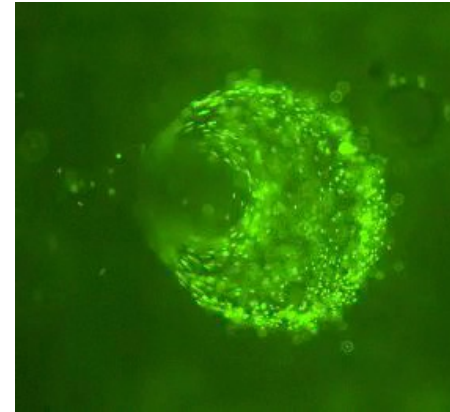
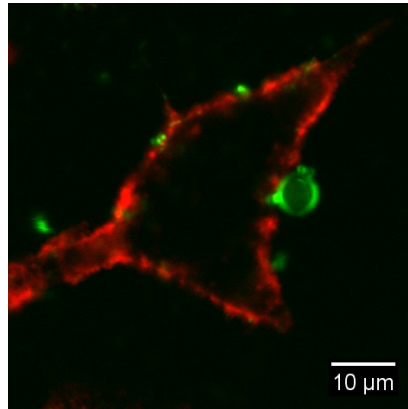
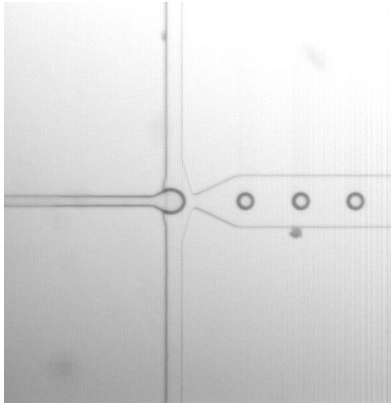


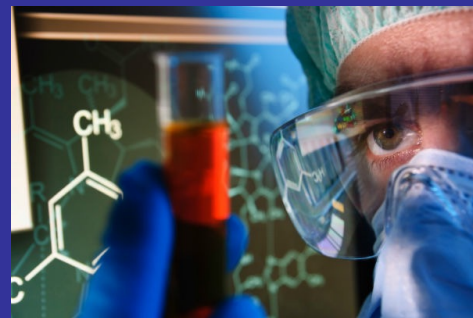
Stimuli responsive systems for targeted delivery of antimicrobial therapy

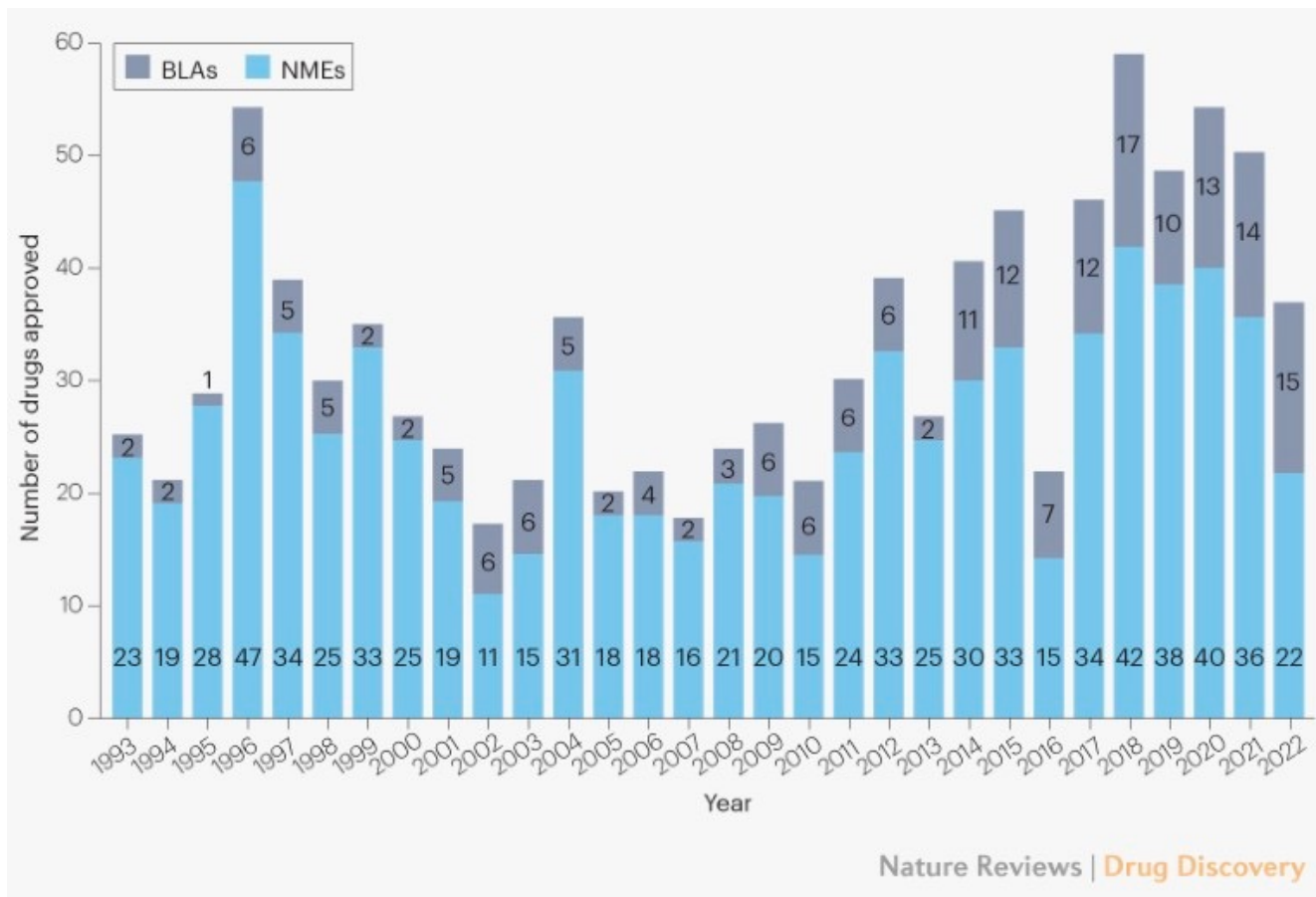


Eleanor Stride

Institute of Biomedical Engineering
University of Oxford

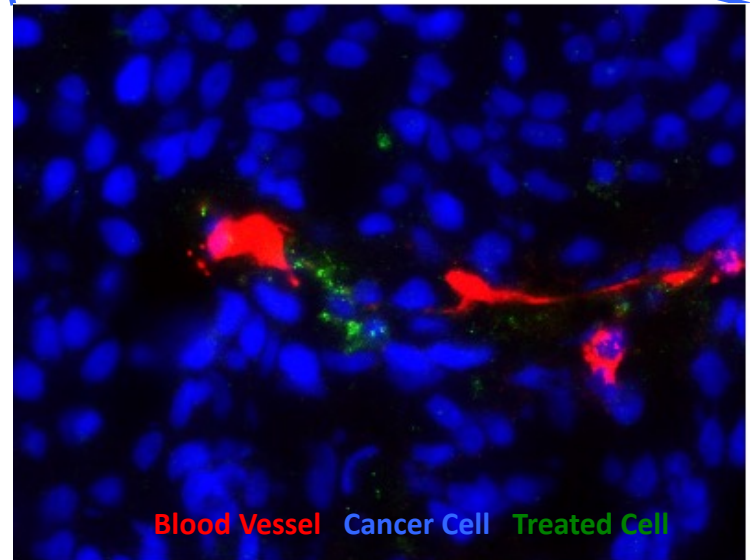
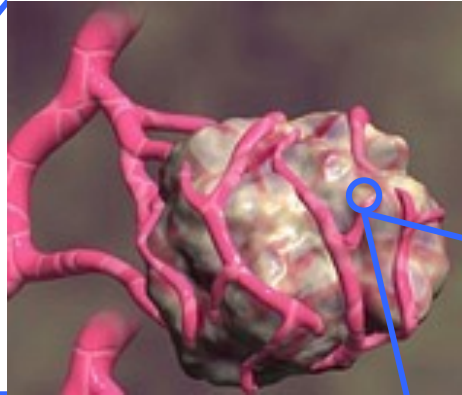
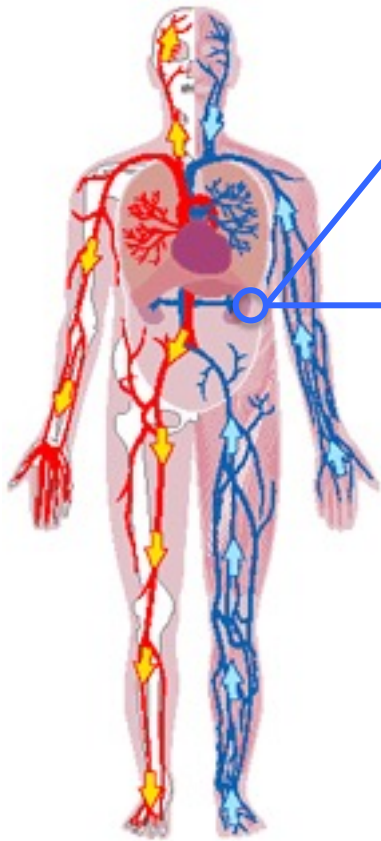






Source: US FDA; in Nature Reviews Drug Discovery 23, 83-88 (2023)

