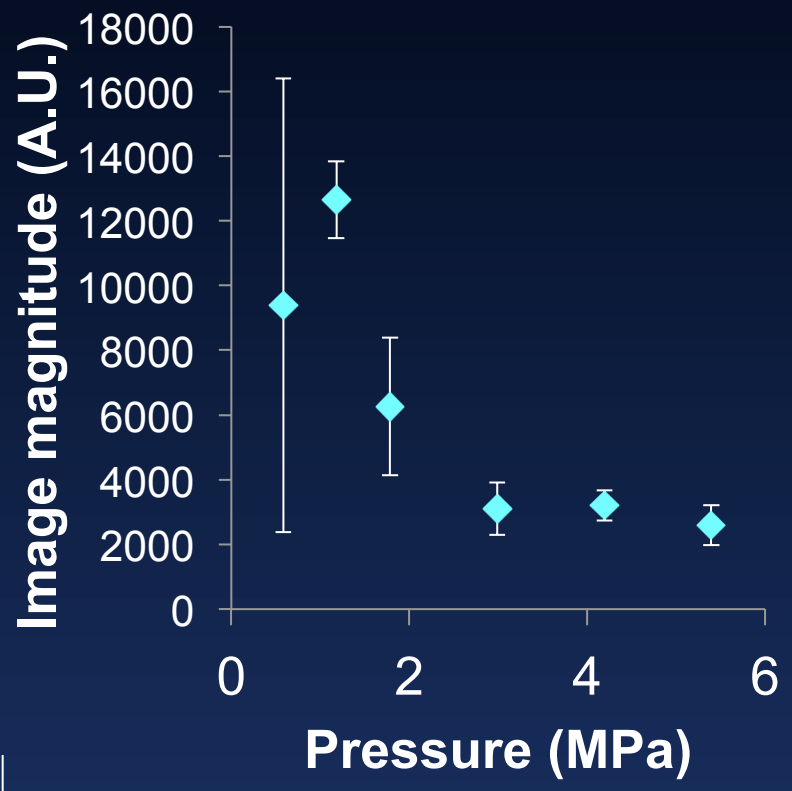


1.8 MPa

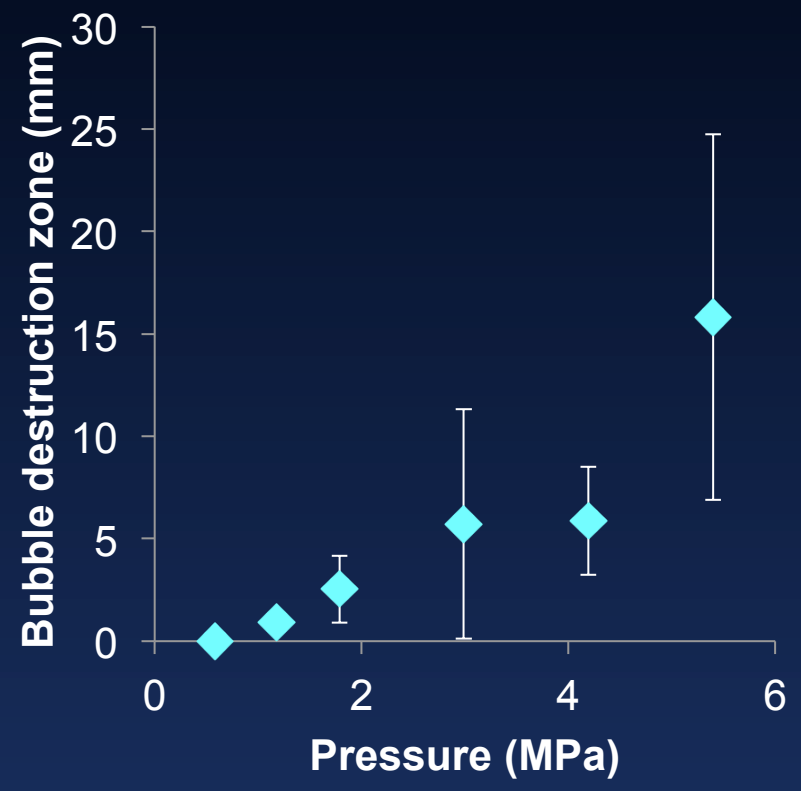


Active cavitation detection in tissue phantoms

Post-treatment image magnitude



Bubble destruction zone (width)

