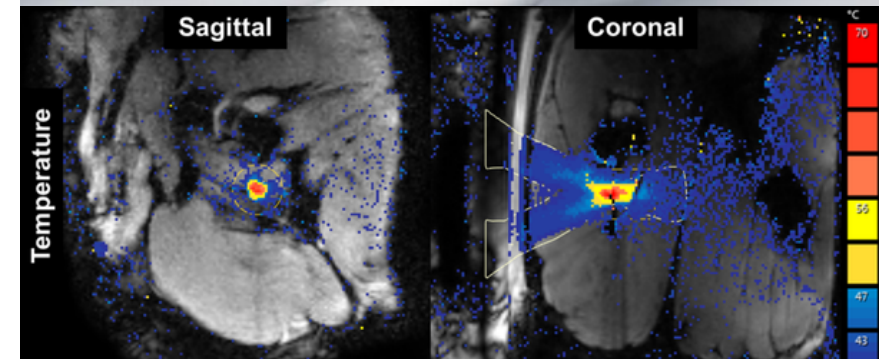
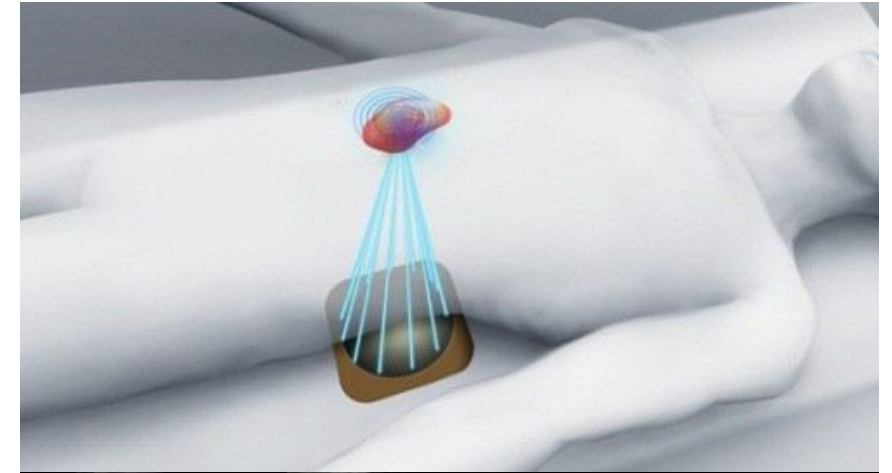
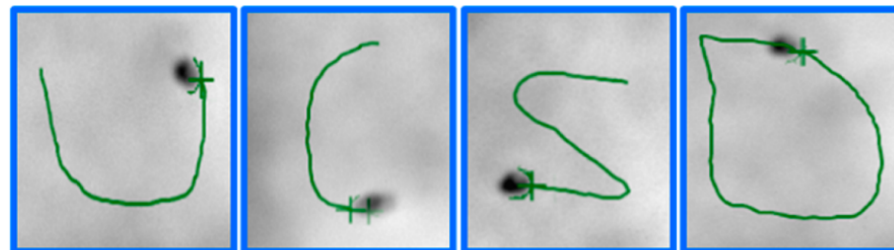
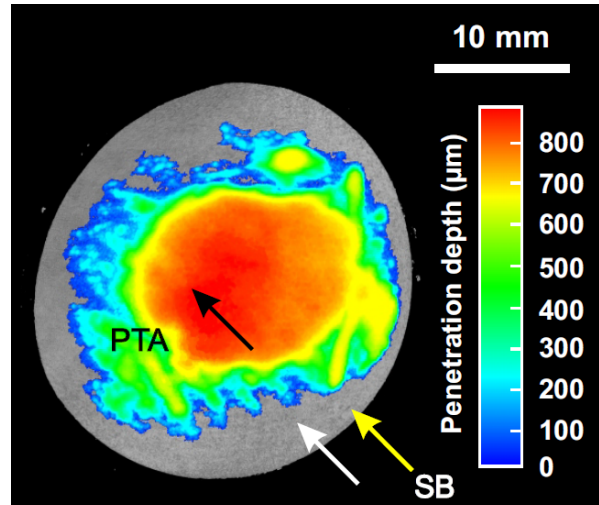


Biomedical Ultrasonics, 5 cr

Heikki Nieminen

7.1.-31.5.2019



Excursion expected...

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An Innovative Therapeutic Platform

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TECHNOLOGY

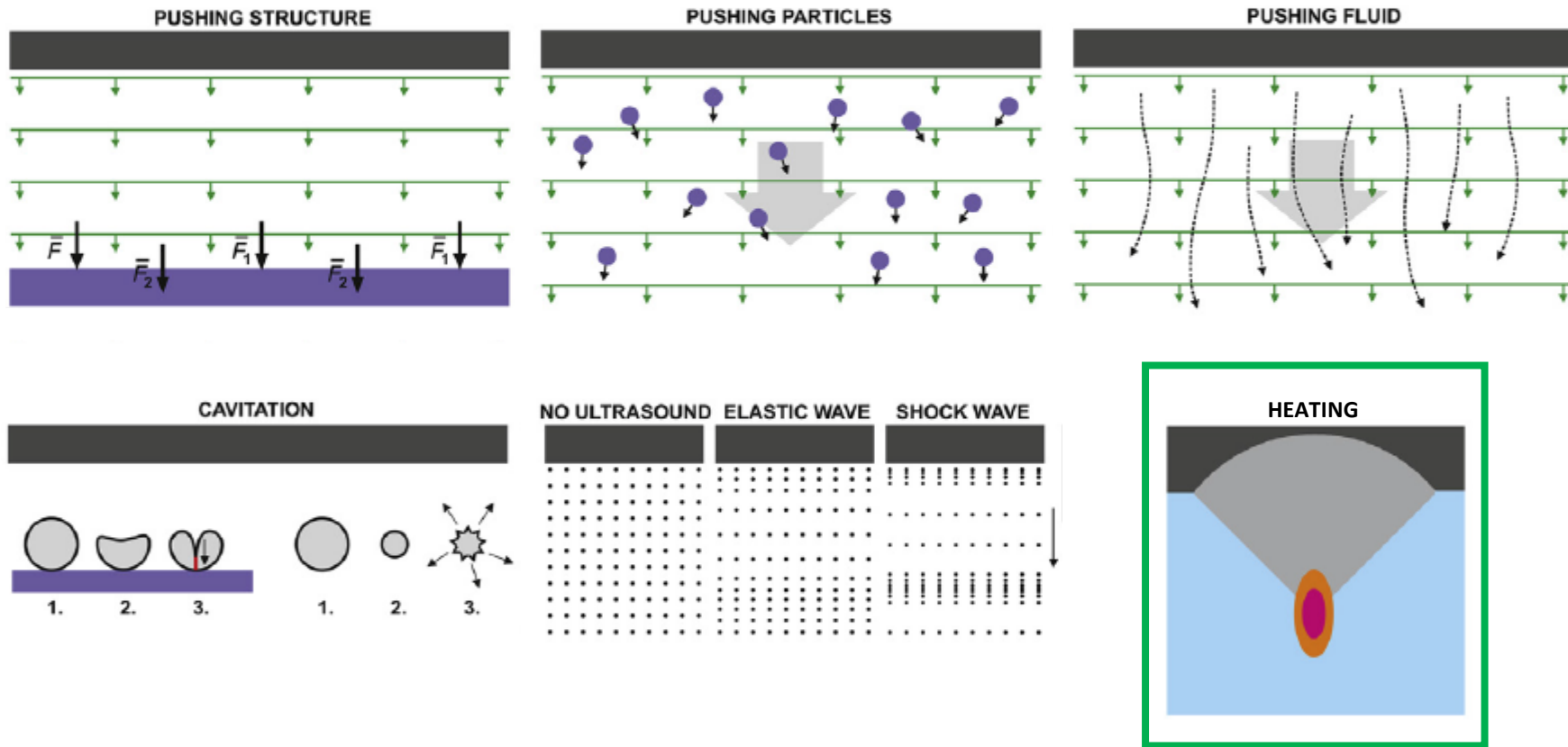
UTERINE FIBROID ABLATION

BONE PAIN PALLIATIVE THERAPY

Reserve your lab time for your project

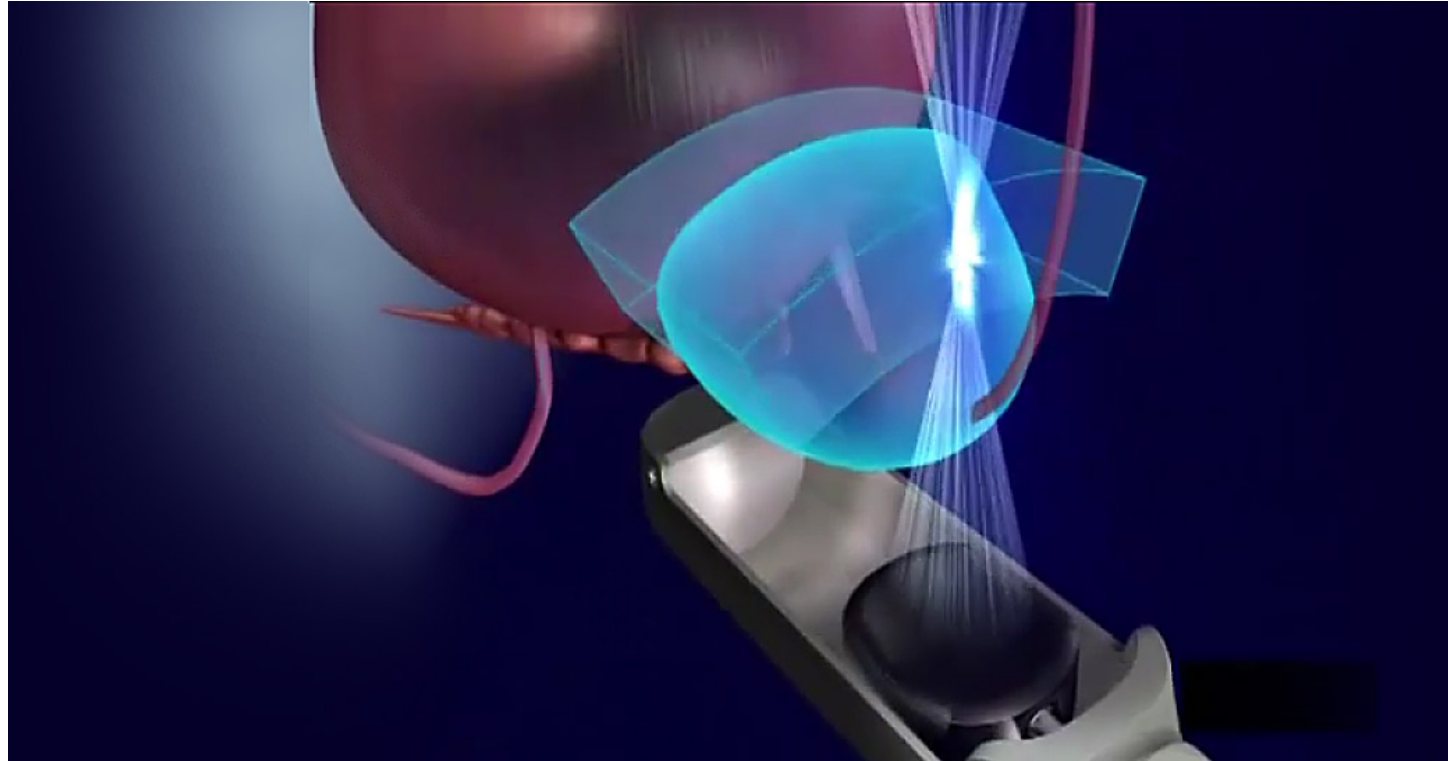
<https://doodle.com/poll/2ftfvf73vtp3y9ce>

(Non-linear) ultrasonics



Thermal therapies

Thermal ablation by high-intensity focused ultrasound (HIFU)



Ultrasound focused into the target region, where sound is absorbed as heat and heat induces damage to the targeted tissue.

Thermal dose

- Thermal dose:

$$TD_{43}(\mathbf{r}, t) = \int_0^t R^{43-T(\mathbf{r},\tau)} d\tau$$

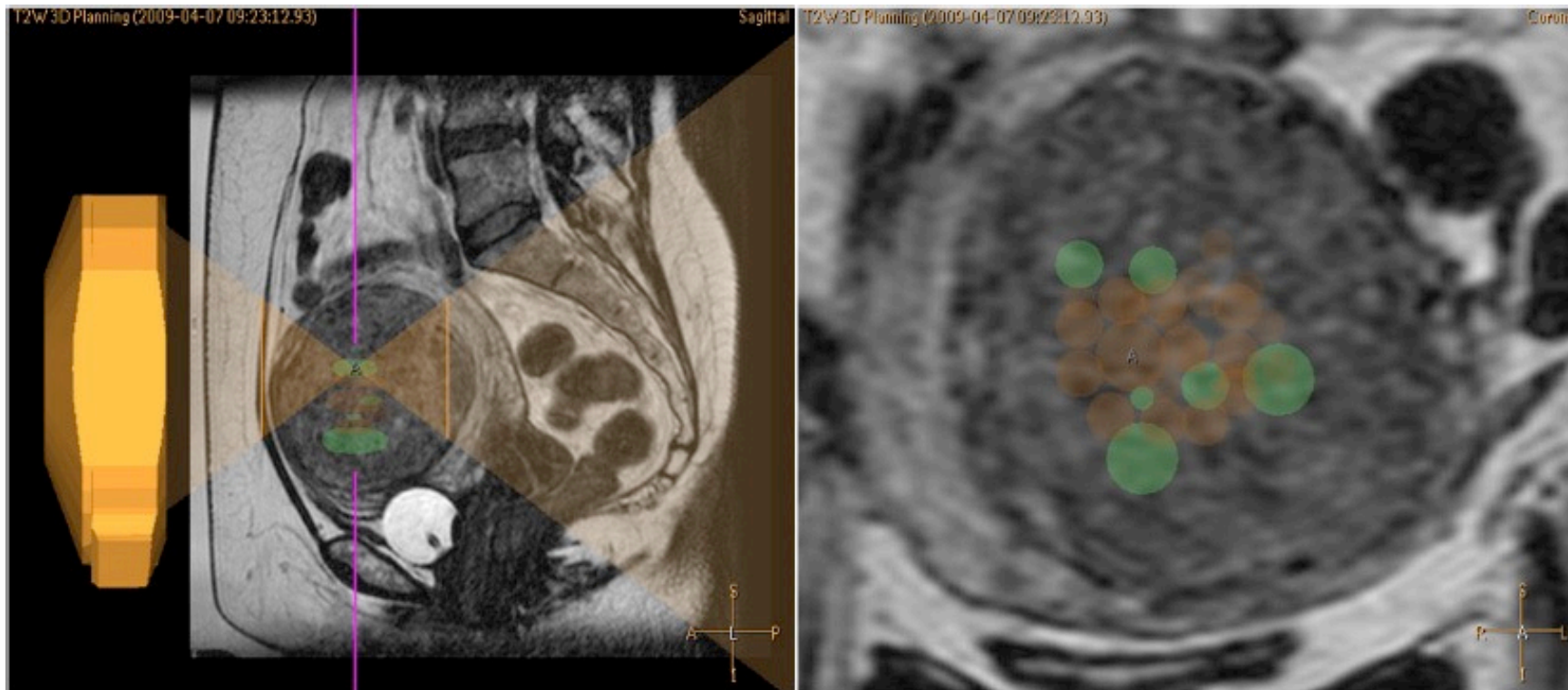
where $R = 0.25$ when temperature, $T(\mathbf{r}, t)$, is less than 43°C and $R = 0.5$ at temperature 43°C or higher.