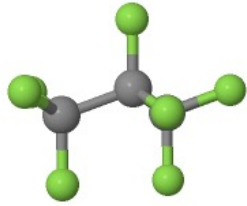






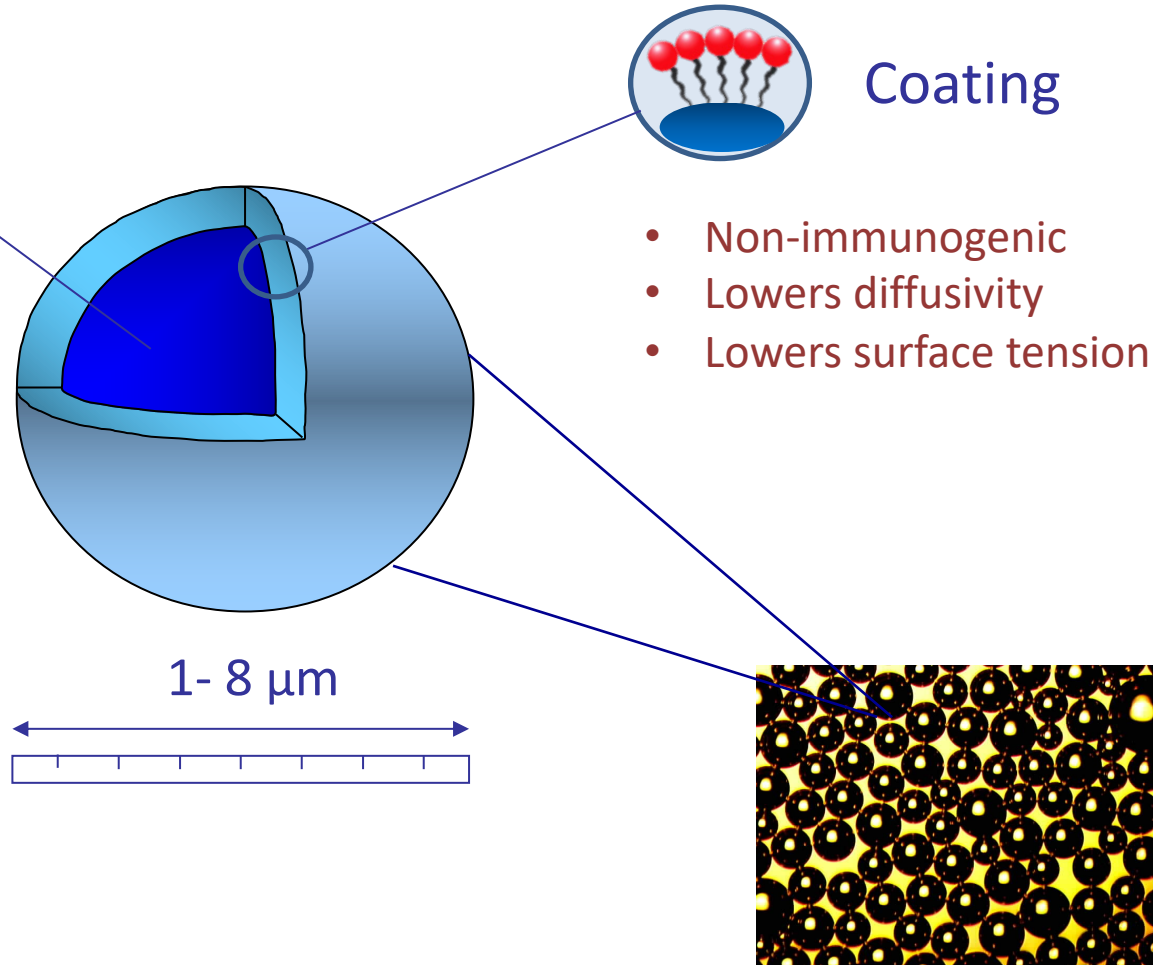
Filling gas

- Non-toxic
- Low diffusivity
- Low solubility

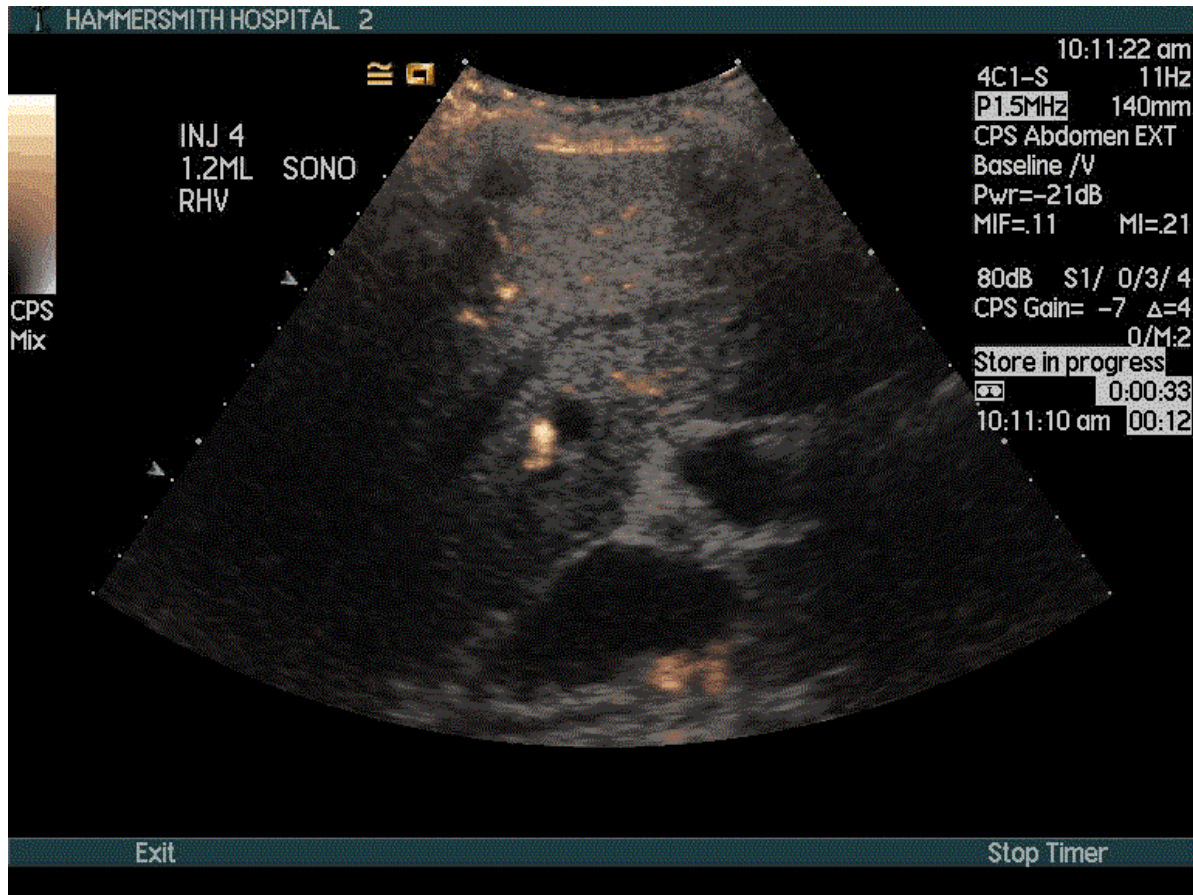


Coating

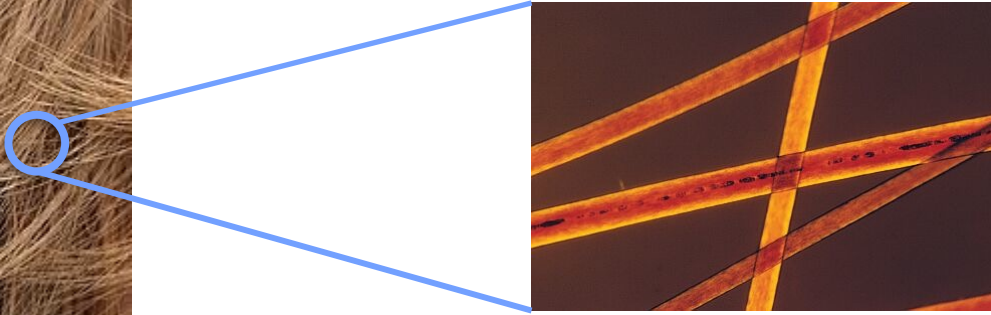
- Non-immunogenic
- Lowers diffusivity
- Lowers surface tension



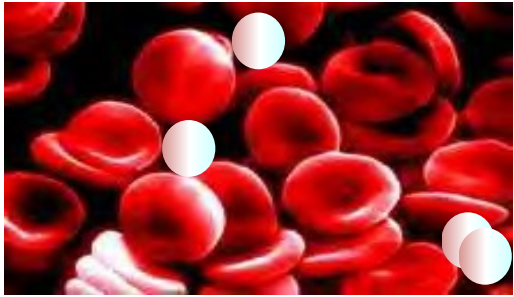
Bubble volume \approx 0.001% blood



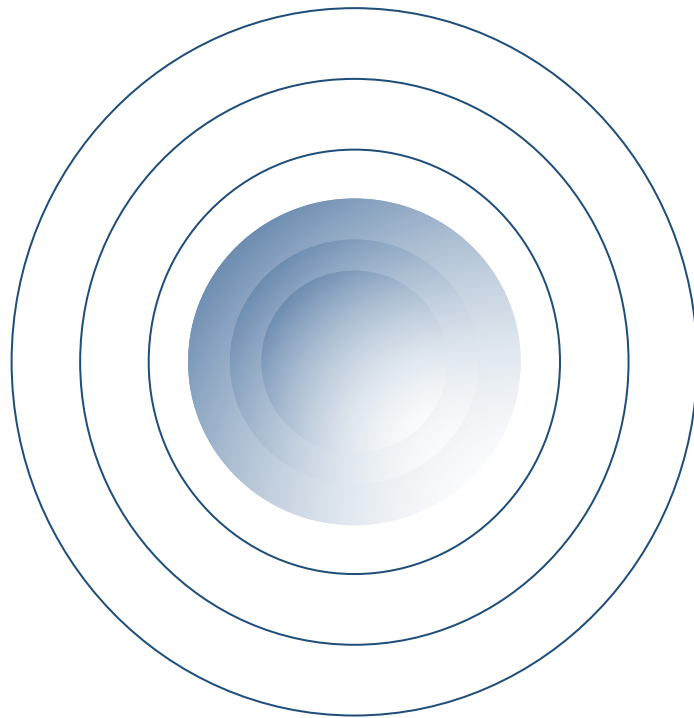
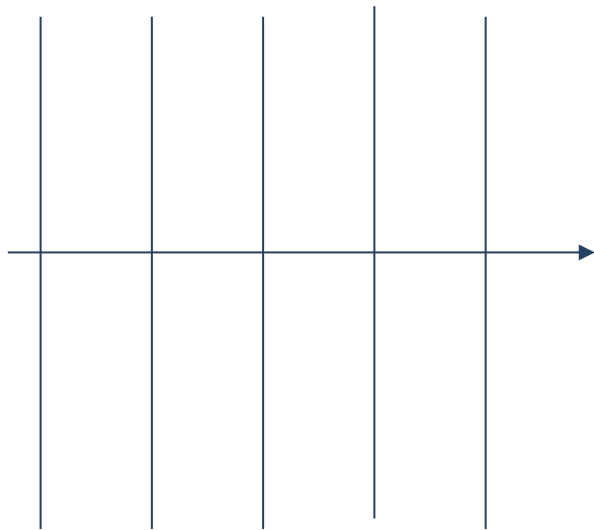
Courtesy of Dr RJ Eckersley & Prof DO Cosgrove, Hammersmith Hospital