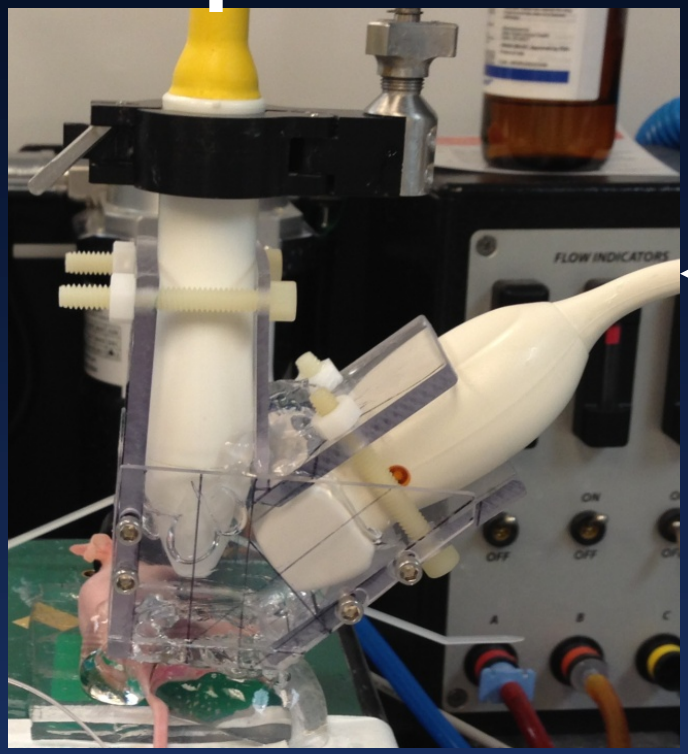


N=4 for each

In vivo treatment platform

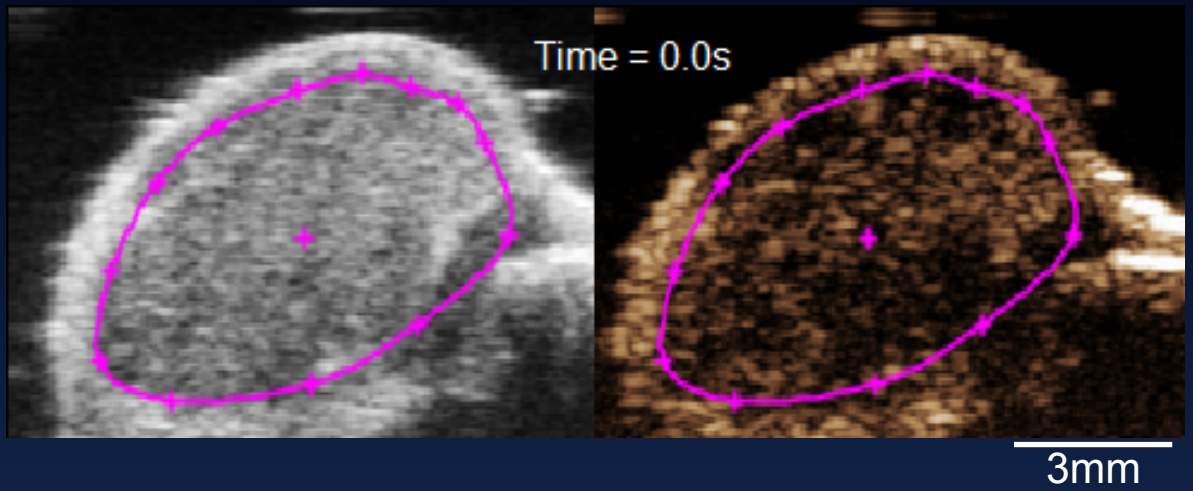
- MBs: PFC core, lipid shelled MBs
- Tumor model: Subcutaneous tumor on mice
- Model drugs:
  - 40nm polymer NPs
  - 130nm PLGA NPs