- Describes the dose due to temperature
- Keeping tissue in 43°C for 240 minutes destroys destroys the tissue
- Keeping tissue in 55°C for few seconds destroys destroys the tissue
- Thermally induced damage is strongly a threshold-like phenomenon
→ tissue near the focus is destroyed, while leaving adjacent tissues intact.

Applications

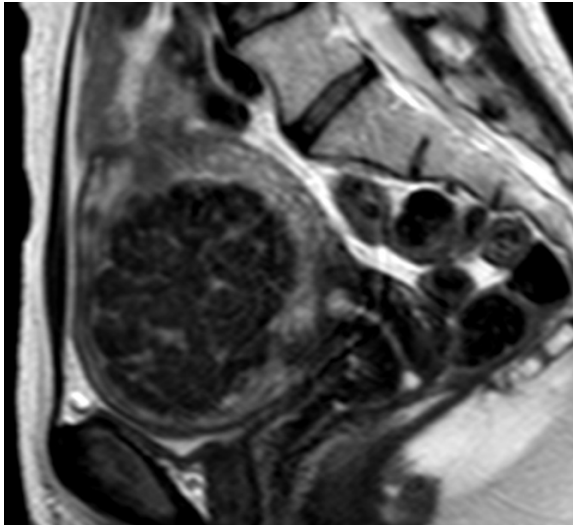
- Thermal ablation: destroying thermally tissue by denaturing proteins
- Hyperthermia: elevating temperature of tissue to enhance drug therapy (influencing the cellular repair mechanisms)
- Drug release: releasing drugs from thermally sensitive microcapsules

Thermal ablation by HIFU: Uterine fibroid

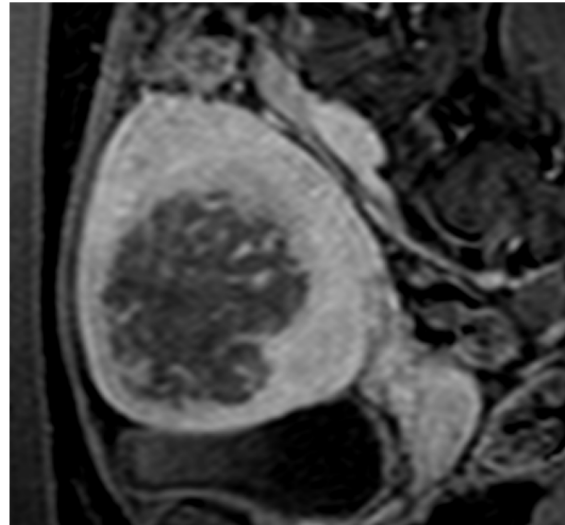


Thermal ablation by HIFU: Uterine fibroid

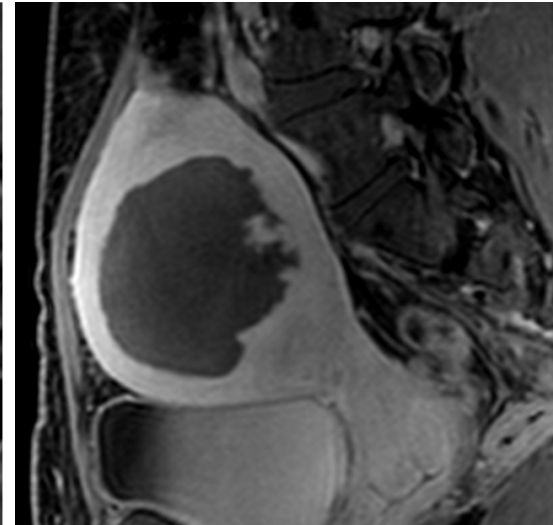
Planning (T2)



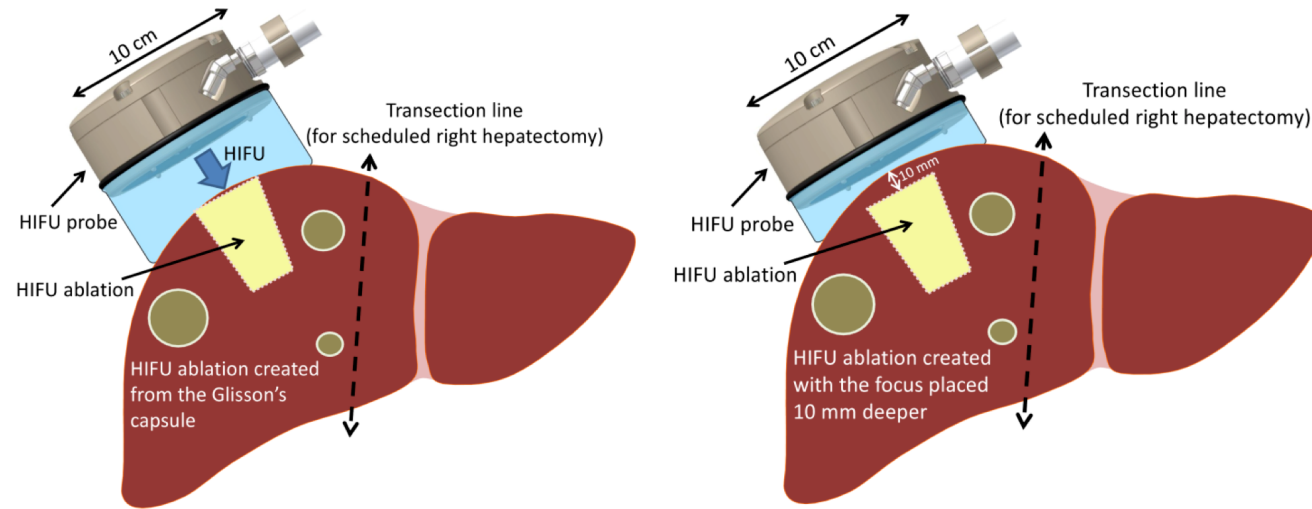
0 day post-treatment
(T1, CE)



0 month post-treatment
(T1, CE)

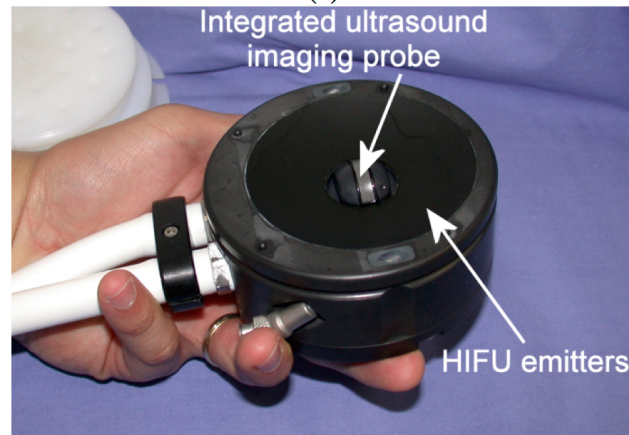


Thermal ablation by HIFU: Liver

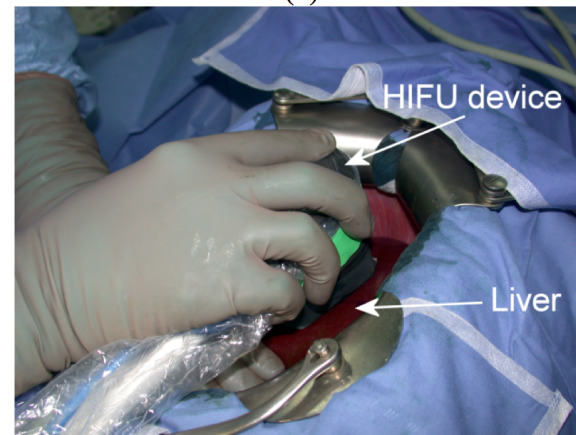


(a)

(b)

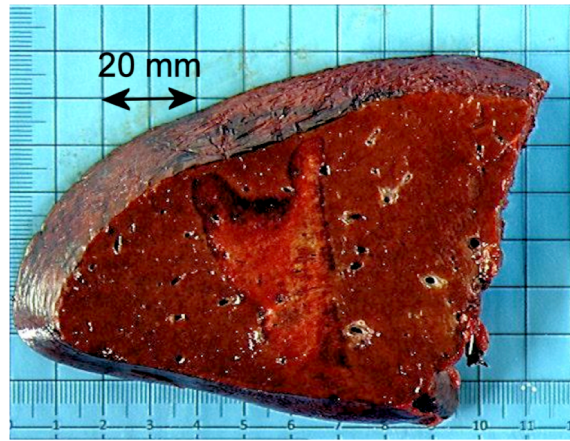


(c)

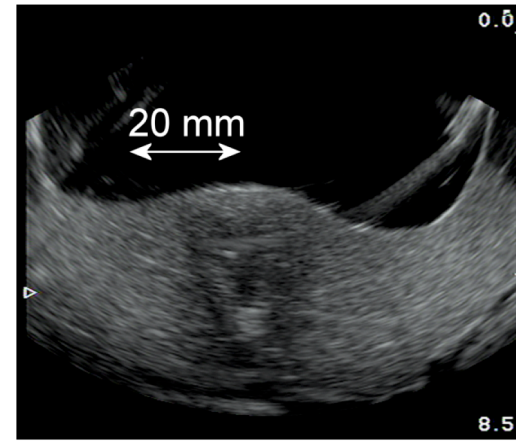


(d)

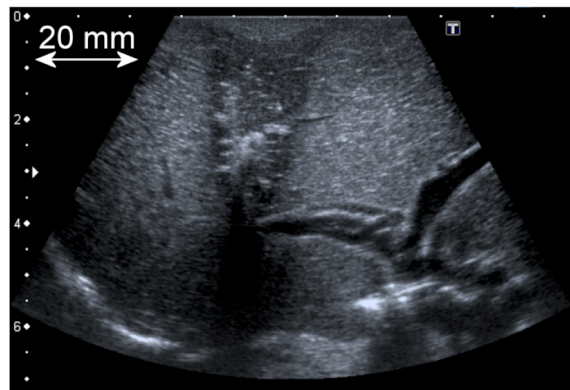
Thermal ablation by HIFU: Liver



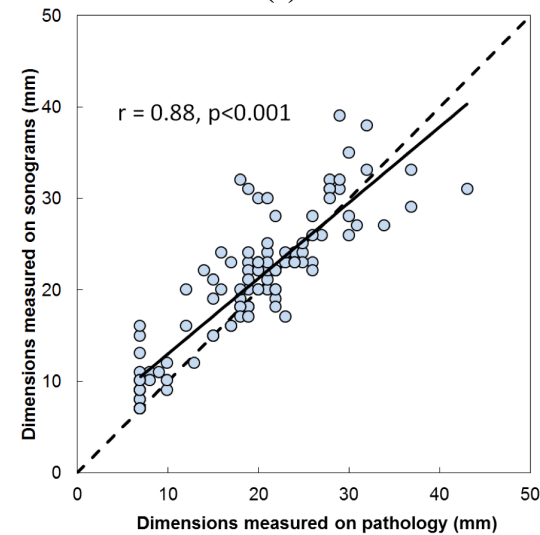
(a)



(b)



(c)



(d)

Hyperthermia

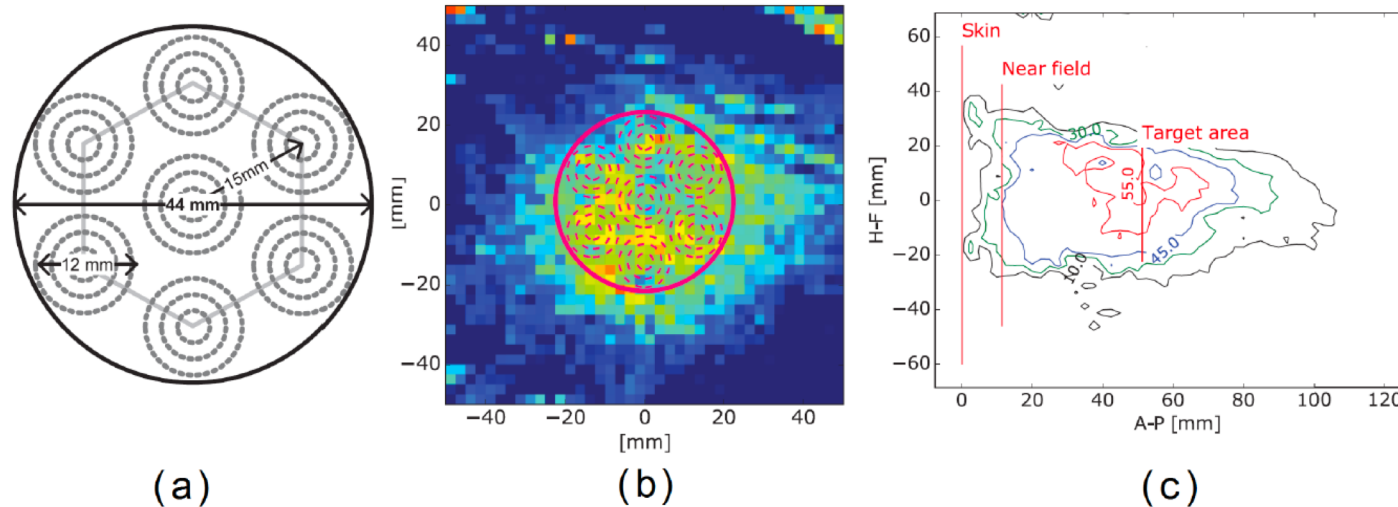


Figure 4.1. (a) A schematic representation of multiposition sonication cells in a plane parallel with the beam axis. The sonication is divided into seven transducer positions arranged on a hexagonal grid with one position in the middle. In each focal position, steering is used. (b) An example of measured focal-plane temperature map in *in-vivo* porcine muscle tissue during heating (sonication cell grid overlaid in magenta). (c) Beam axis view of one hyperthermia sonication. The contours represent the minutes the area was within hyperthermia temperature range (41–45°C) during sonication. (Modified from Publication I)