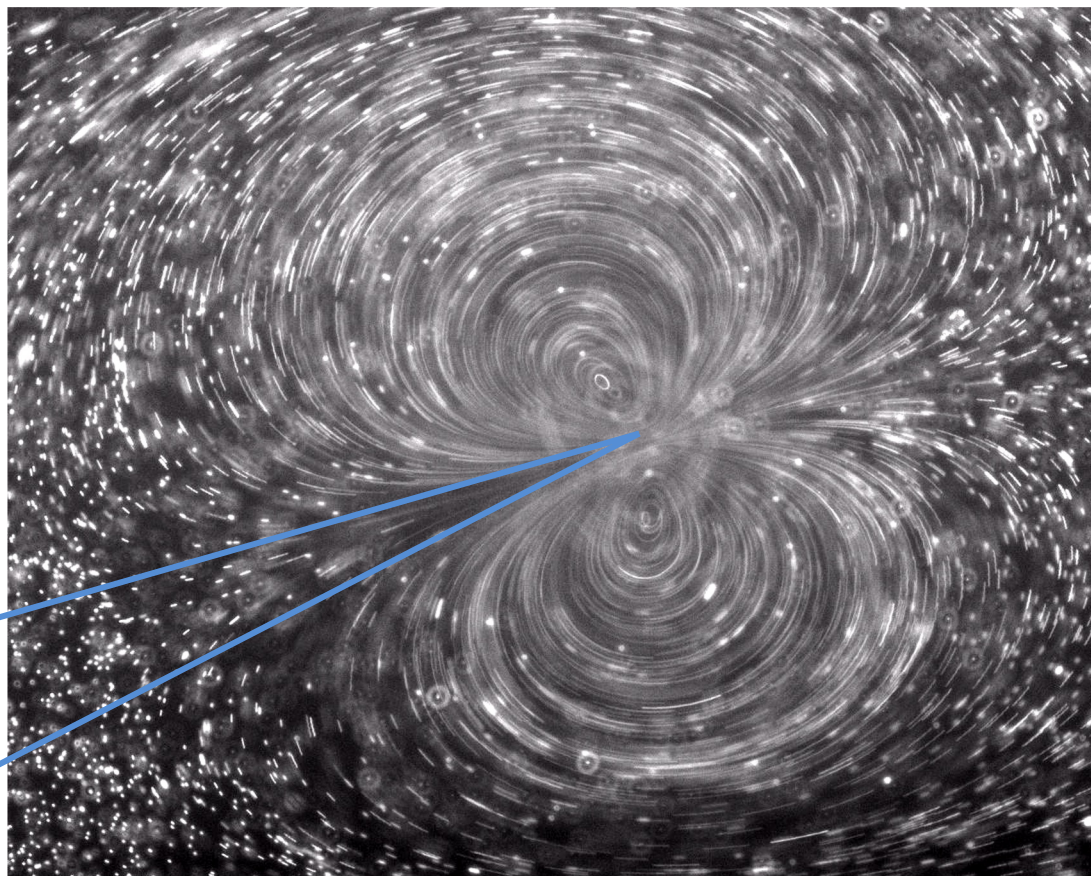


0.1 mm



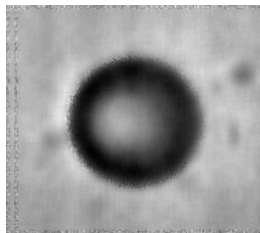
0.002 mm

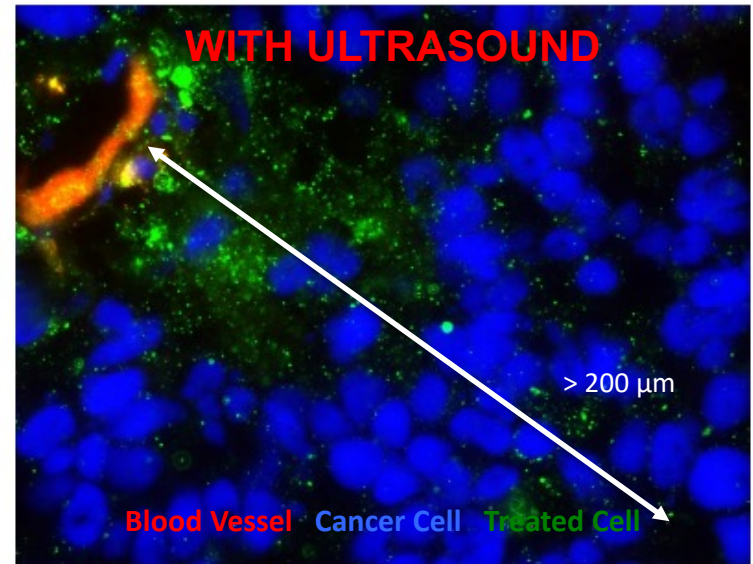
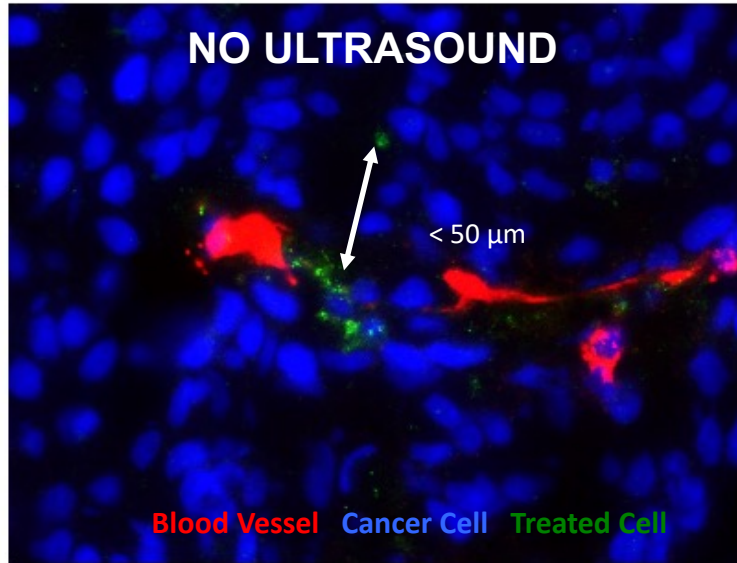




200 μm

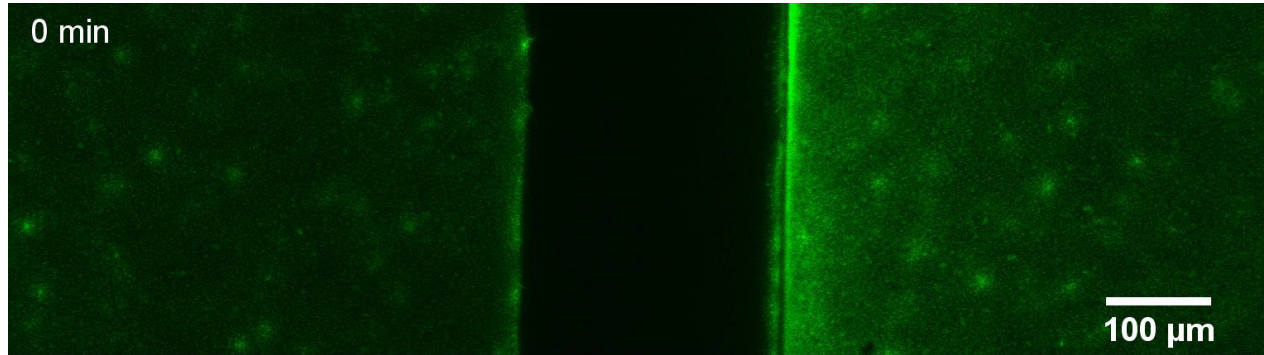
2 μm



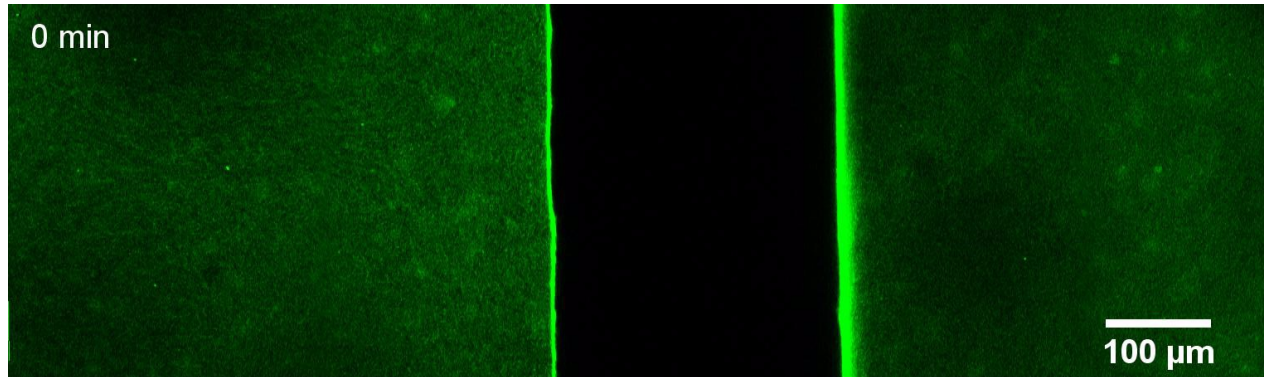


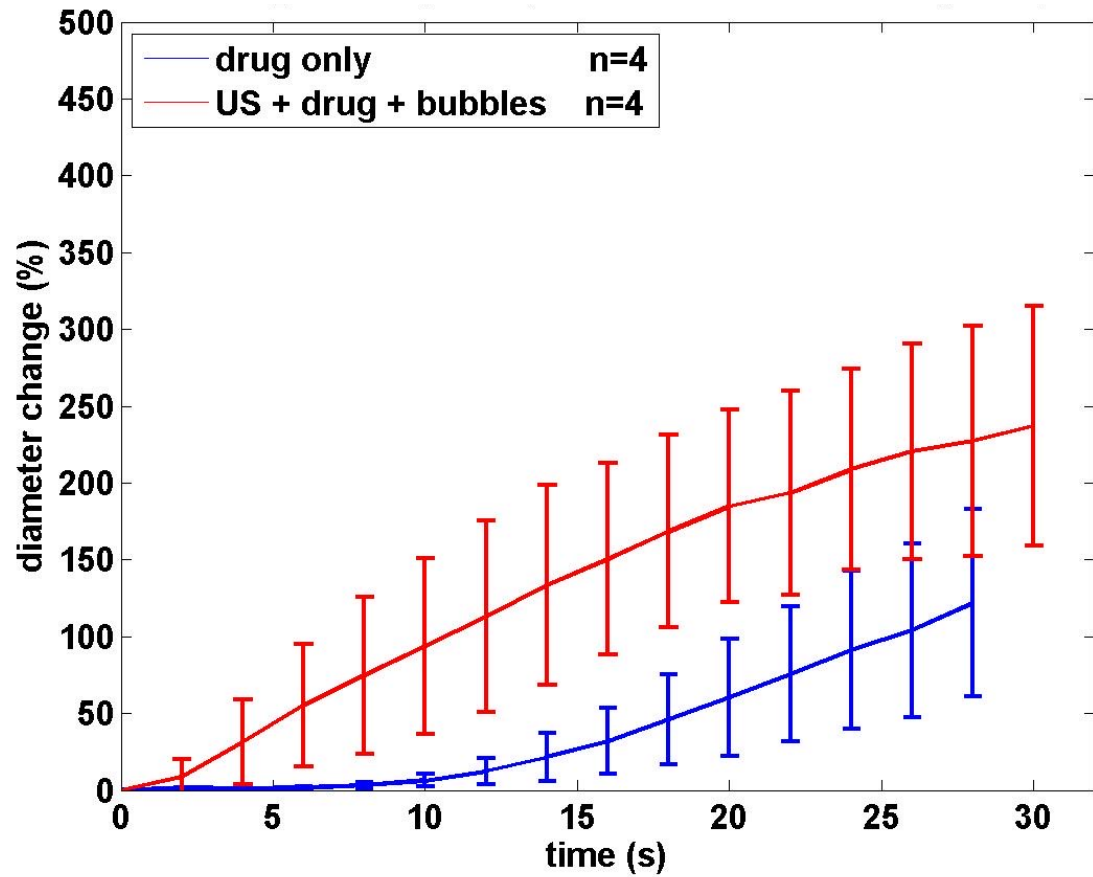


Drug only (0.75 $\mu\text{g}/\text{ml}$)