Vevo 2100 US imager



Verasonics US system

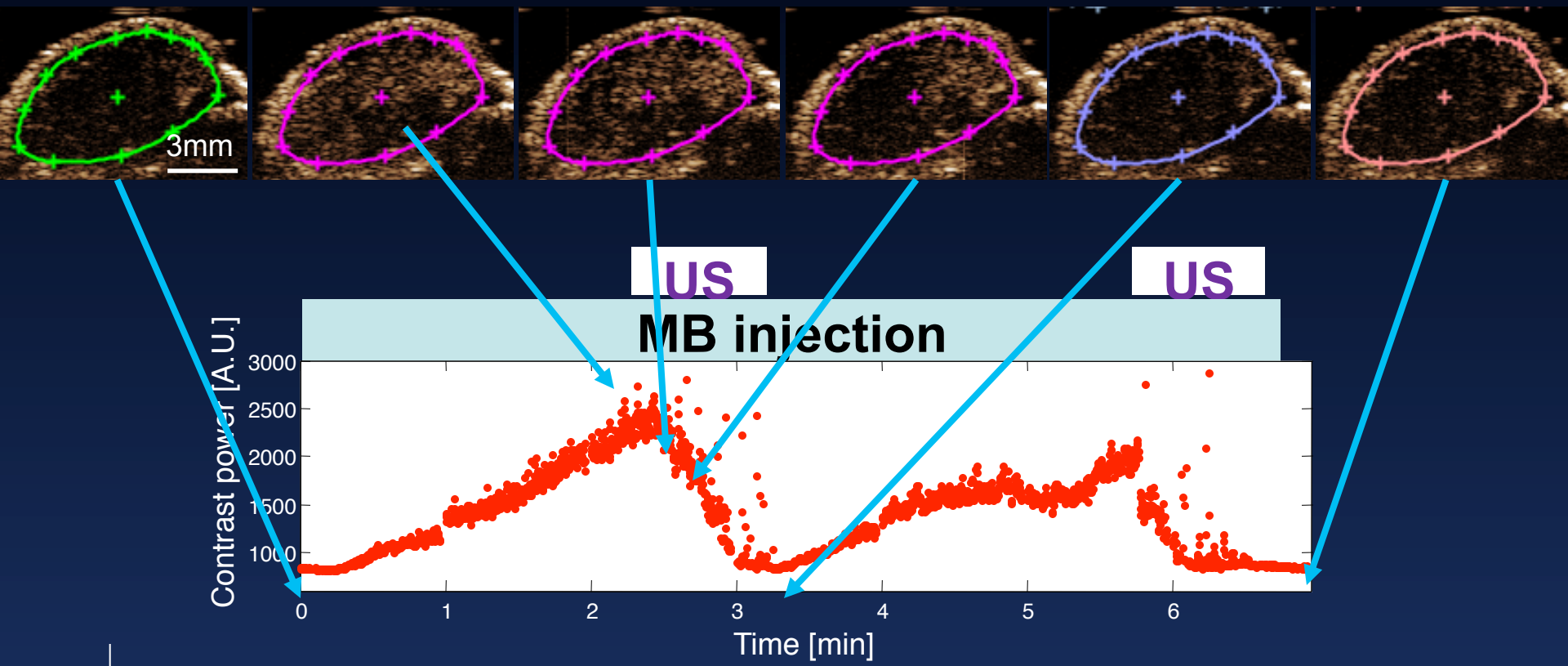
Active cavitation detection *in vivo*



MB destruction @ 3 MPa