Hyperthermia

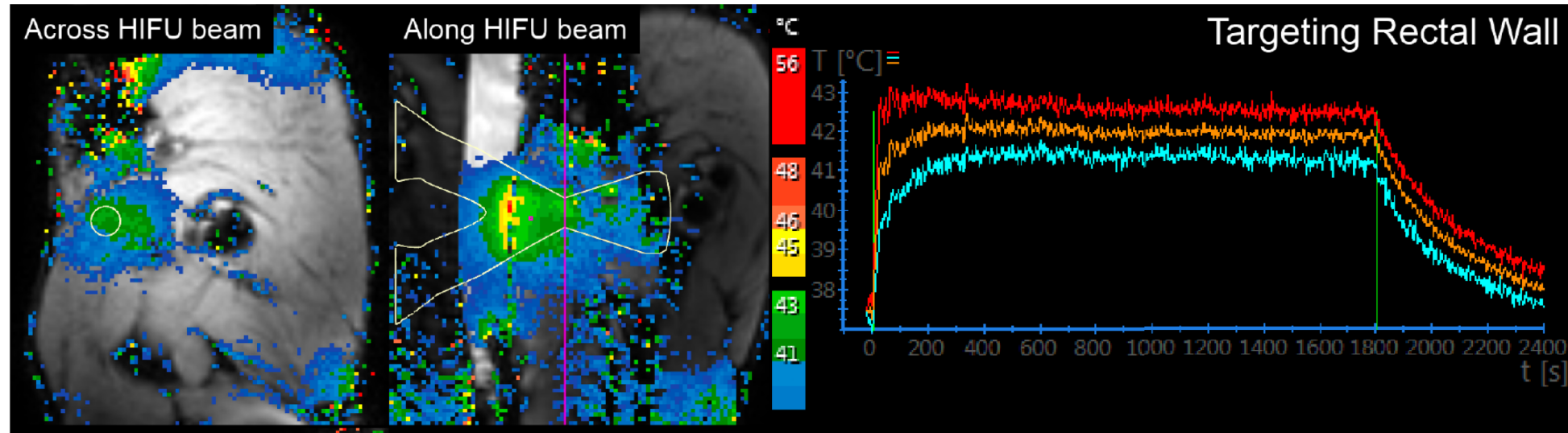
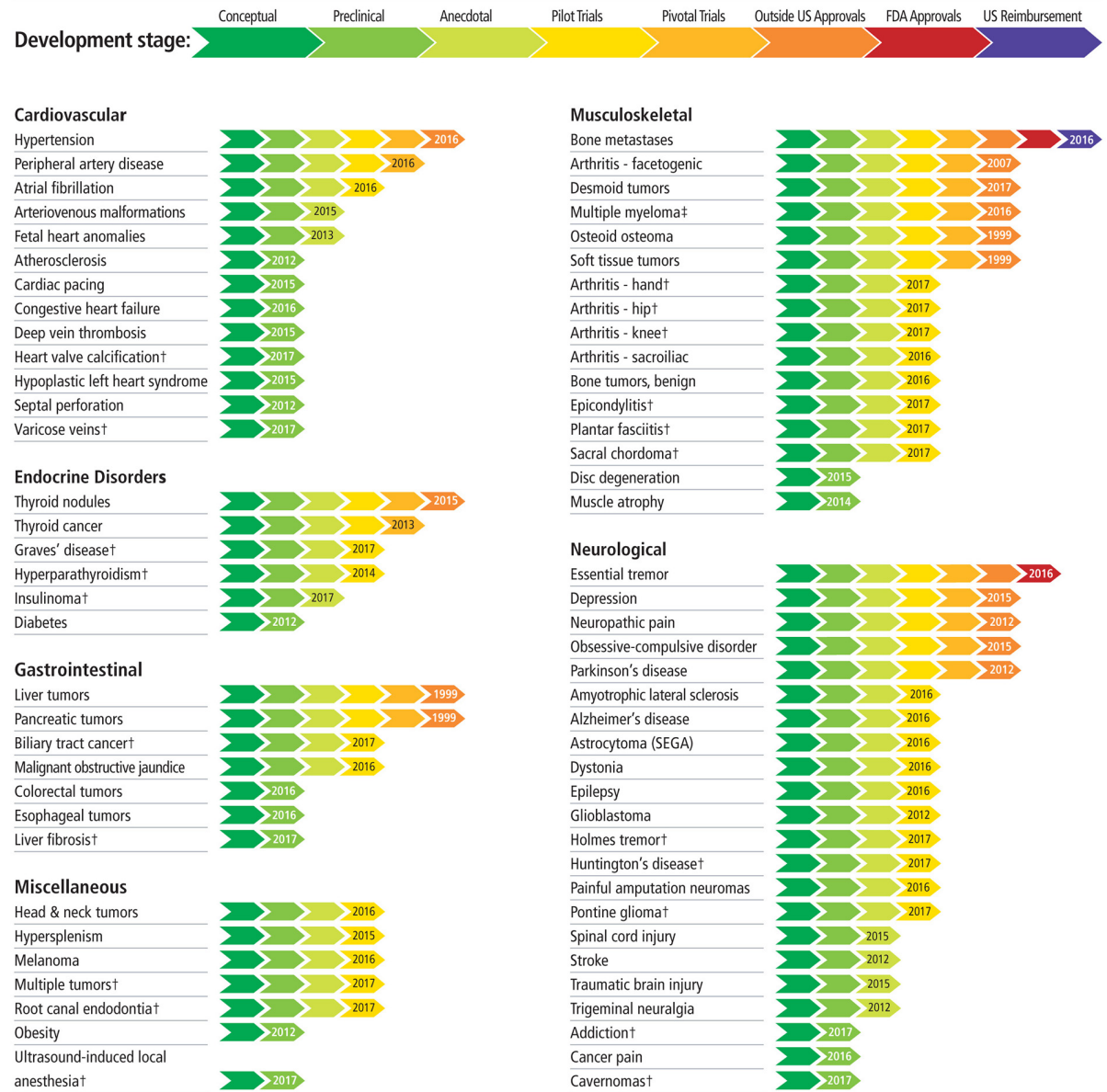


Figure 4.2. Coronal (left) and sagittal (center) temperature maps for a hyperthermia sonication near the porcine rectal wall. The plot on the right shows the temperature evolution of spatial average, spatial T10, and spatial T90 temperatures for the target area at focal depth. (Modified from Publication II)

APPLICATIONS

HIFU applications status (FUS Foundation)

State of Research and Regulatory Approval by Indication

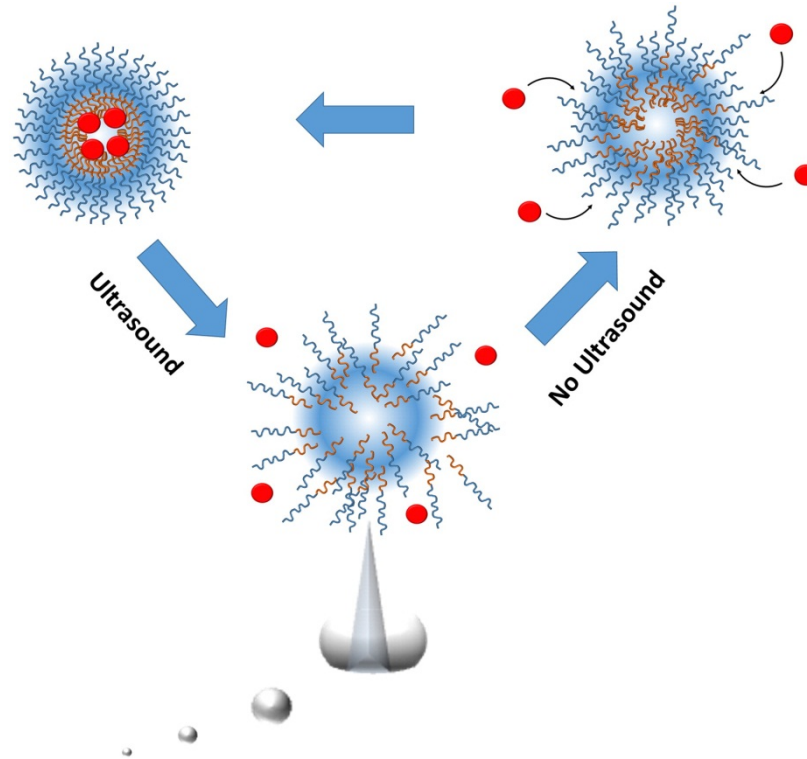


† New in 2017

‡ Multiple myeloma approval is based on bone metastases.

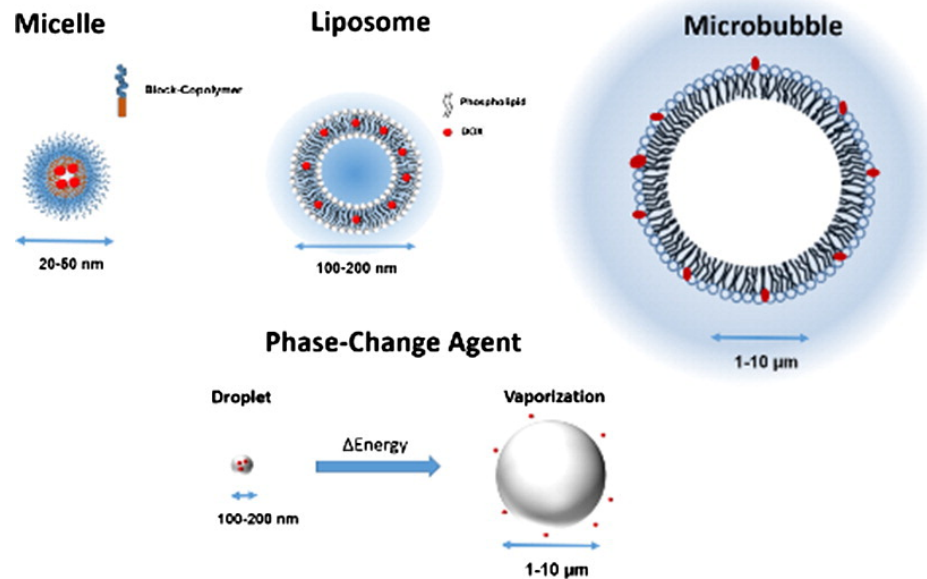
Year denotes first in world occurrence of development stage.

Ultrasonic drug delivery



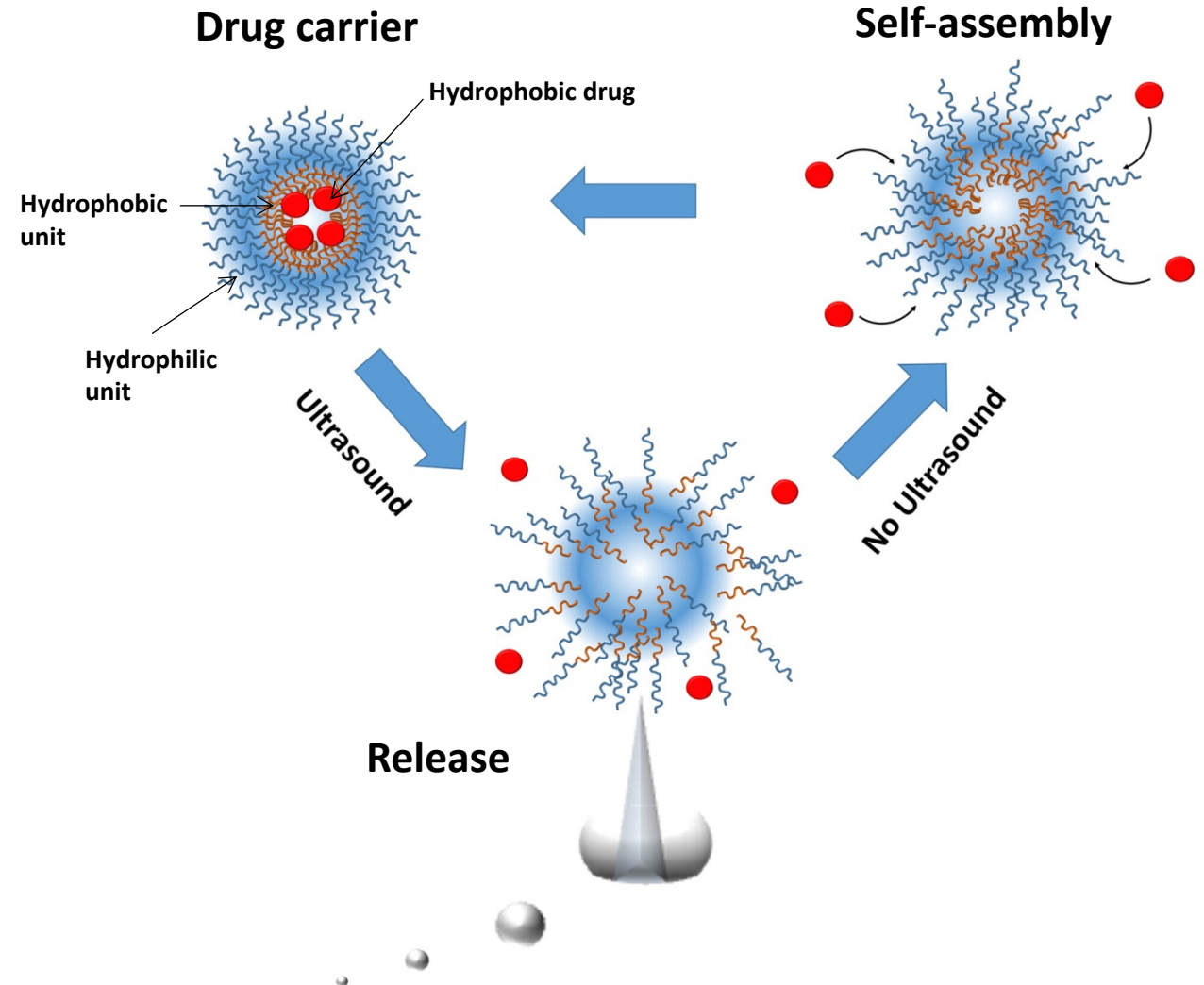
Ultrasound triggered drugs

- In the following we deal with drug delivery systems that can be used for ultrasonic drug delivery
- These systems can be categorized to the following:
 - Nanocarriers
 - Micelles
 - Liposomes
 - Microbubbles
 - Soft-shelled microbubbles
 - Hard-shelled microbubbles
 - Nanocarrier-microbubble hybrids
 - Microbubble-loaded hydrogels
 - Phase change agents
 - Advanced systems