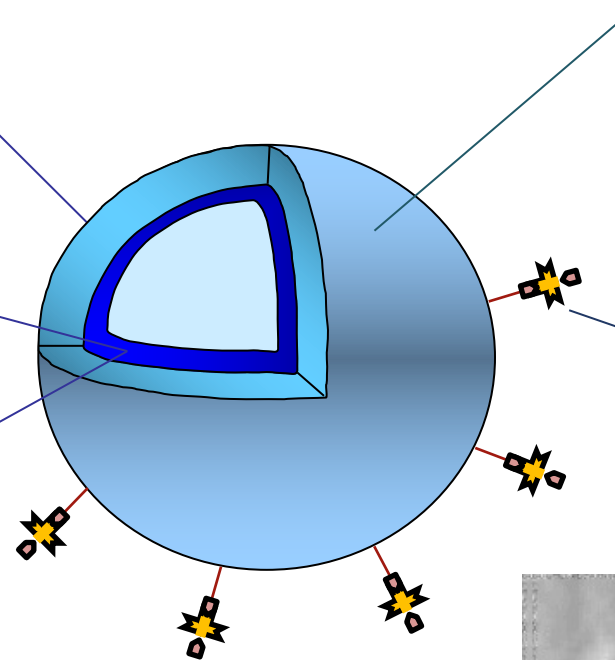
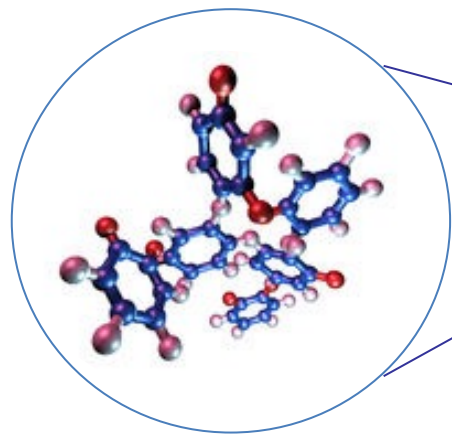
Drug + Microbubbles





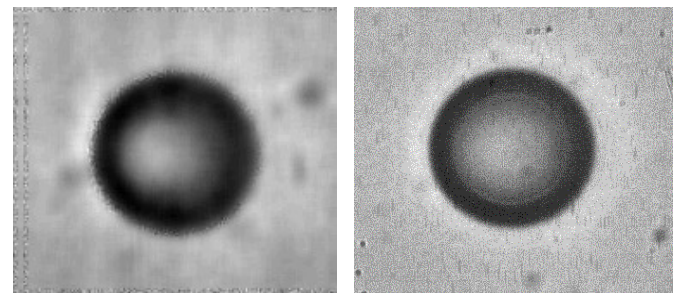
• Gas core

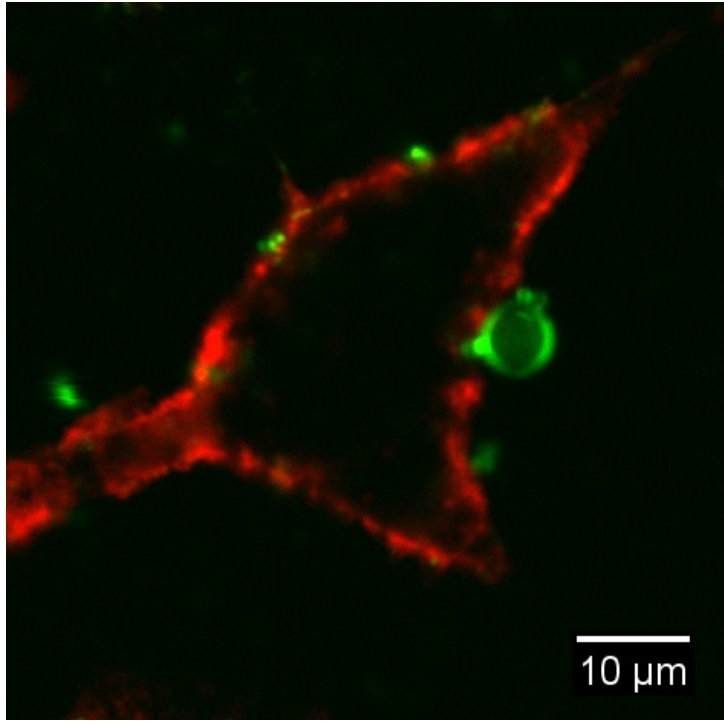
• Surfactant shell



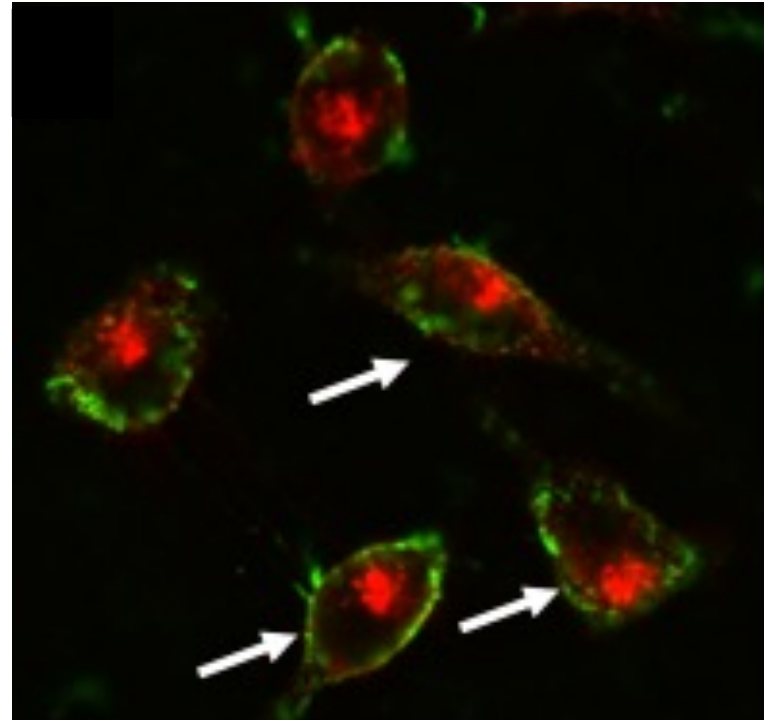
• Targeting molecules

• Drug molecules



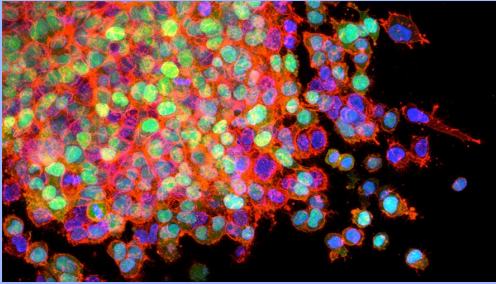


Bubbles only

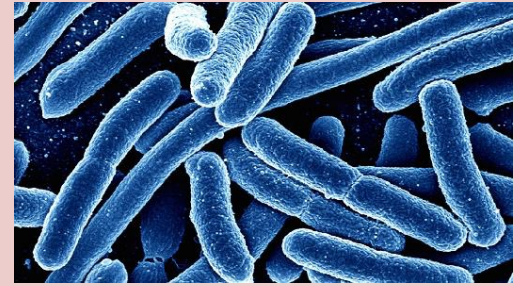


Bubbles + ultrasound

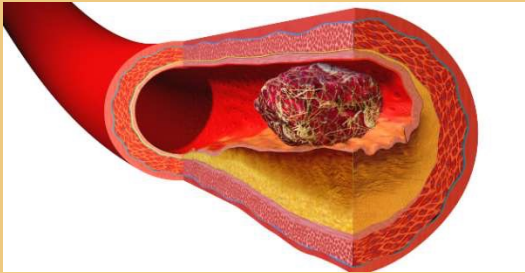
Cancer



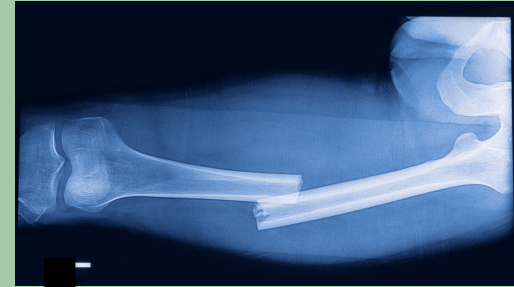
Infection



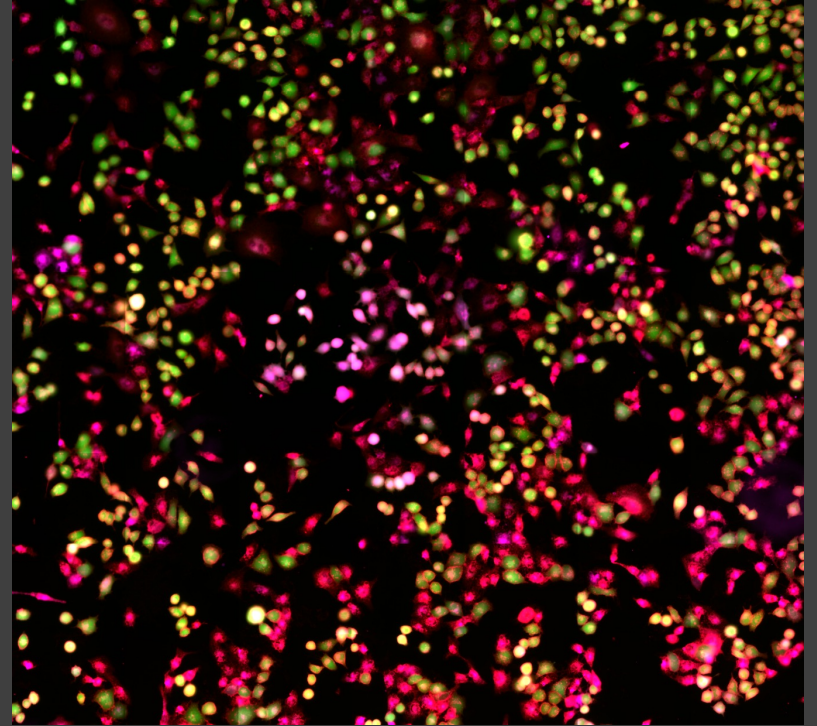
Cardiovascular



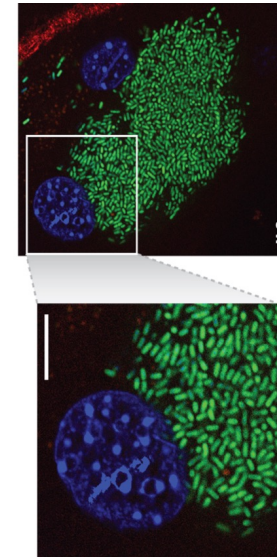
Orthopaedic



(i) Improving
antimicrobial
delivery



- Urinary tract infections (UTI) affect >10 million patients per year globally.
- ~30% patients suffer recurrent infections.
- Causes:
 - Intracellular bacterial colonies
 - Poor penetration of systemic antibiotics
 - Poor tolerance of high systemic doses
 - Increasing antibiotic resistance