Active cavitation detection

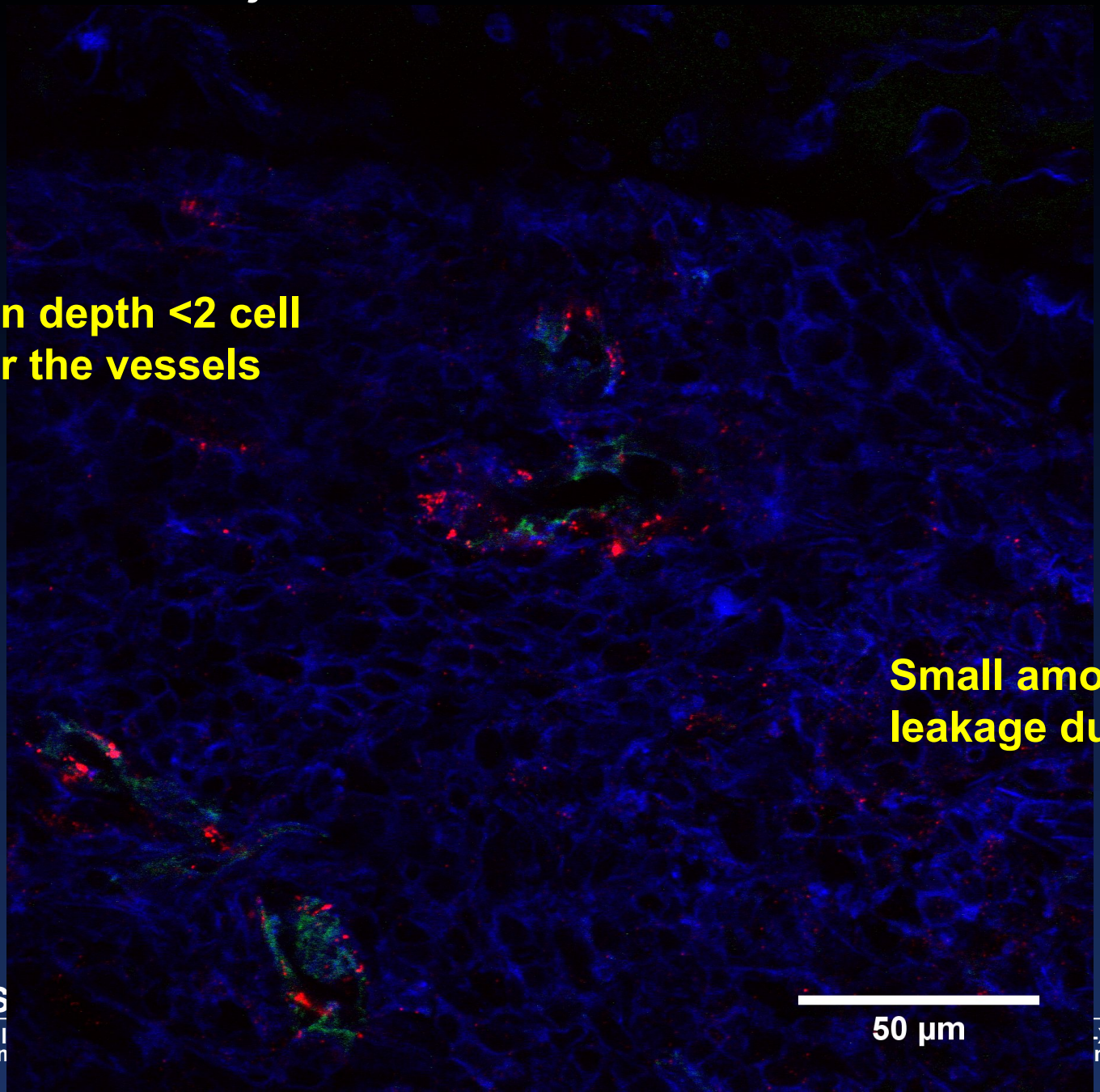
- Treatment monitoring



MB destruction @ 3 MPa