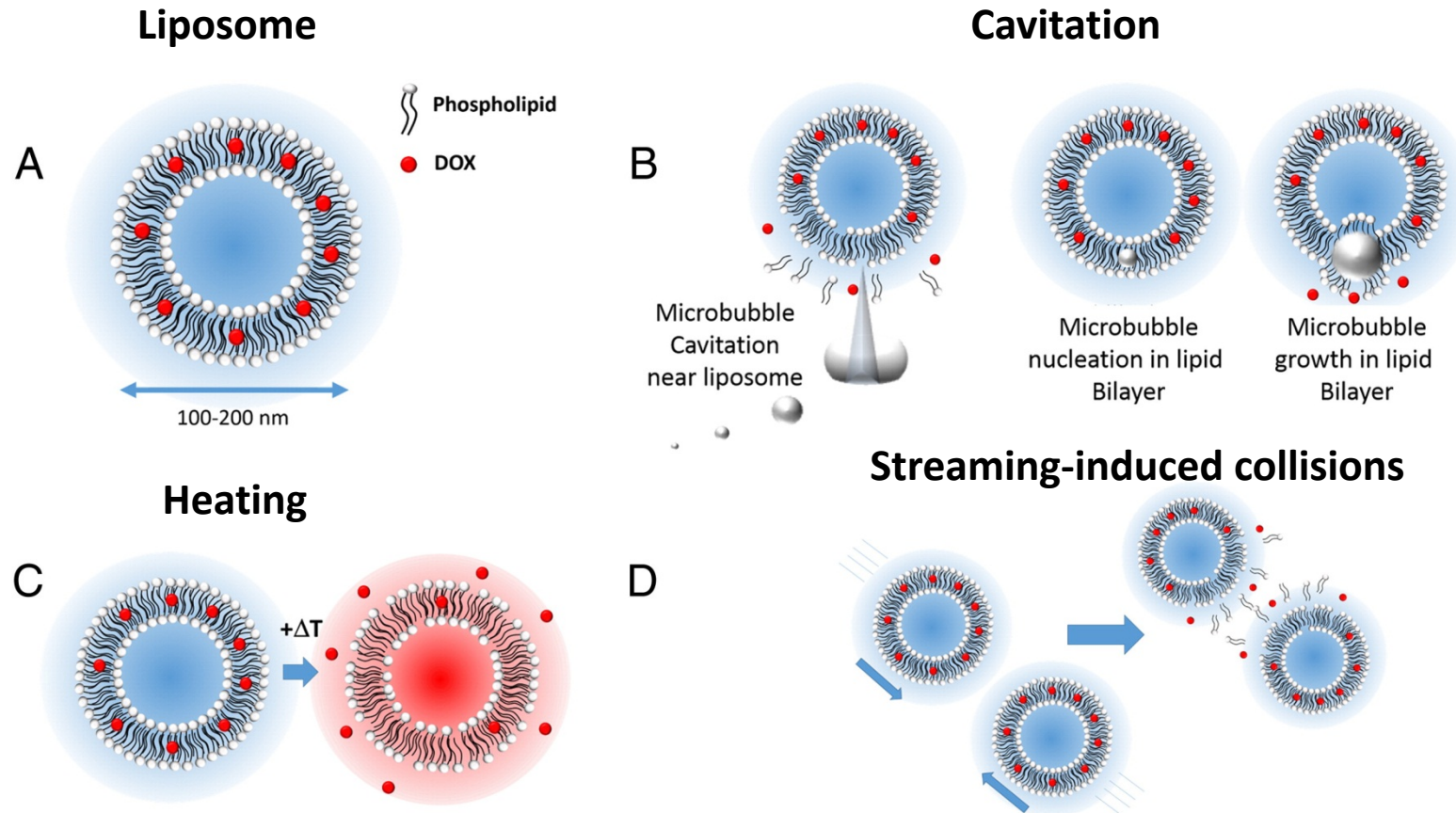


Nano-carriers: Micelles

- Composed of amphilic molecules
- Relatively easy to make due to self-assembly above critical concentration
- Micelles are typically 10-100 nm in diameter
- **Ultrasonic release from micelles mainly associated with cavitation, although hyperthermia plays a role with thermosensitive micelles**
- Release typically conducted kHz range although studies at MHz range also exist



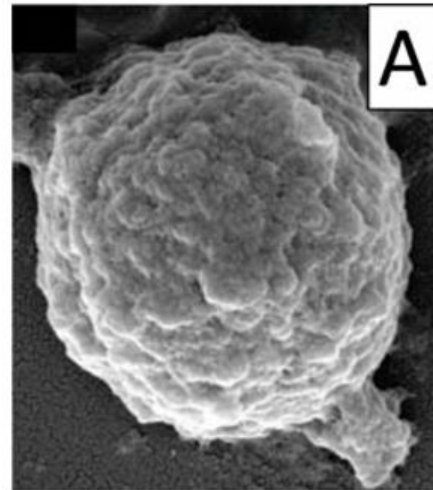
Nano-carriers: Liposomes



- Liposomes typically 100-200 nm in diameter
- Drugs loaded to 1. the phospholipid bilayer or 2. aqueous core
- **Release mechanisms: 1. cavitation, 2. heat** (phase transition above physiological temperature → mild hyperthermia) and **3. acoustic streaming**

Micro-bubbles as drug carriers

- Micro-bubbles commonly used as vascular contrast agents
- Responsive to external driving pressure (ultrasound)
- Size typically 1-10 μm
- Structure:
 - Gas-filled core
 - Stabilizing shell:
 - Polymer
 - Lipid
 - Protein

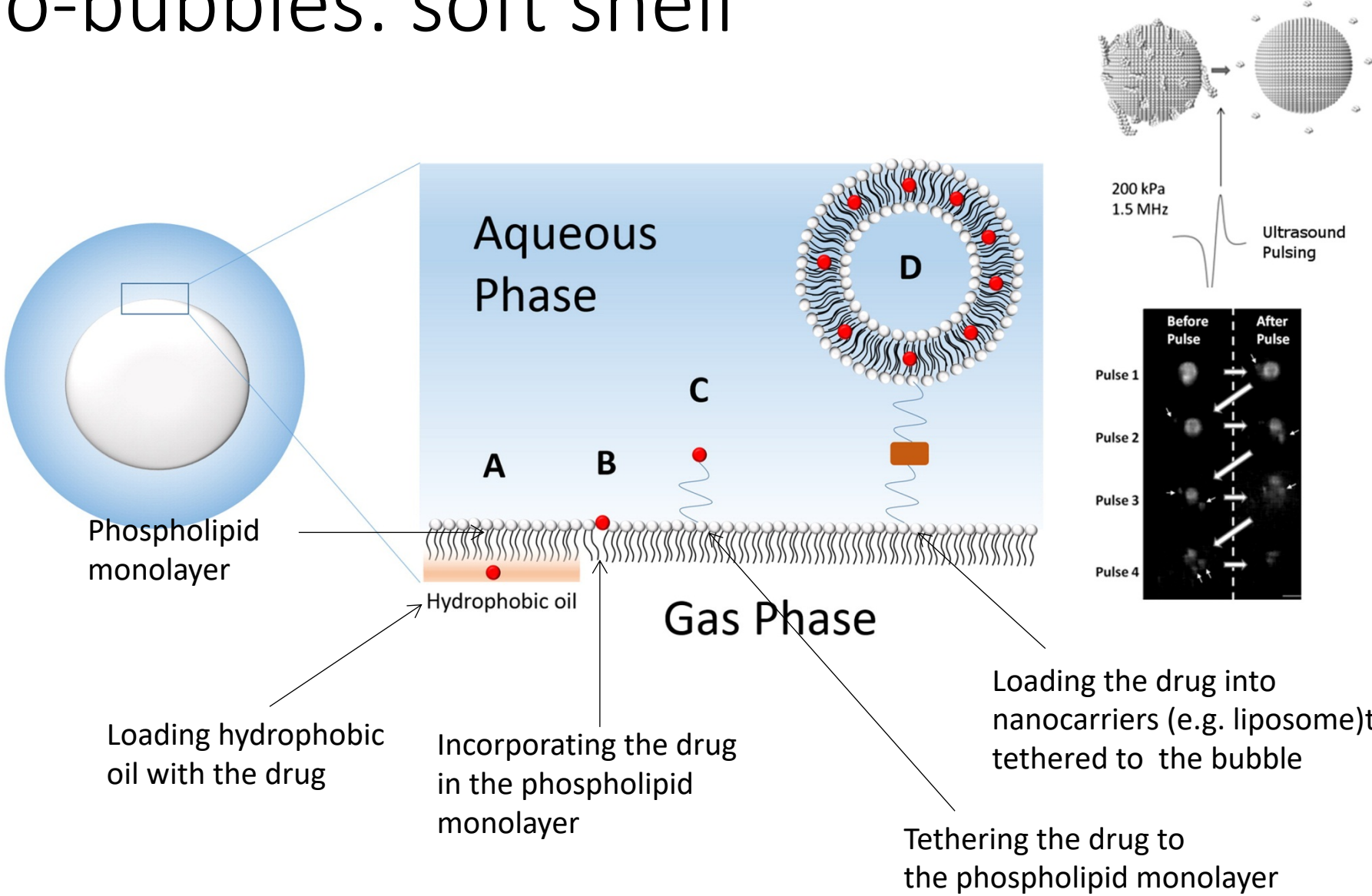


1 μm micro-bubble with a protein shell

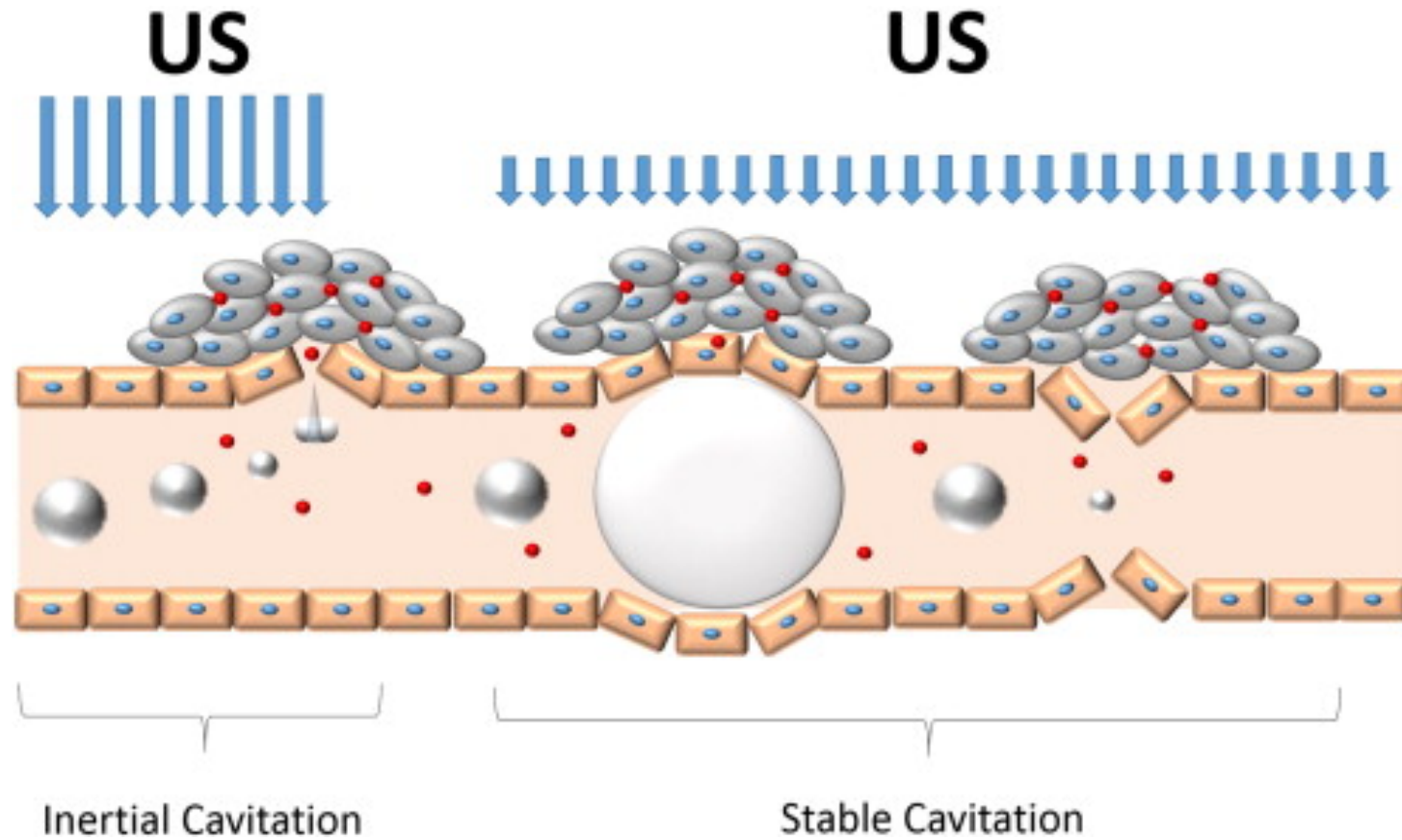
Micro-bubbles: soft-shelled bubbles

- Microbubbles used in ultrasonic drug delivery are commonly soft-shelled, *i.e.* they have a thin shell made of phospholipids or proteins
- Compliant shell → sensitive to the driving pressure → stable or inertial cavitation may occur