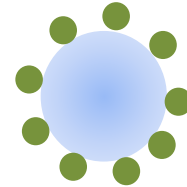
Hunstad & Justice, 2010



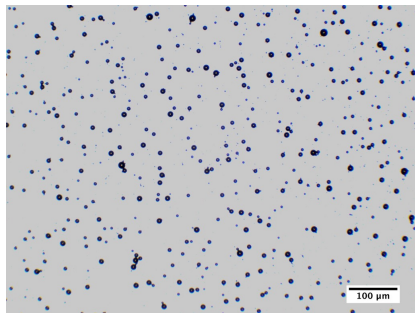
*Free drug
(gentamicin)*

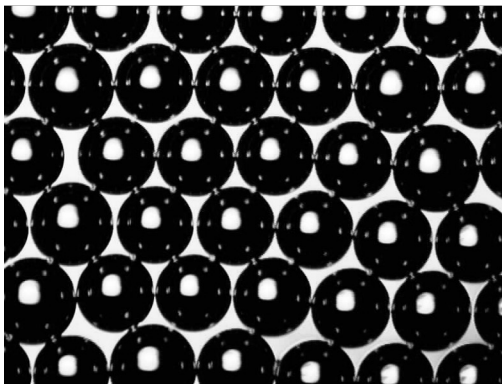
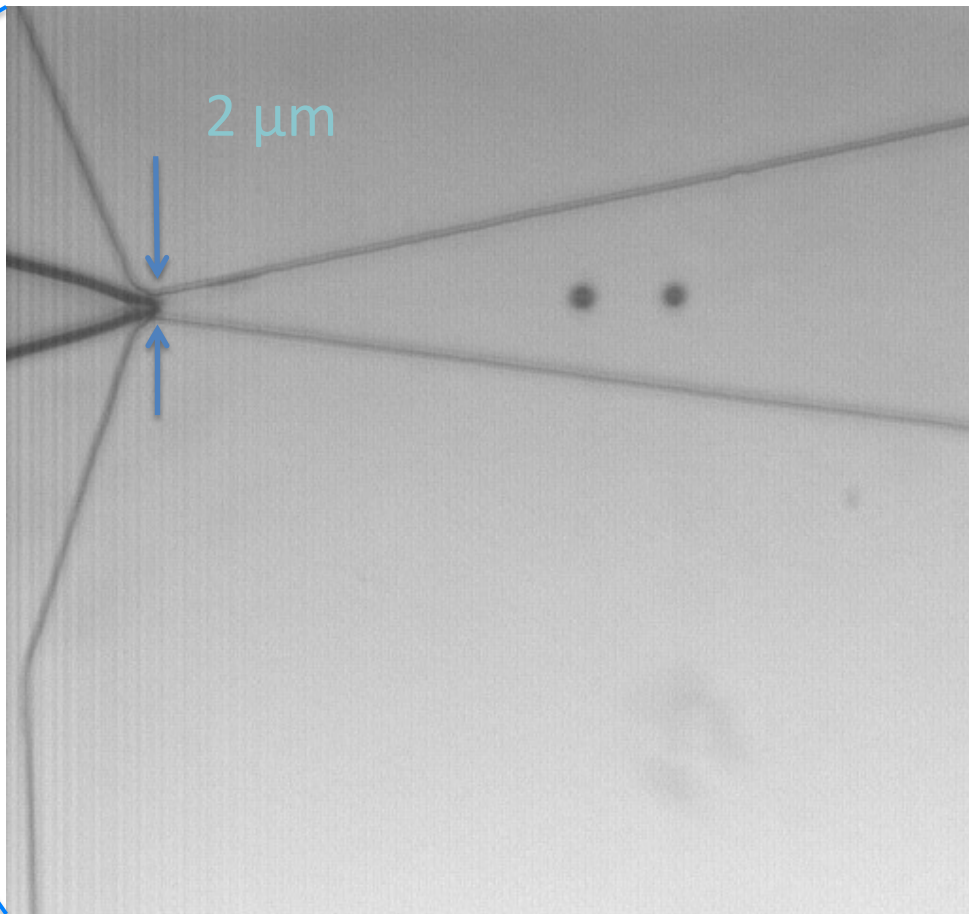
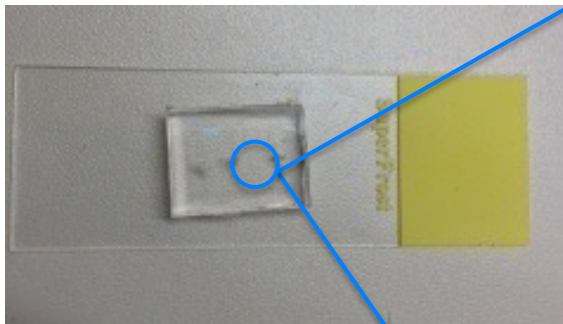