Control: tail vein injection, 4hrs

40nm SPNs CD31 F-actin



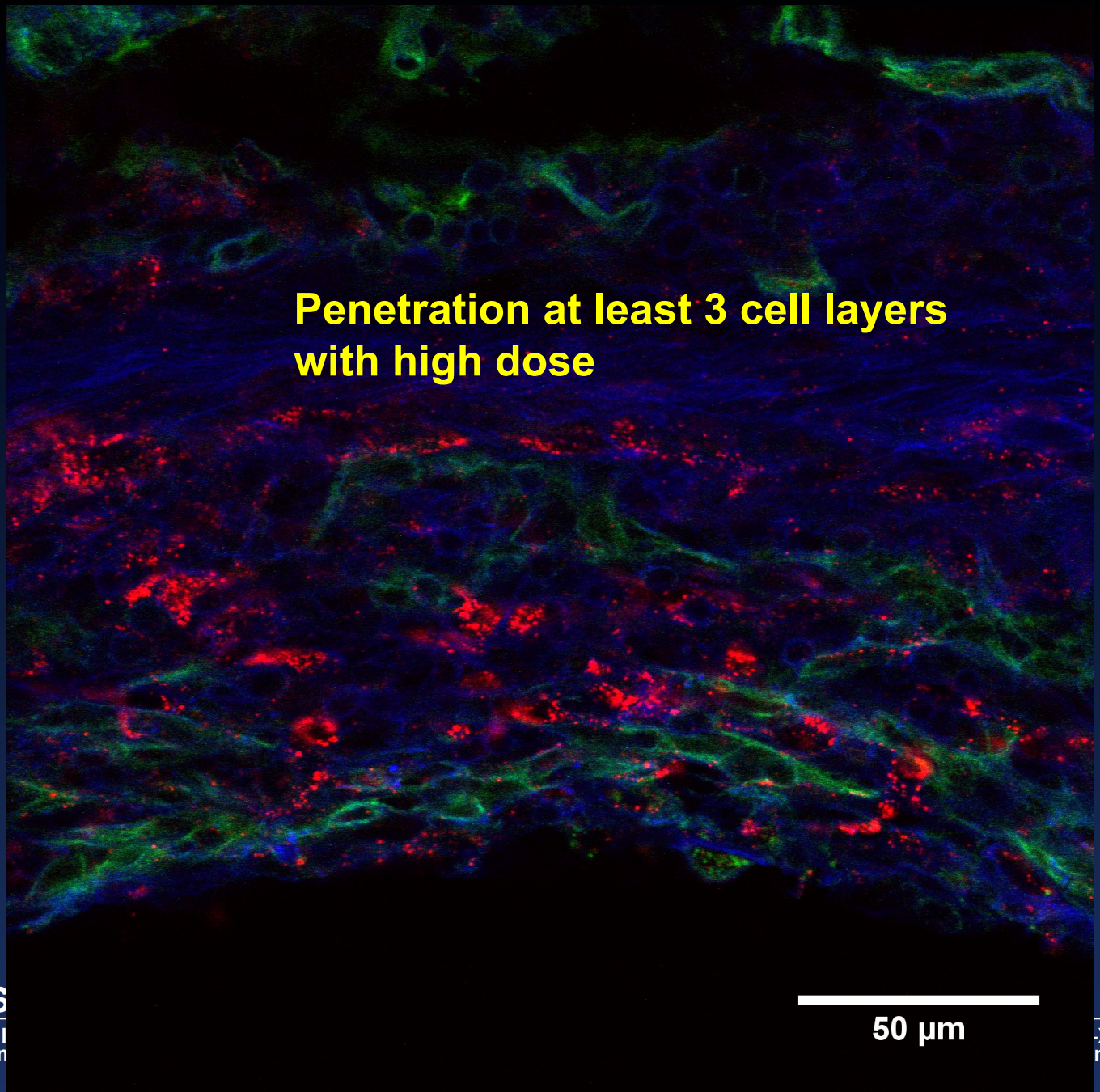
Penetration depth <2 cell layers near the vessels