Micro-bubbles: soft shell

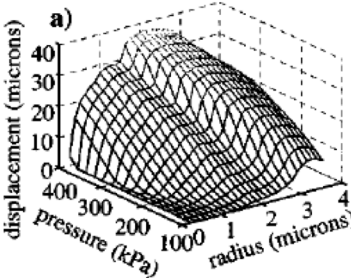


Extravasation by micro-bubbles

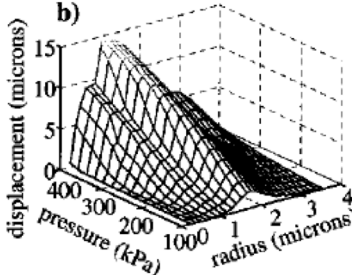


Bubble translation

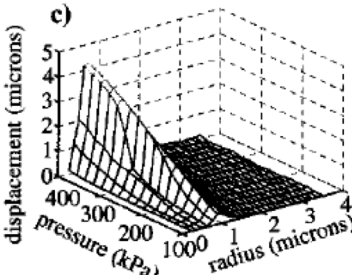
20 cycle pulse



1 MHz



2.25 MHz



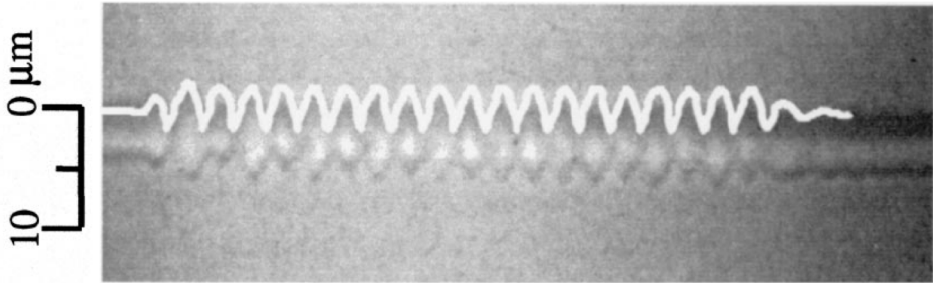
5 MHz

Max. translation:

- Maximized at bubble resonance

2.25 MHz, 100 kPa

| Initial radius (microns) | Radiation force (Newtons) | Maximum radius (microns) | $\langle R - R_0 \rangle$ (microns) |
|--------------------------|---------------------------|--------------------------|-------------------------------------|
| 0.5 | 4.8×10^{-9} | 0.55 | 0.00 |
| 1.38 | 4.0×10^{-6} | 1.8 | 0.09 |
| 1.63 | 1.07×10^{-5} | 2.3 | 0.15 |
| 2.88 | 3.60×10^{-6} | 3.2 | 0.01 |
| 3.50 | 2.43×10^{-6} | 3.7 | 0.00 |



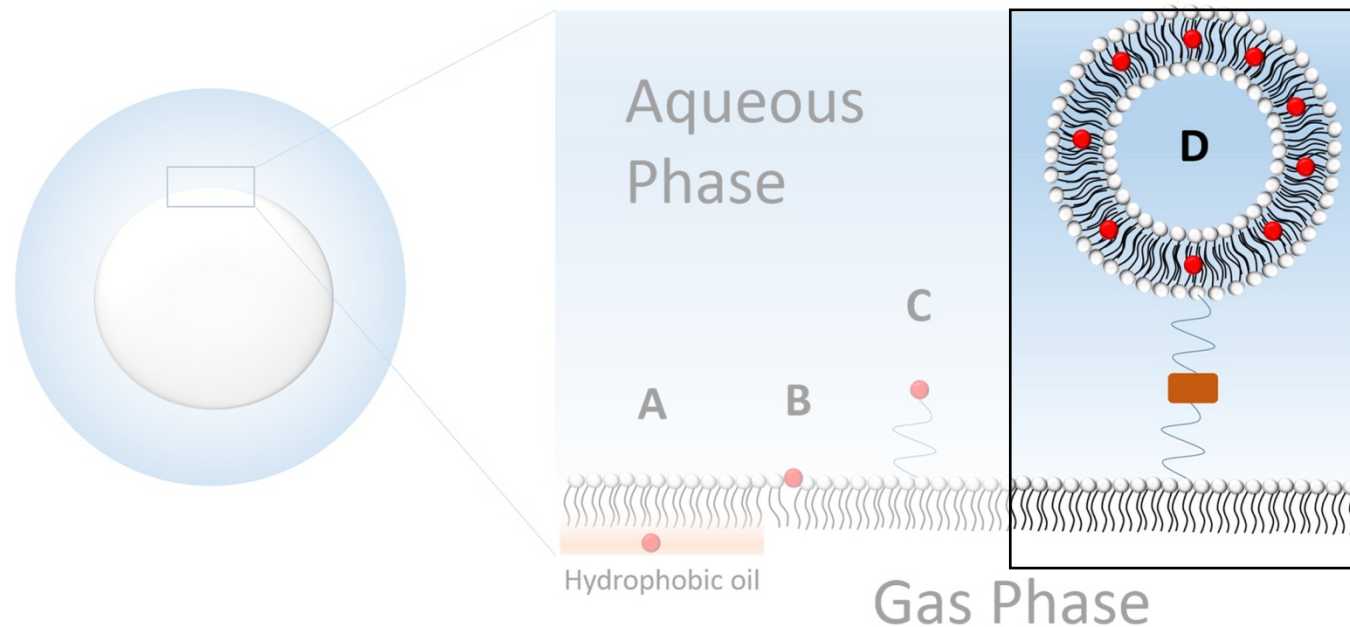
Medical ultrasound may generate micro-bubble speed as high as 0.5 m/s (5 μ m distance in 20 cycles of 380 kPa, 2.25 MHz ultrasound).

Micro-bubbles: hard-shelled bubbles

- Hard shell → negligible radial oscillation due to low compliance of the shell
 - High pressure (>1 MPa) cracks the shell
 - gas expands and is released
 - potentially propels the vehicle to vessel walls & contributes to extravasation
- *Hard-shelled microbubbles are typically pressure sensitive*

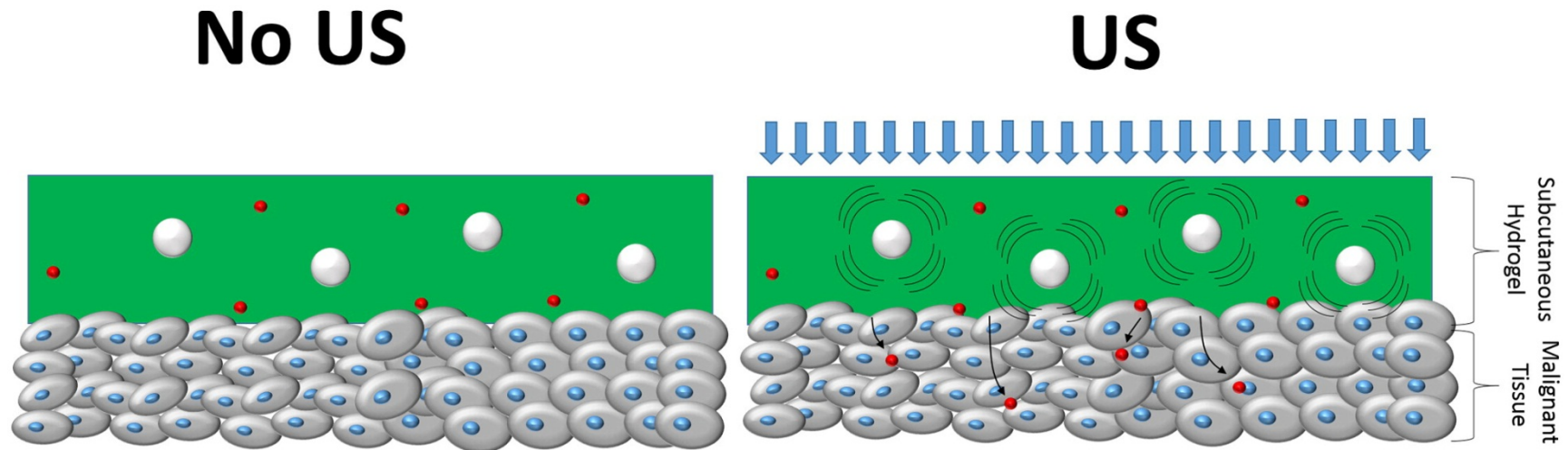
Nanocarrier-microbubble hybrids

- Drug-containing liposomes, micelles or nanoparticles are attached to the microbubble
- High-loading capacity (10^3 - 10^4 liposomes per bubble)

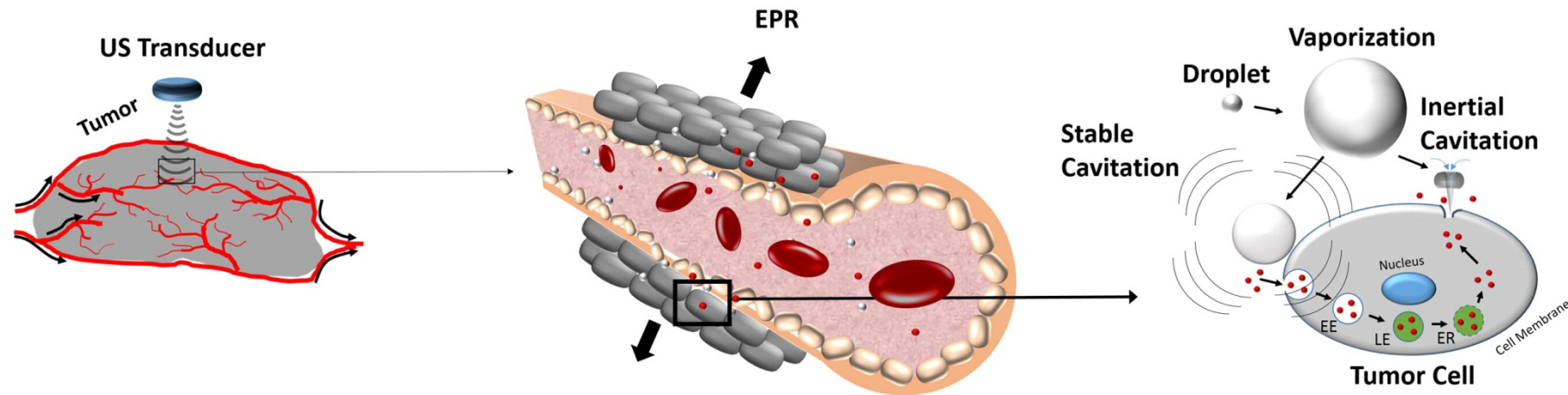


Microbubble-loaded hydrogels

- Drugs & microbubbles embedded into hydrogel
- Enables drug-release-on-demand implants



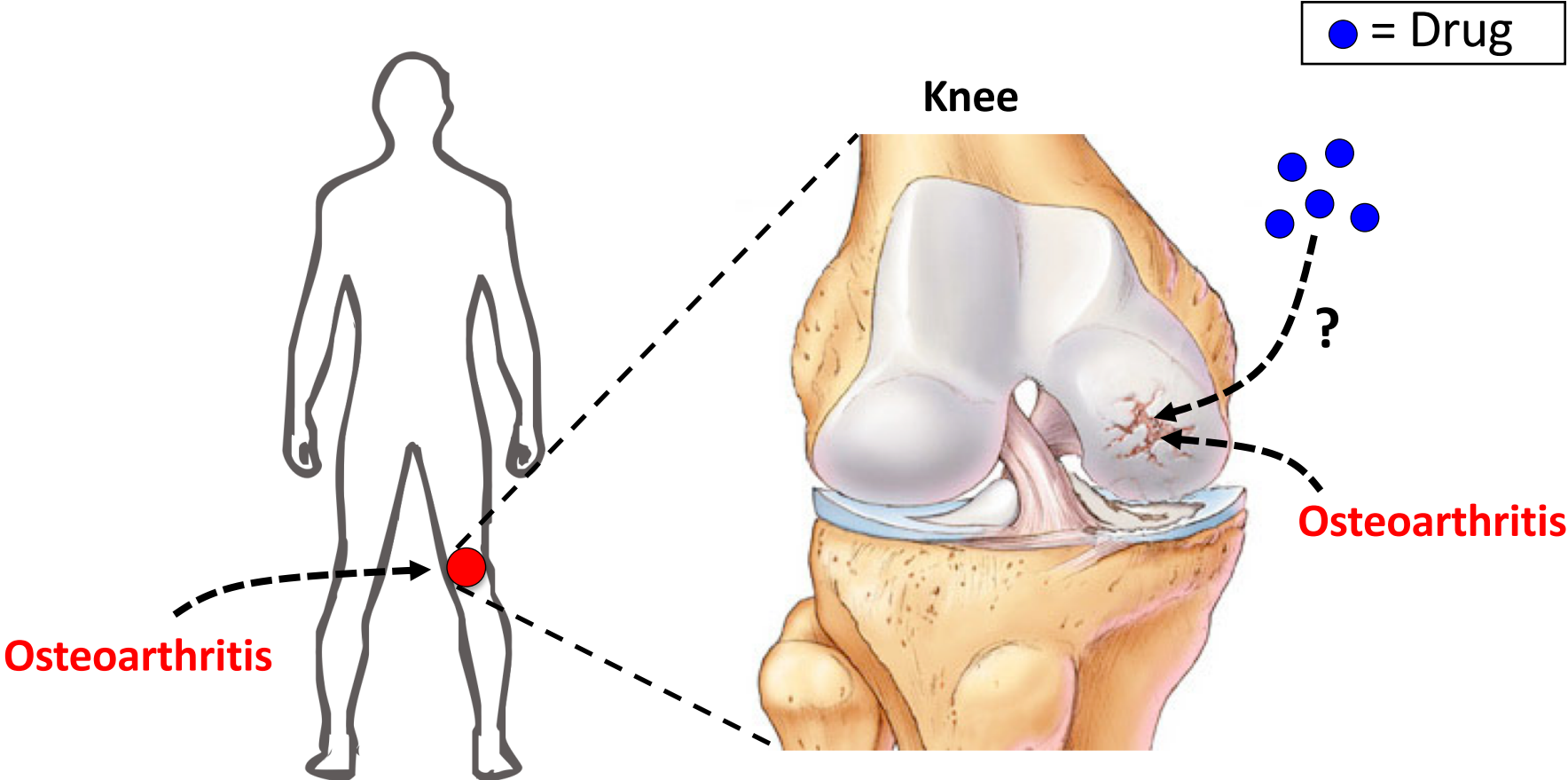
Phase-change agents



- Micelle contains thermally "sensitive" liquid containing the drug → during the positive phase of the driving sound, the droplet is heated and vaporized
- Gas bubble interacts by means of cavitation to deliver the drug to the target (cell)
- Directed propulsion can be achieved (> 6 m/s)
- Simultaneously with drug delivery therapy feedback can be achieved with ultrasound imaging.