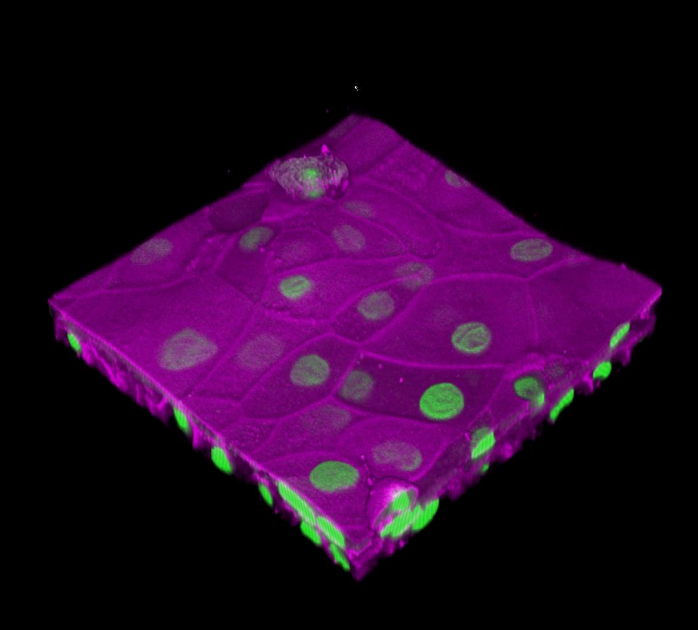
*Drug-filled
nanoparticles*



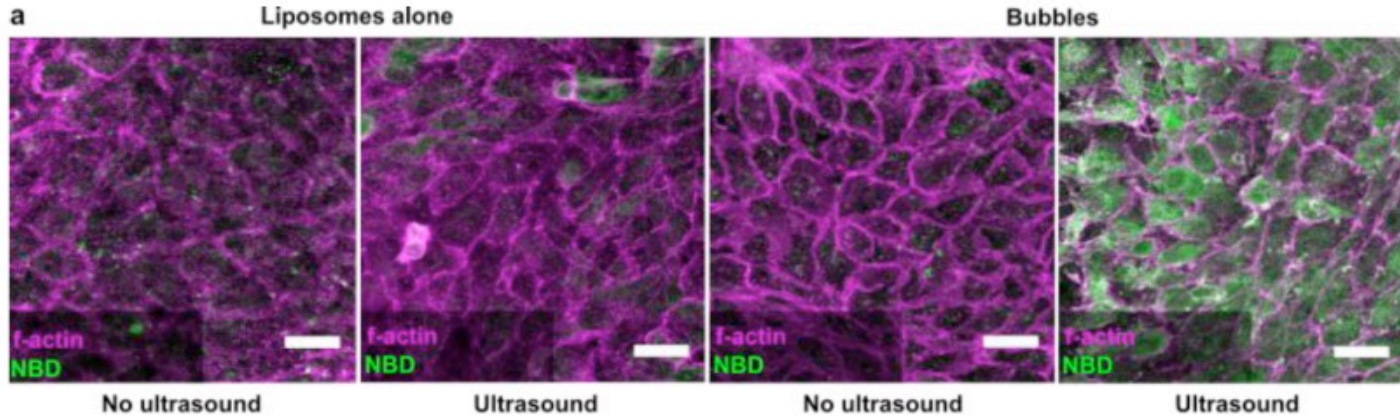
*Nanoparticle
loaded
microbubbles*



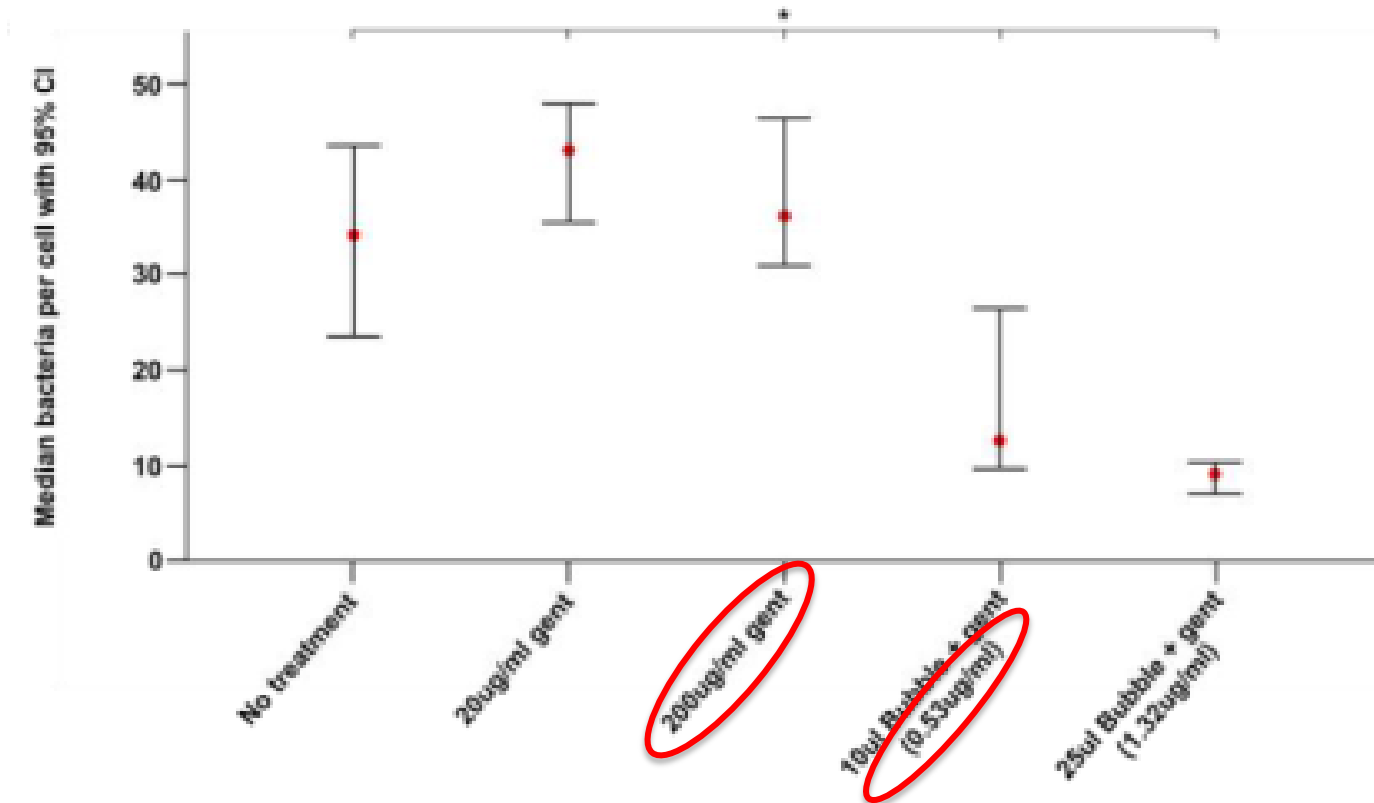


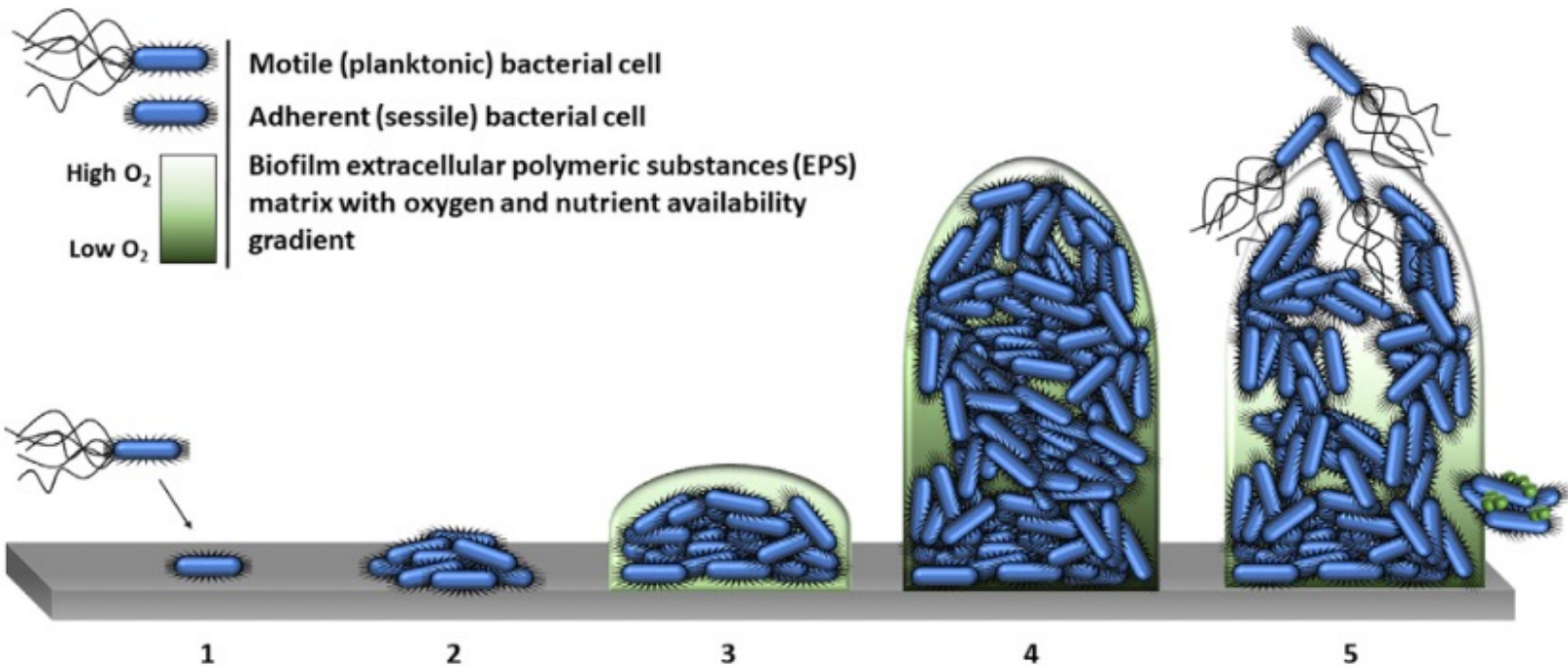


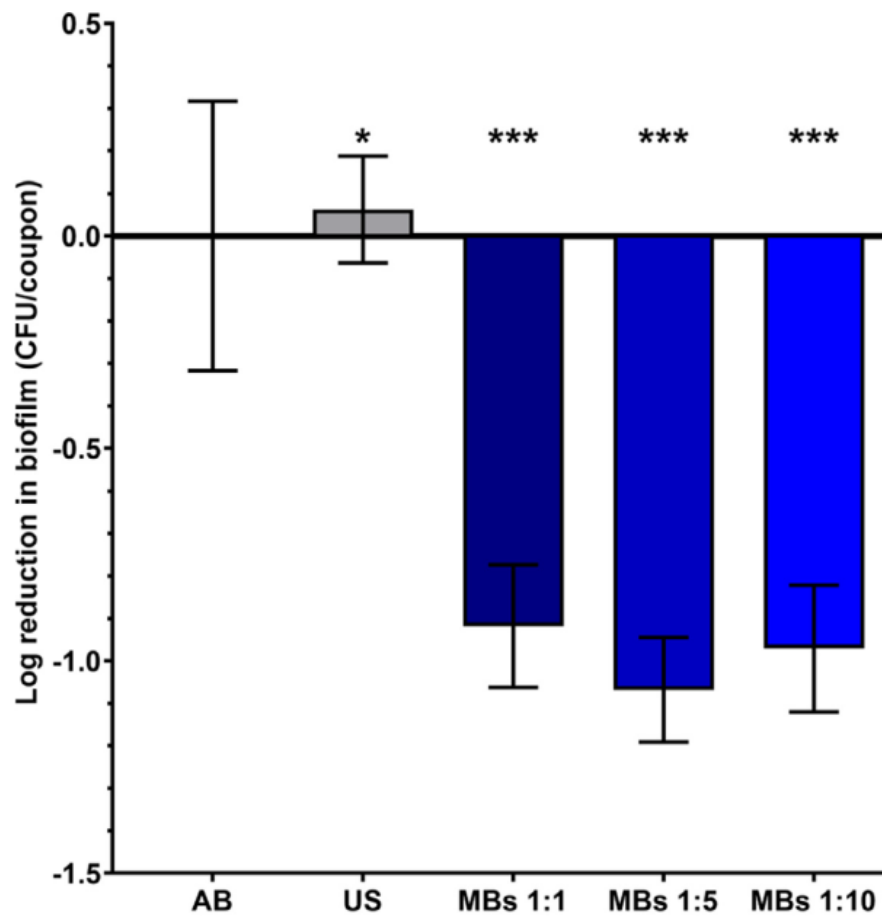
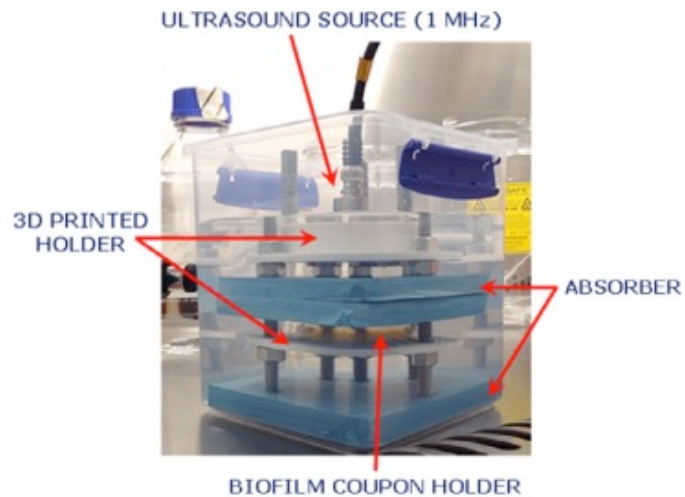
- *Cellular delivery (drug surrogate labelled green)*



- *Bacteria per cell*

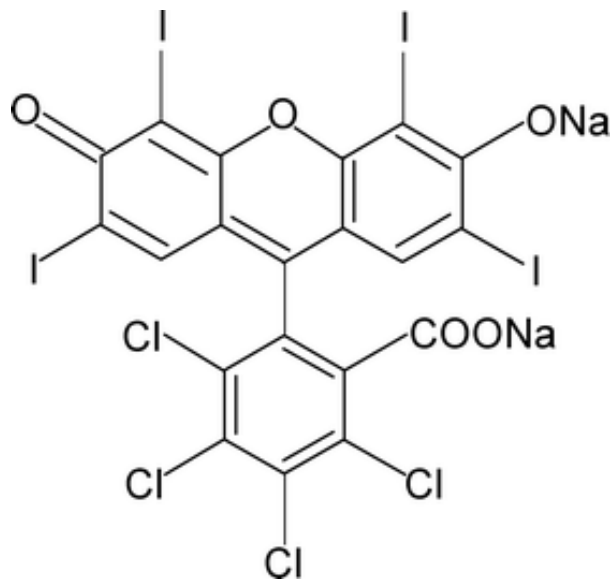




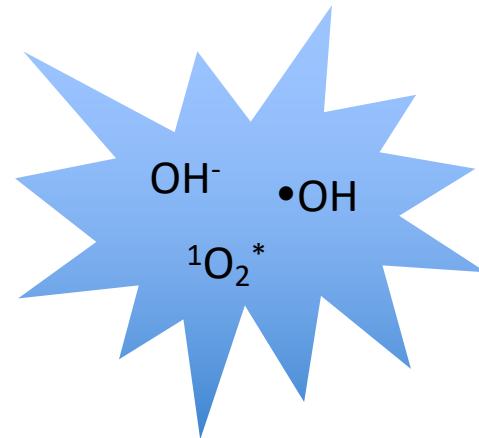
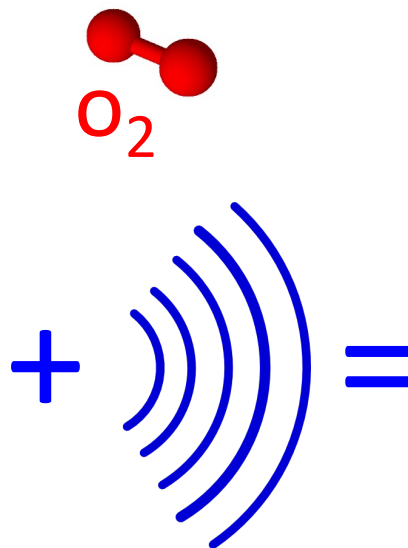