Small amount of leakage due to EPR

MIPS
Molecul
Progran

Ultrasound + microbubble, 4hrs

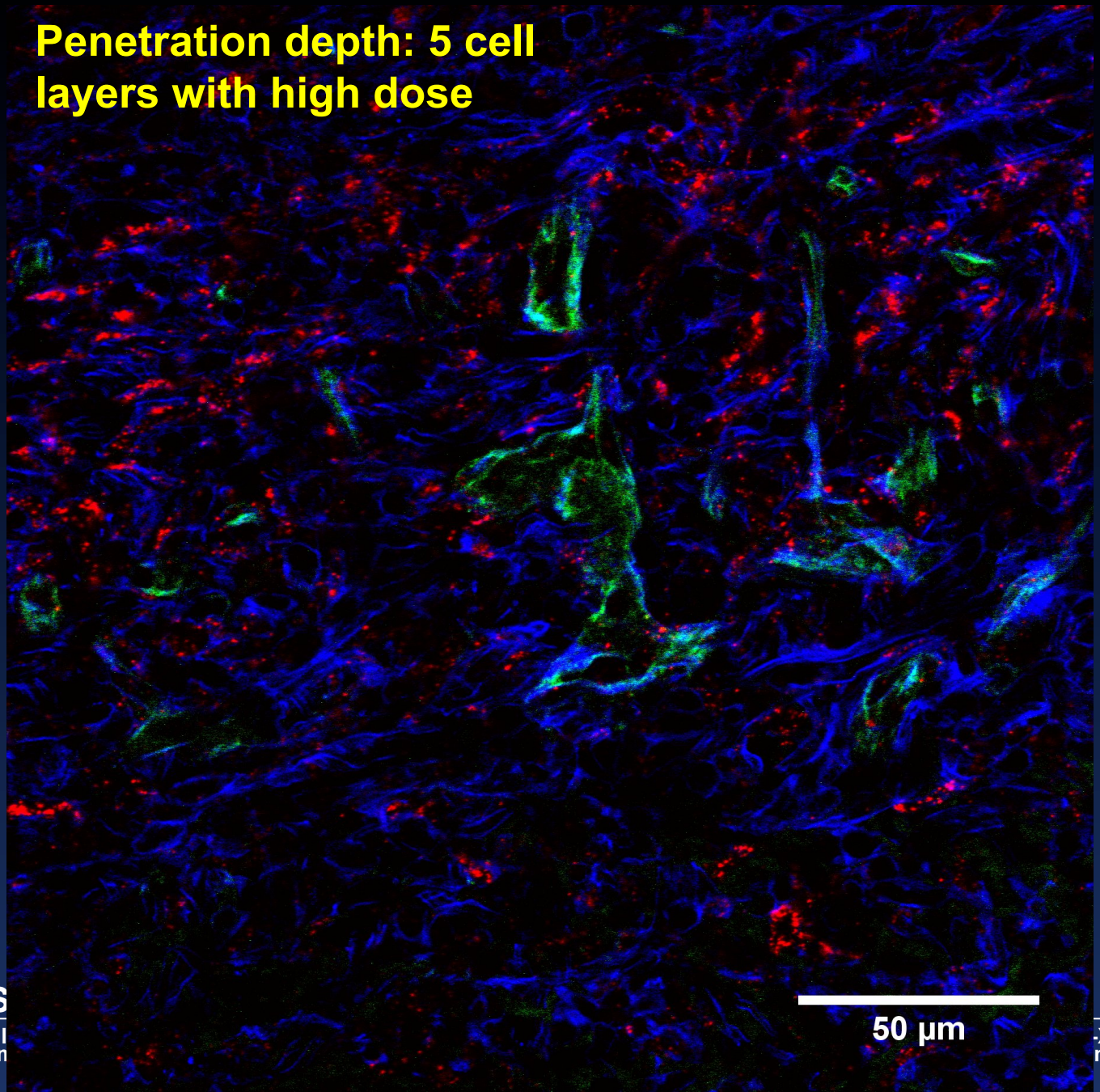
40nm SPNs CD31 F-actin



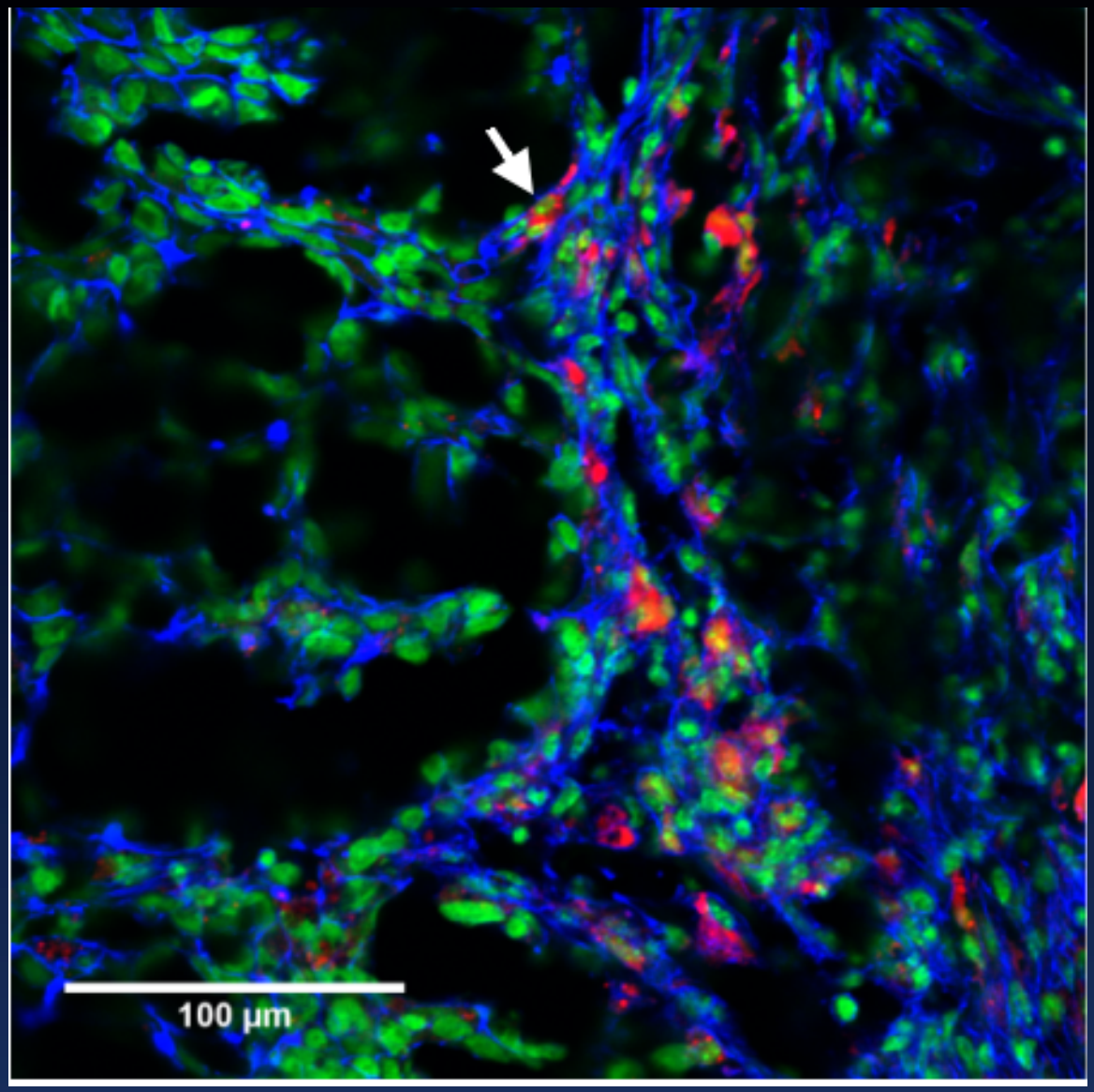
MIPS
Molecul
Progran

Ultrasound + microbubble, 24 hrs

40nm SPNs CD31 F-actin



130nm PLGA-NP Nucleus F-actin



Summary

- Ultrasound image-guided drug delivery platform in vivo allows for treatment monitoring in real-time.
- Successful microbubble cavitation was achieved in phantoms and in vivo.
- Detectable delivery of 40-nm polymer nanoparticles into tumors with US and MB treatments.

Future work

- Effects of acoustic parameter, MB parameters, scanning protocol in drug delivery in vivo
- Spatial extent of drug distribution
- Maximum deliverable size of drugs