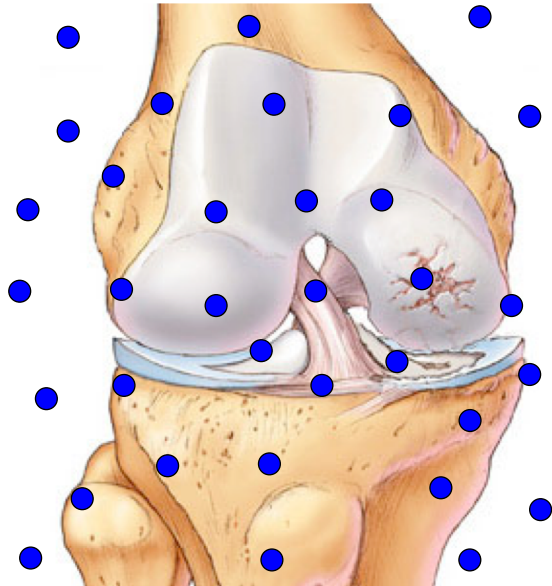
Ultrasonic drug transport

Drug transport by ultrasound



1.

Systemic delivery



2.

Localized therapy



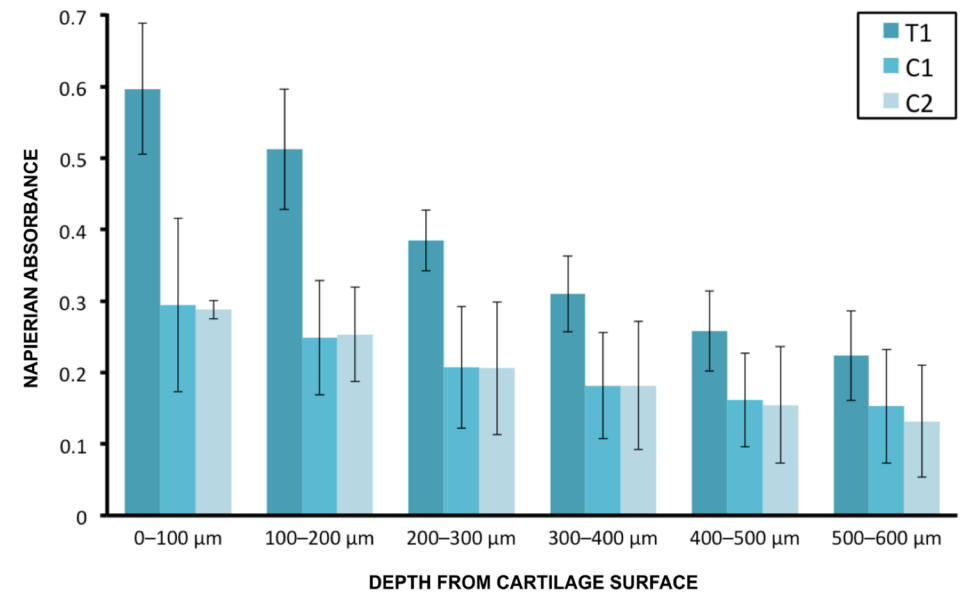
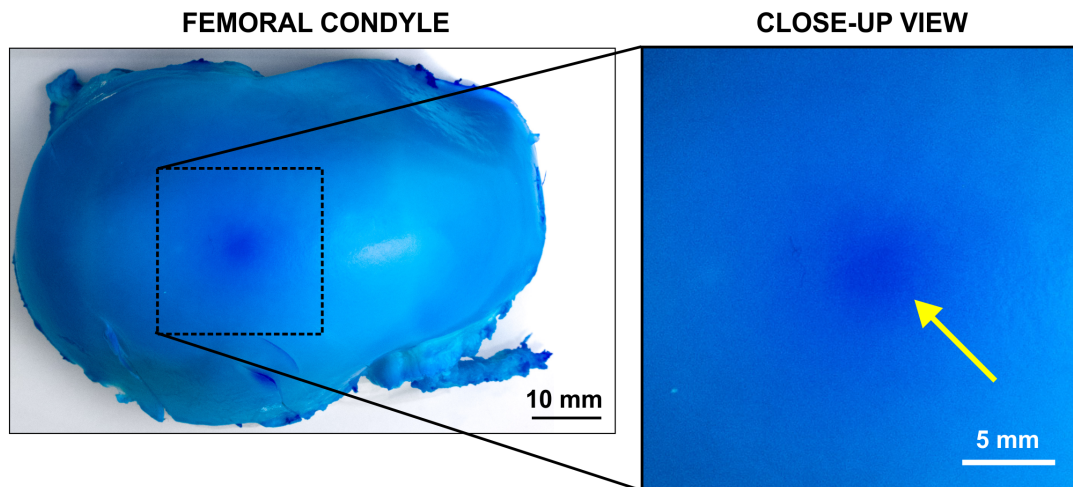
3.

Targeted delivery

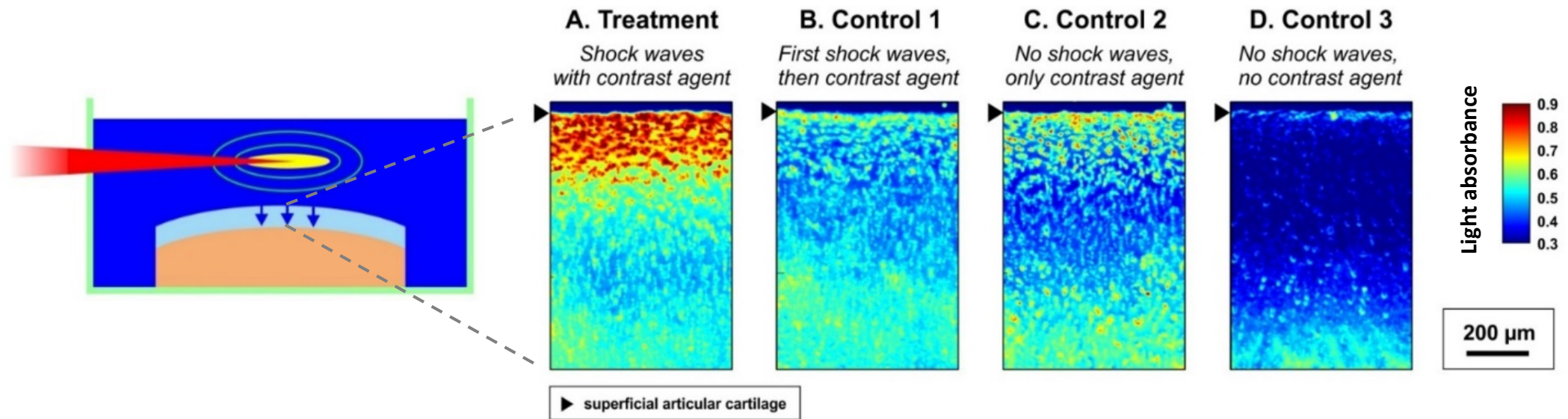


● = drug

Drug transport by focused ultrasound



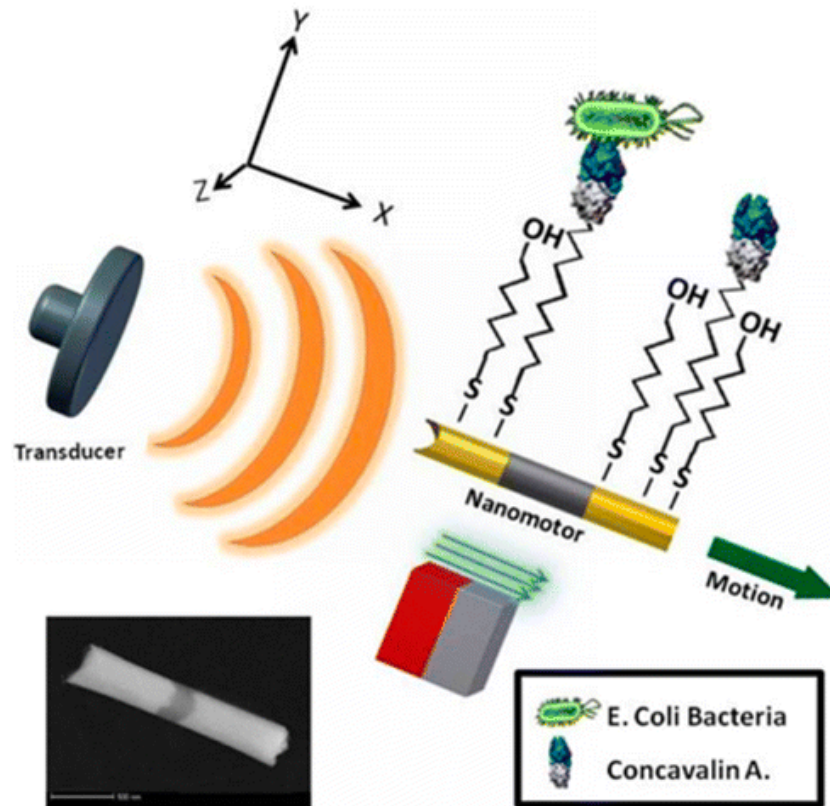
Laser-ultrasonic drug transport



Ultrasonic microvehicles

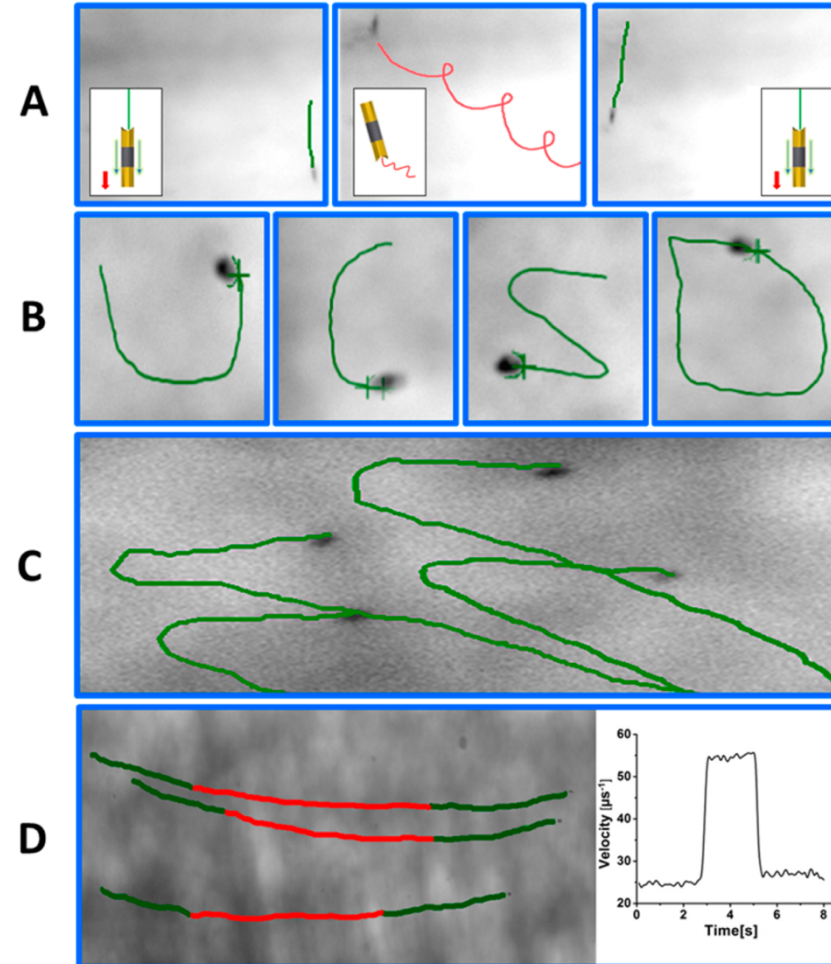
Deterministic functionalized transportation

- Almost all delivery approaches are statistical
- Deterministic delivery system:



Magnet on Magnet off Magnet on

a b c



Speed modulation by ultrasound

Deterministic functionalized transportation

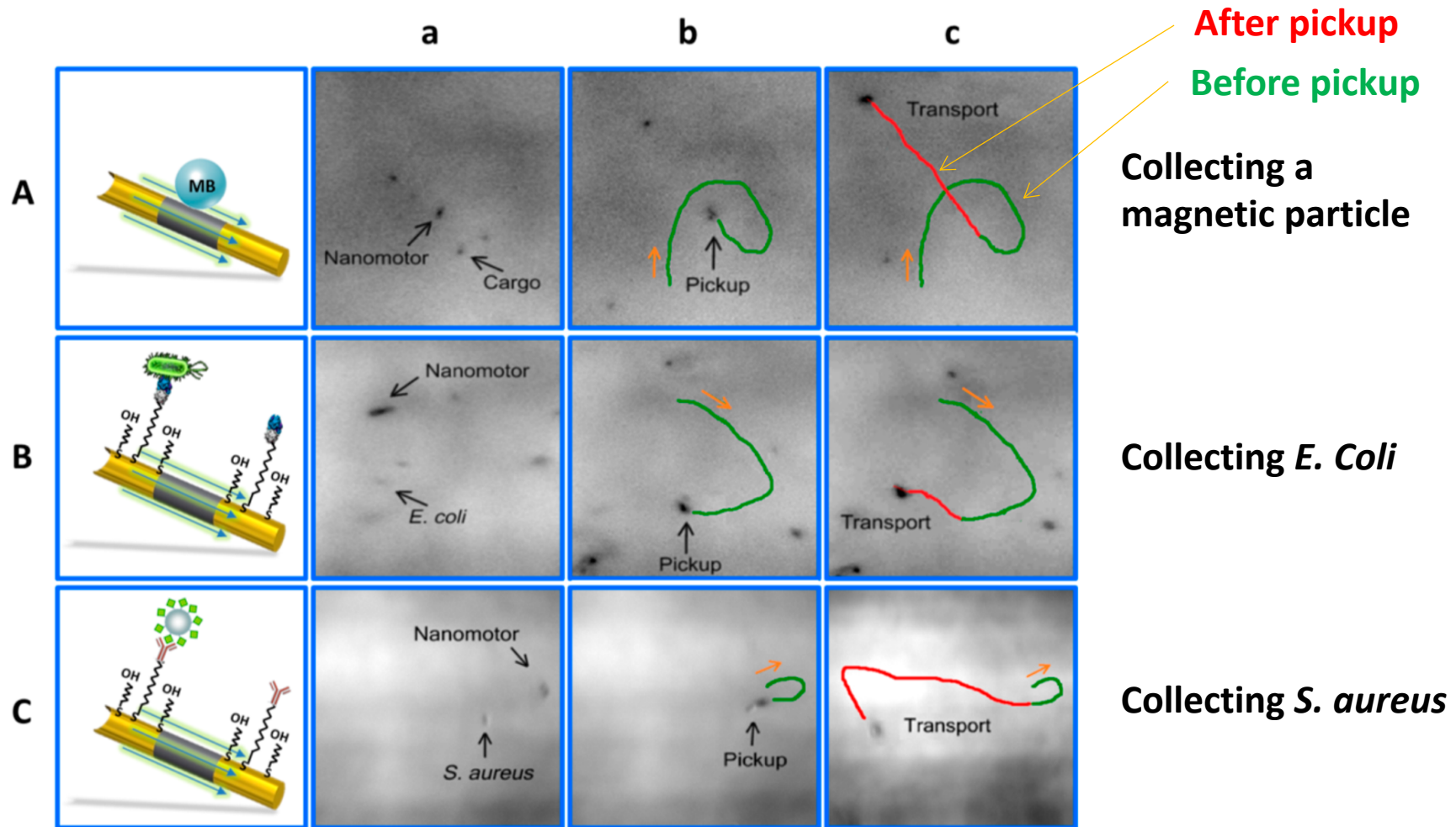


Figure 5. (A) Capture and transport of a $0.89\ \mu\text{m}$ magnetic bead by an ultrasound-propelled Au/Ni/Au unmodified nanomotor approaching (a), capturing (b), and transporting (c) the magnetic particle. (B) Capture and transport of *E. coli* bacteria by a lectin-modified ultrasound-propelled nanomotor: (a) approaching, (b) pickup, and (c) transport the *E. coli* bacteria. (C) Capture and transport of *S. aureus* bacteria by a Con A-modified ultrasound-propelled nanomotor: (a) approaching, (b) pickup, and (c) transport the *S. aureus* bacteria. Conditions: media, deionized water (A) and PBS (pH 7.0) solutions (B and C); ultrasound field, 6 V and 2.51 MHz.

Deterministic drug delivery to a cancer cell

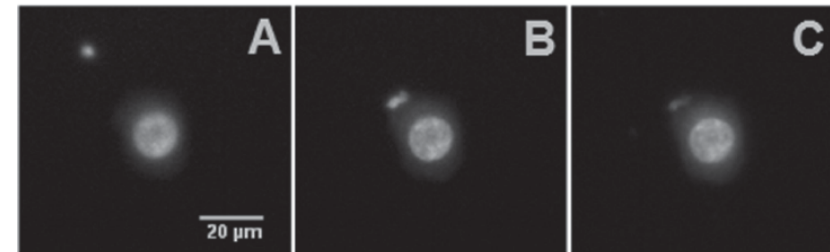
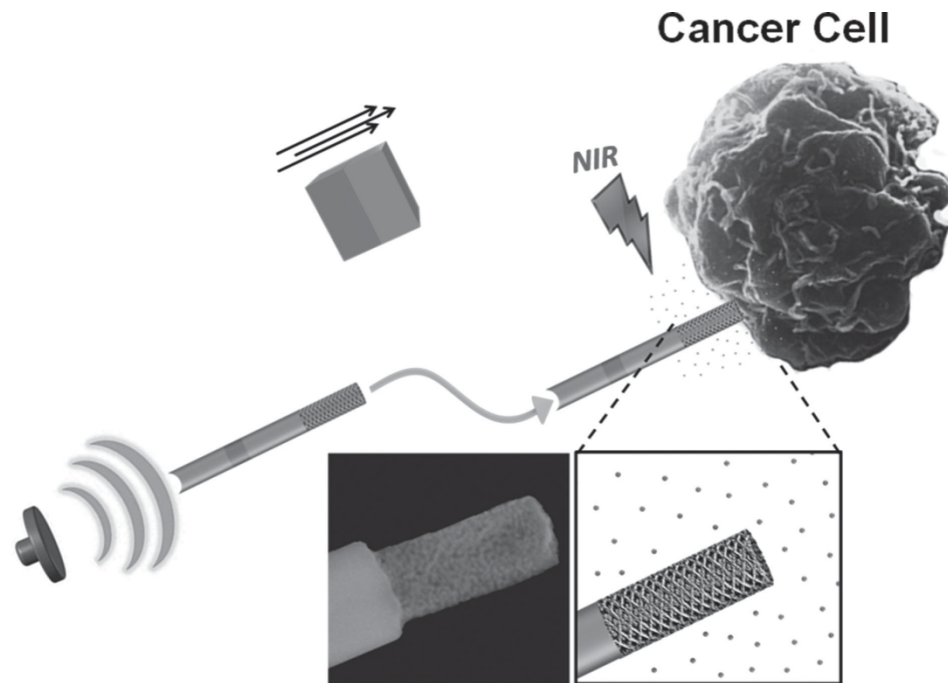


Figure 6. Time-lapse fluorescent images of the DOX-loaded NPAu nanomotor A) travelling towards a HeLa cell, B) approaching the HeLa cell, and of C) the nanomotor and the HeLa cell after 15 min of NIR irradiation. DOX release conditions, as in Figure 4. Motion of NPAu nanomotors was achieved under ultrasound propulsion at 6 V and 2.01 MHz.

Nebulization

Ultrasonic nebulization

- Ultrasonic nebulization is an old technique since 1950's to generate small drug droplets using HIU
- Generates droplets/particles $< 5 \mu\text{m}$ in size
- Especially useful in treating asthma, COPD (chronic obstructive pulmonary disease) or other respiratory diseases
- Small droplets have large reaction area and dissolve quickly
- Claimed advantages: 1. finer droplets than with conventional techniques, 2. high sphericity, 3. uniformity in size

First reported nebulizer



Sales-Girons in 1858

Conventional nebulizer



<http://www.rtmagazine.com>

Ultrasonic nebulizer

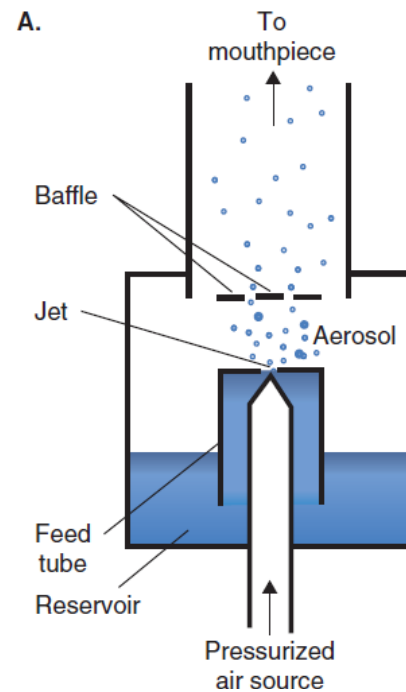


<http://www.rmdmediaids.com>

Working principle

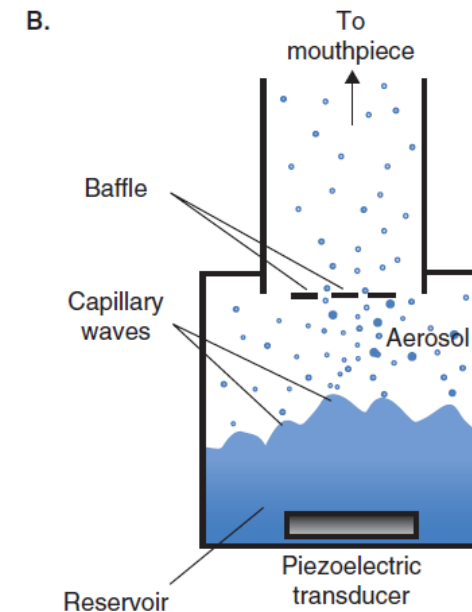
CONVENTIONAL

Air pressurization & rapid air flow through a nozzle with fluid



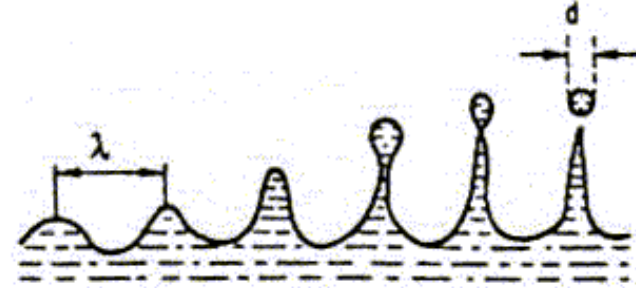
ULTRASONIC

Acoustic radiation force ejects droplets from the liquid surface



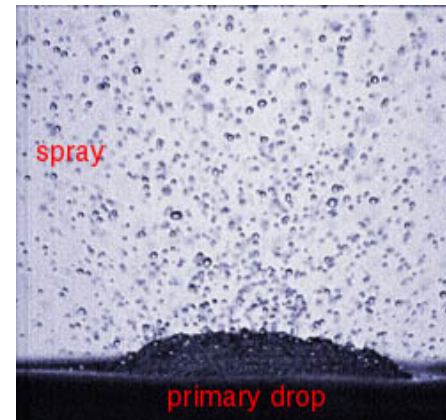
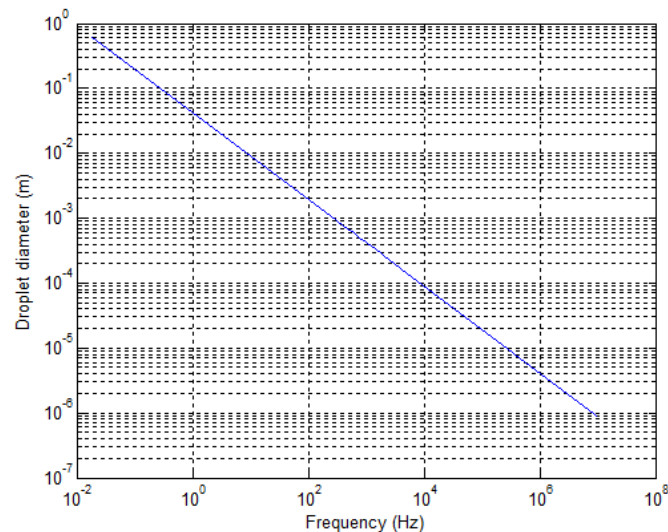
Threshold for nebulization

- Sonicating liquid-air interface generates capillary waves at the liquid air surface
- High capillary wave amplitude results in extrusions or "pinching out" of droplets / liquid jets that generate small droplets



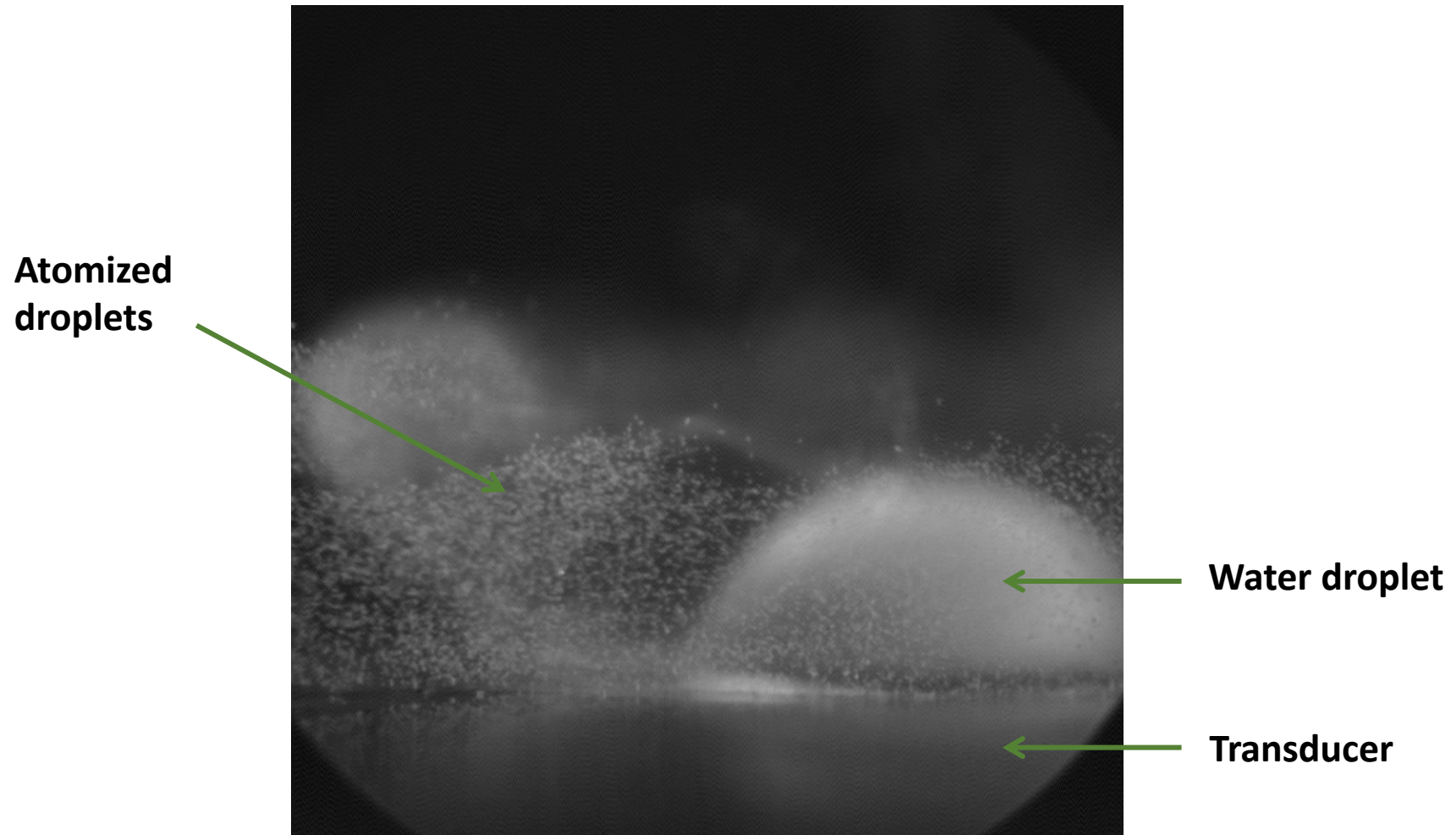
$$d \approx 0.34 \left(\frac{8\pi\gamma}{\rho f^2} \right)^{1/3} \quad (\text{median droplet size})$$