**(i) Replacing
conventional
antibiotics**

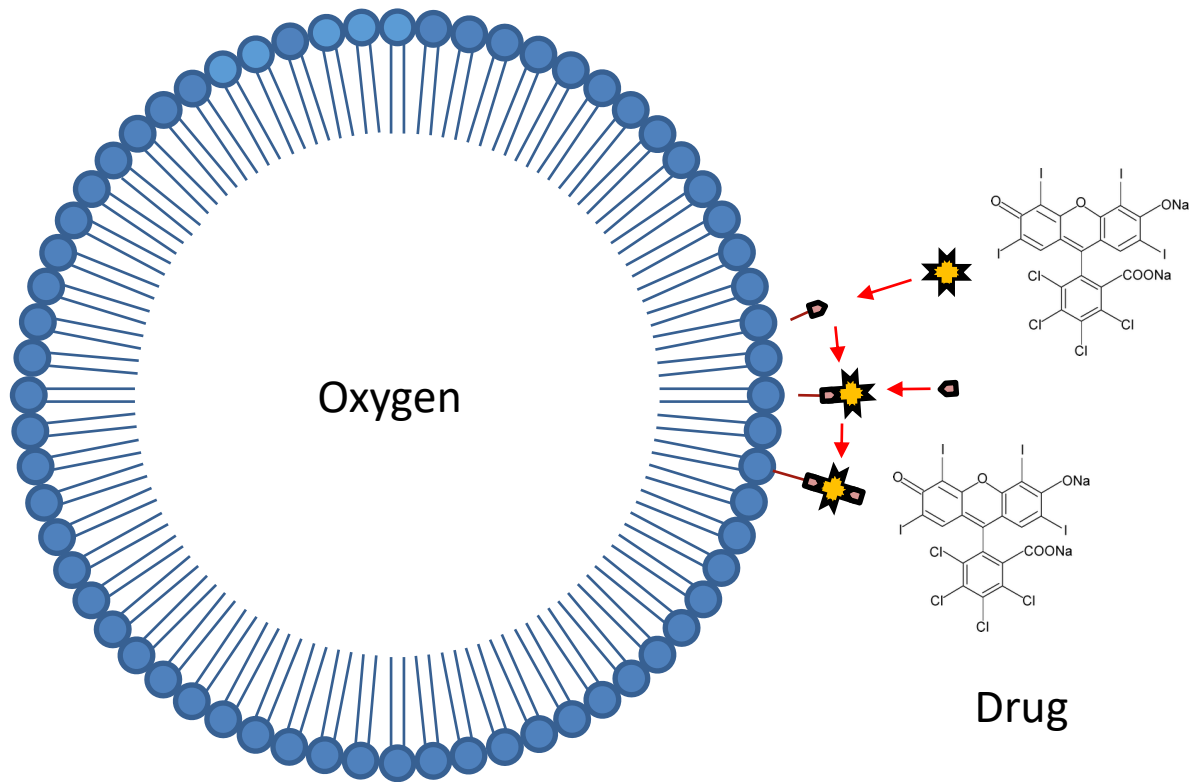


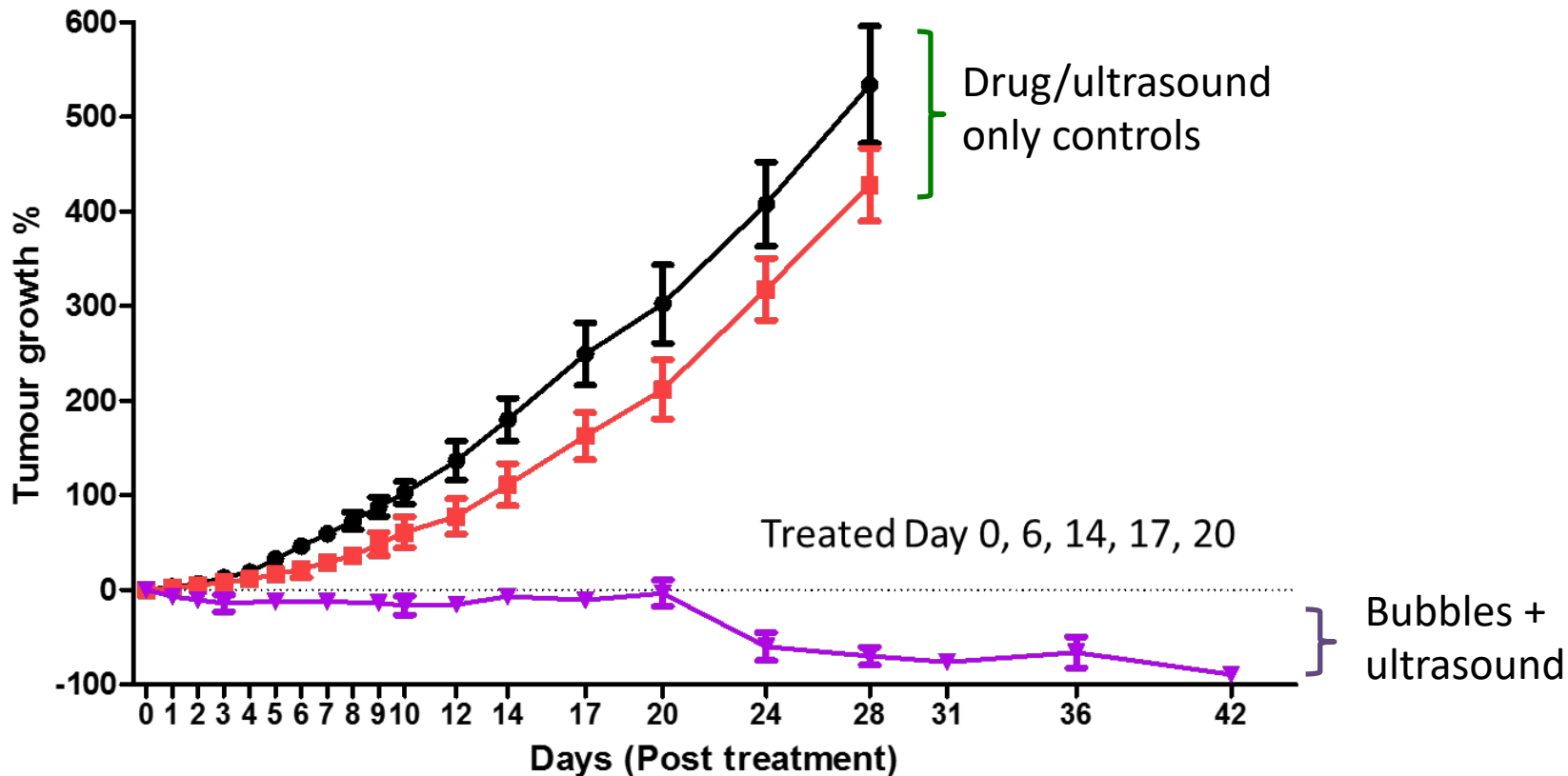


Inactive drug

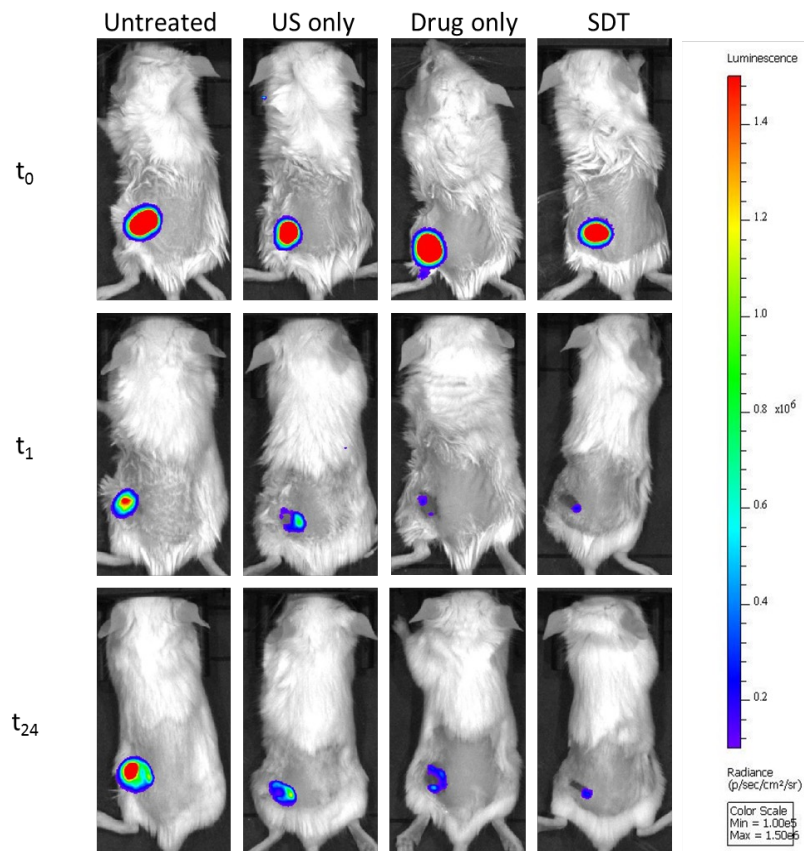


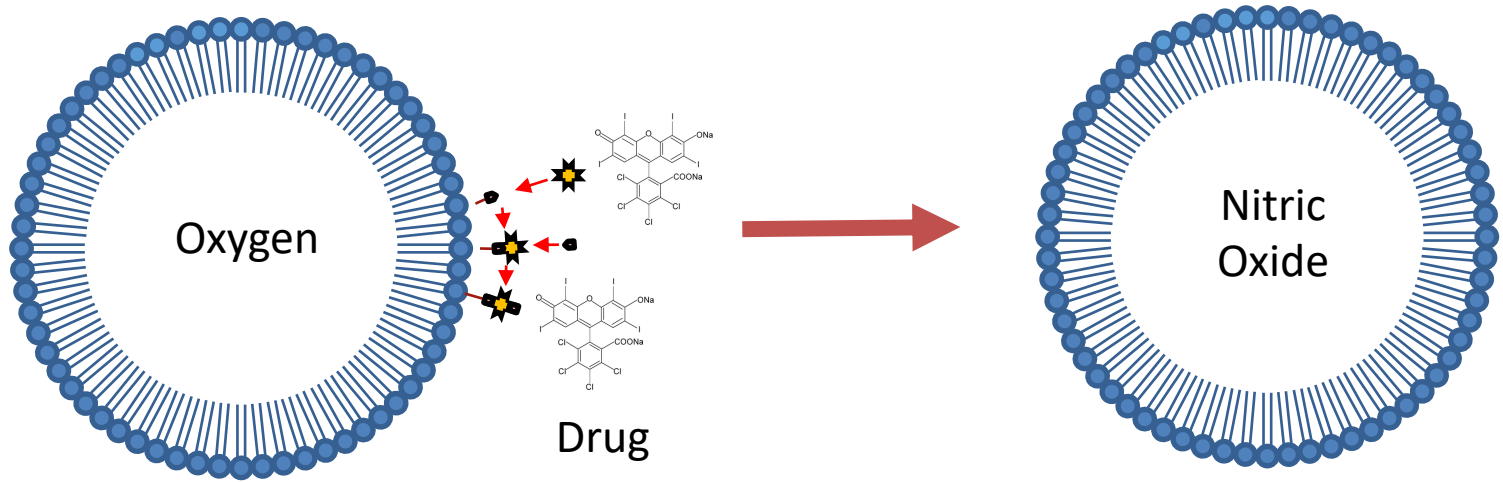
Reactive oxygen species



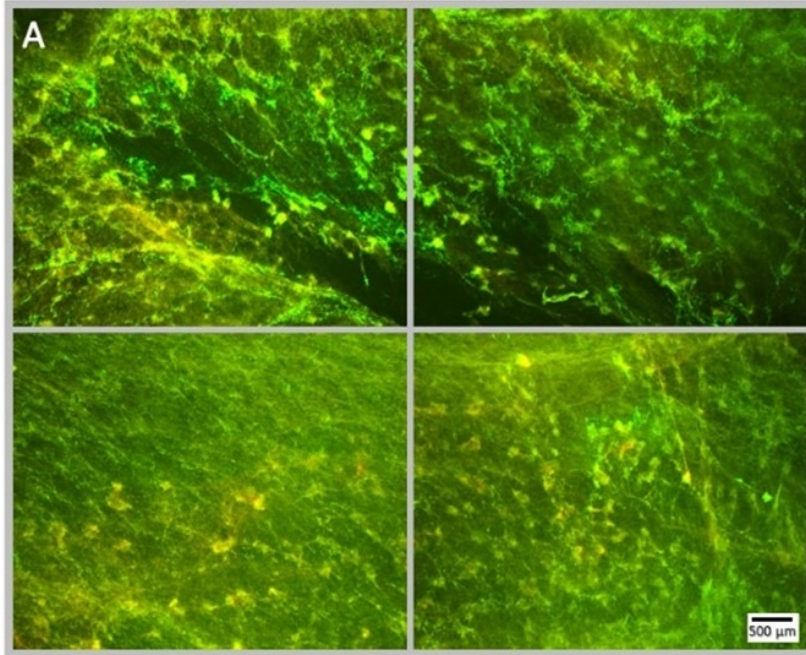


- *Pseudomonas aeruginosa* infected wounds in BALB/C mice