Applies for low flux: 0.1ml/s/cm²

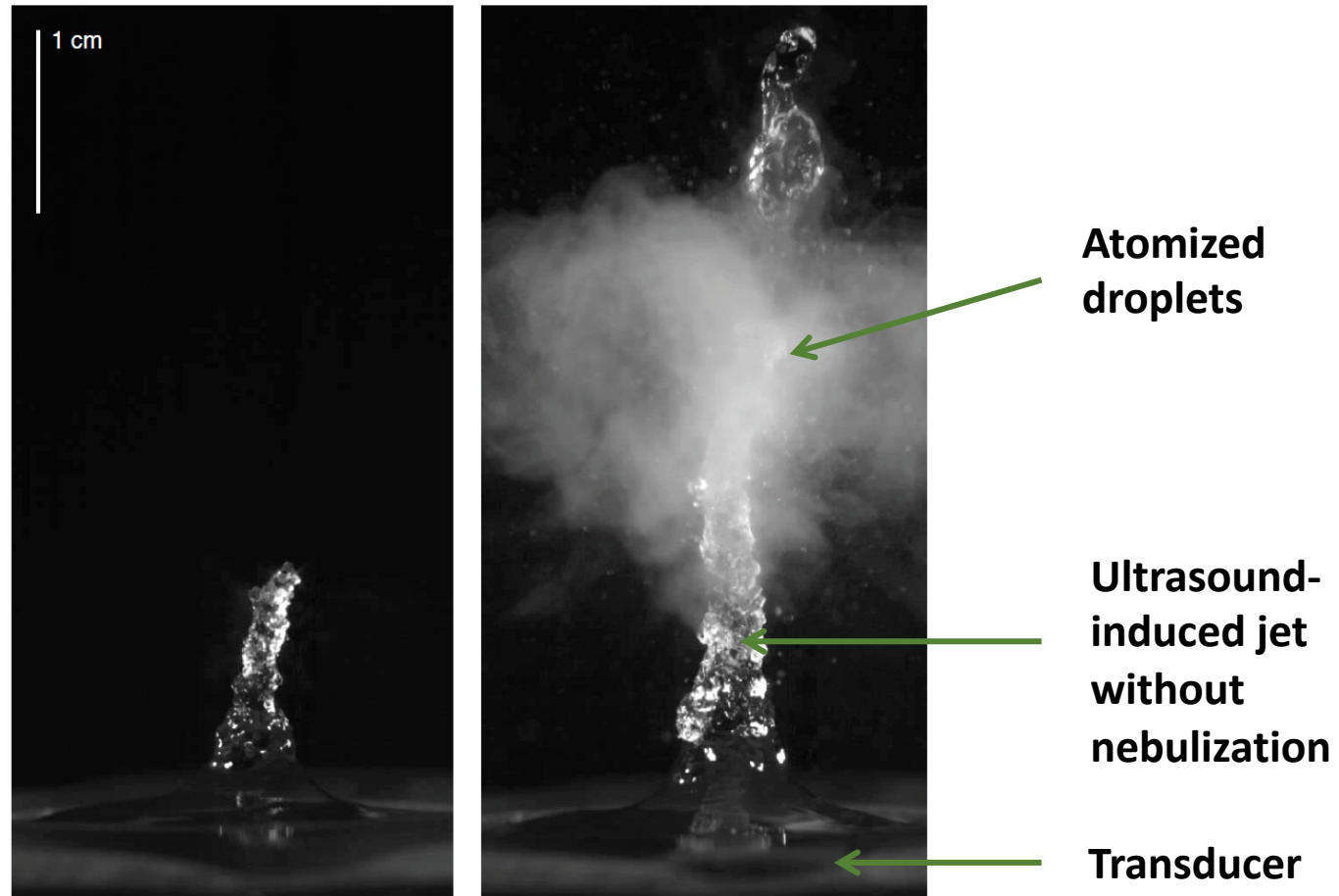


<http://www-old.me.gatech.edu/bvukasinovic/VIDA.html>

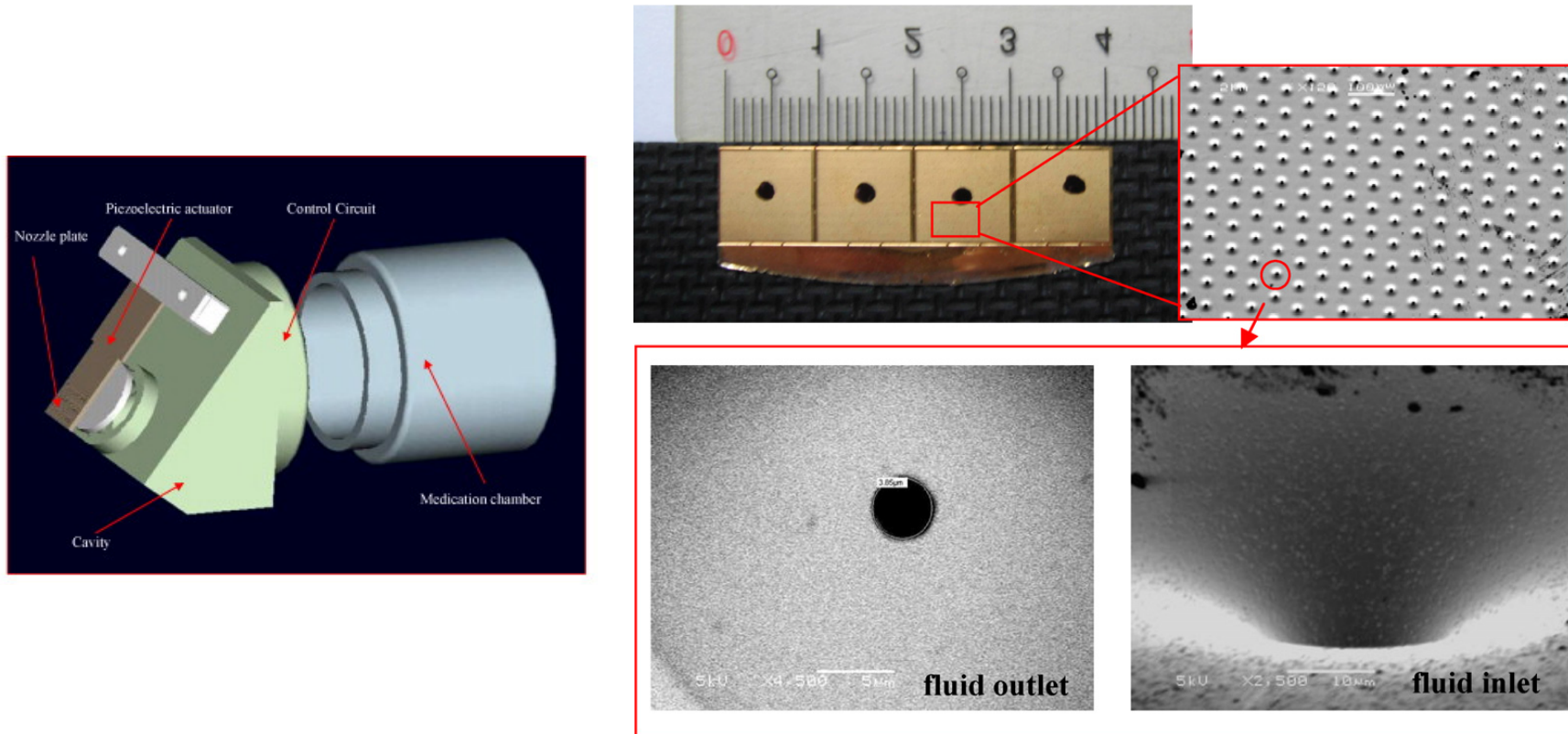
Atomization of a droplet



Atomization from a acoustic streaming induced jet (waveguide)



Ultrasound nebulizer



Shen et al 2008:

<http://www.sciencedirect.com/science/article/pii/S0924424707008898>

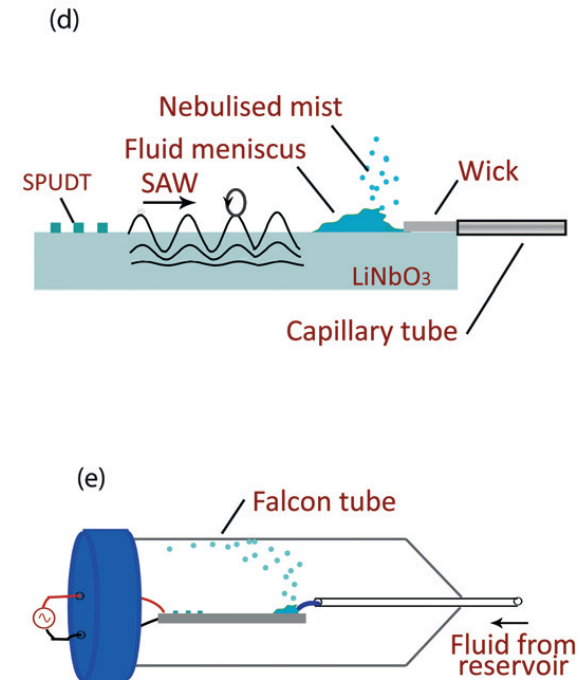
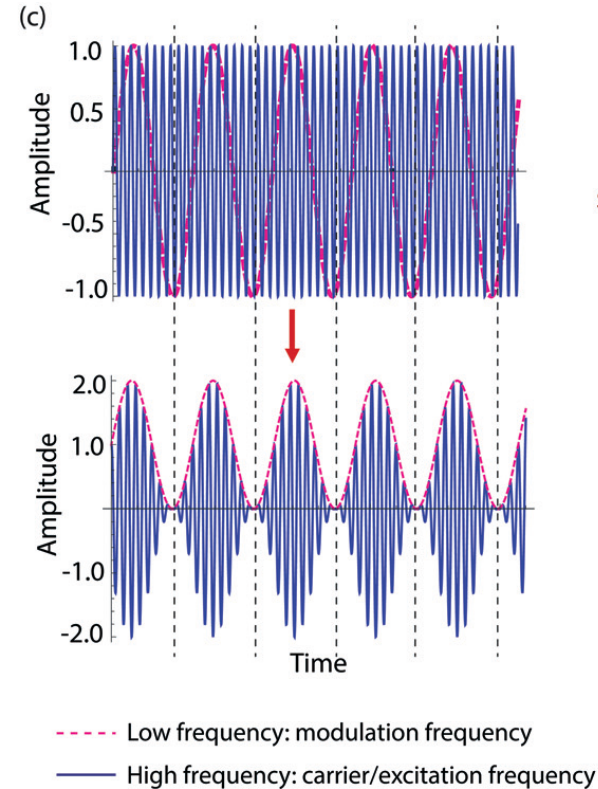
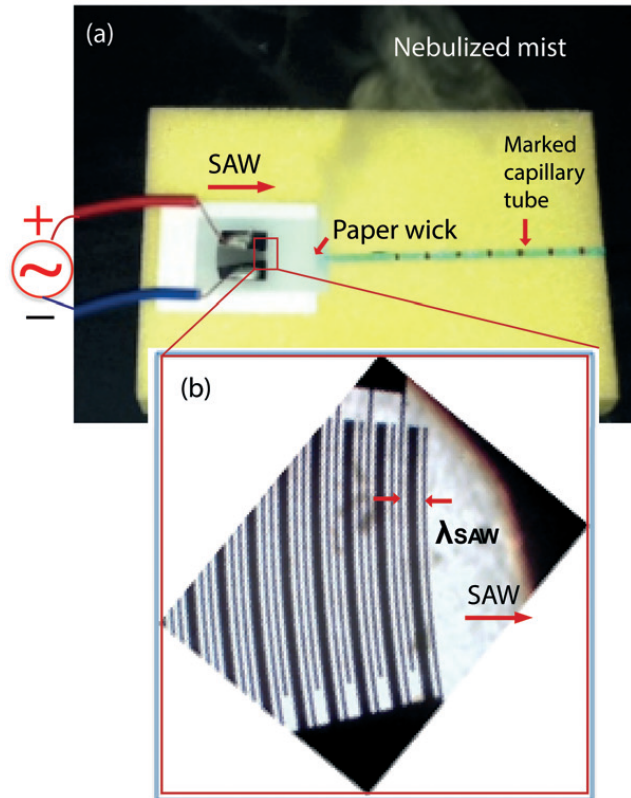
Video: Ultrasound nebulizer in action



Shen et al 2008:

<http://www.sciencedirect.com/science/article/pii/S0924424707008898>

Nebulization with surface acoustic waves (SAWs)



Modulated frequency: 0.5-40 kHz