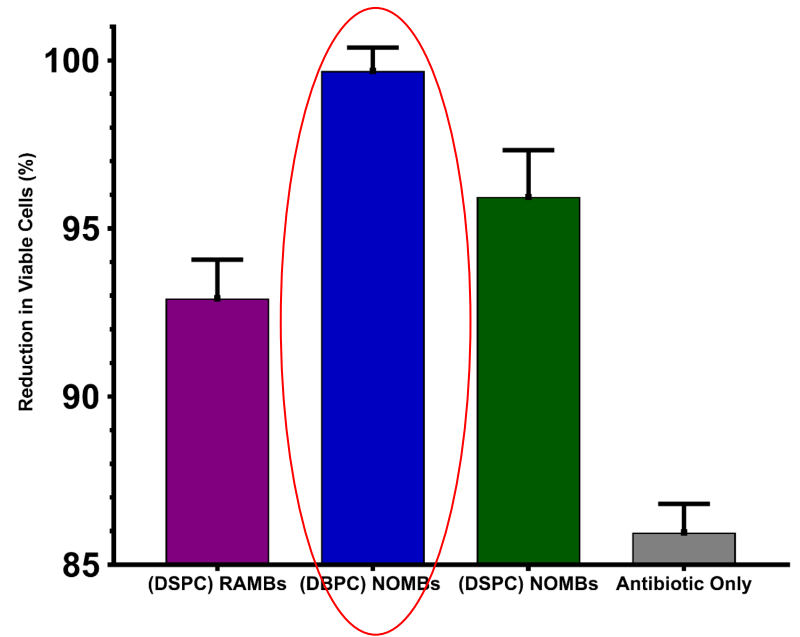
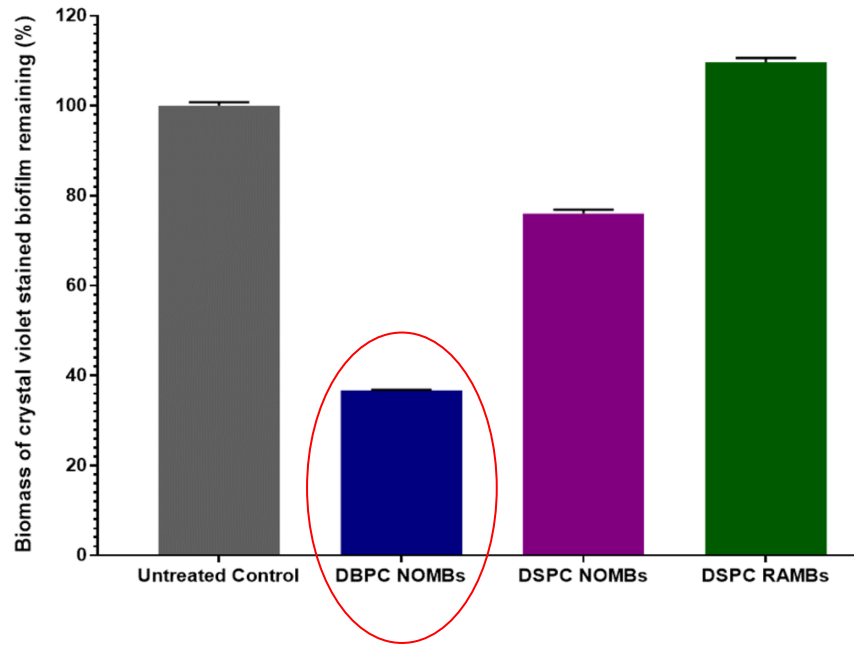
- *Pseudomonas aeruginosa* biofilm



Treated with air bubbles



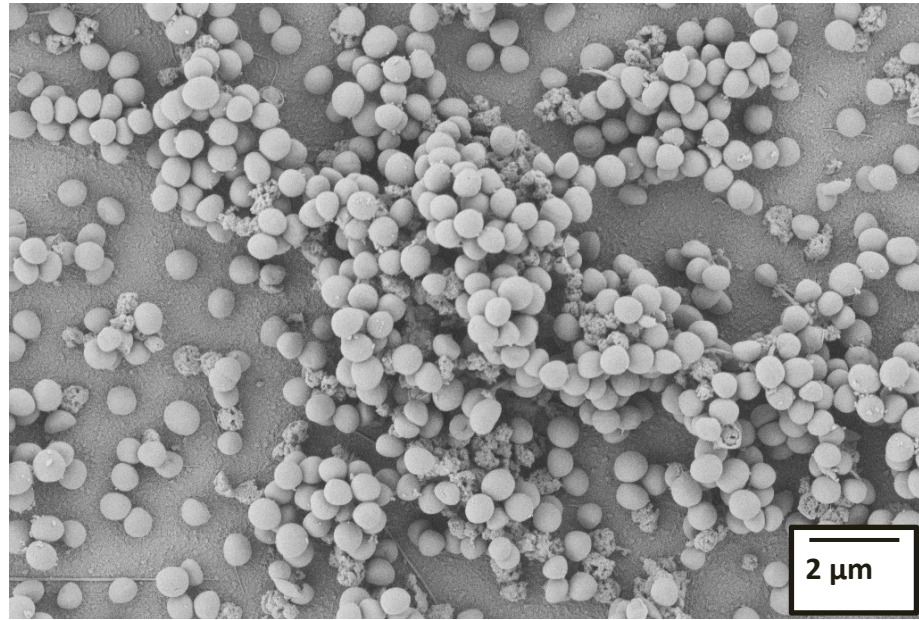
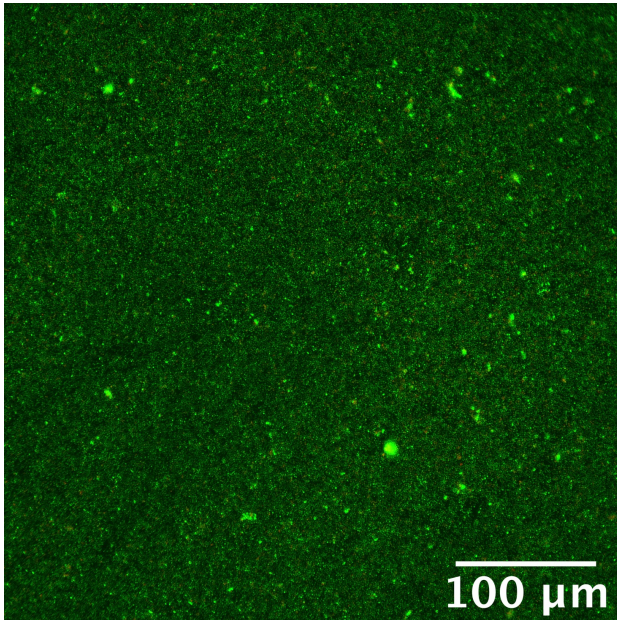
Treated with NO bubbles

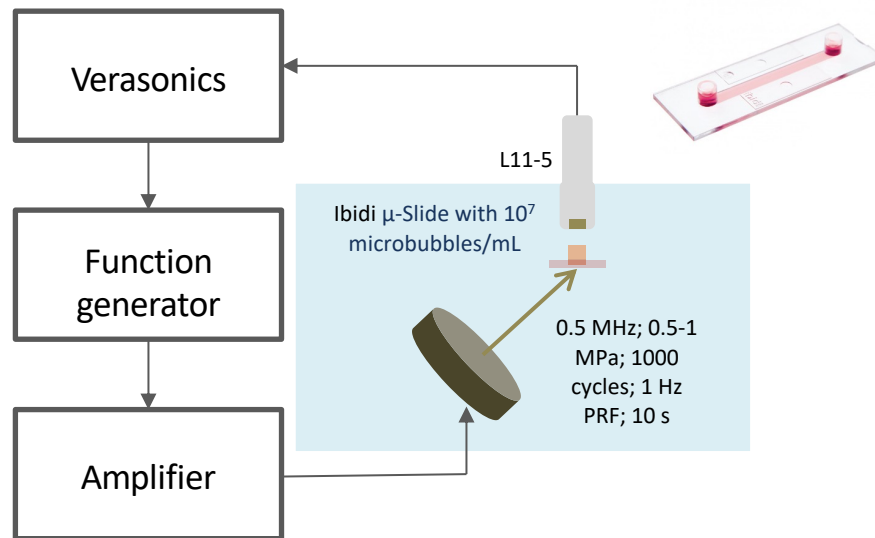
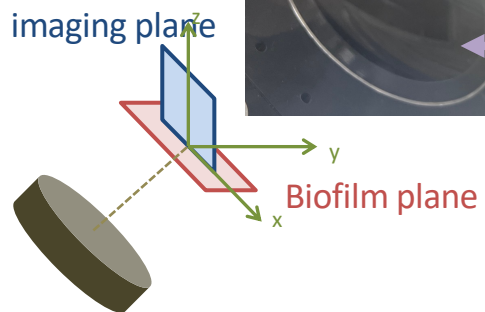
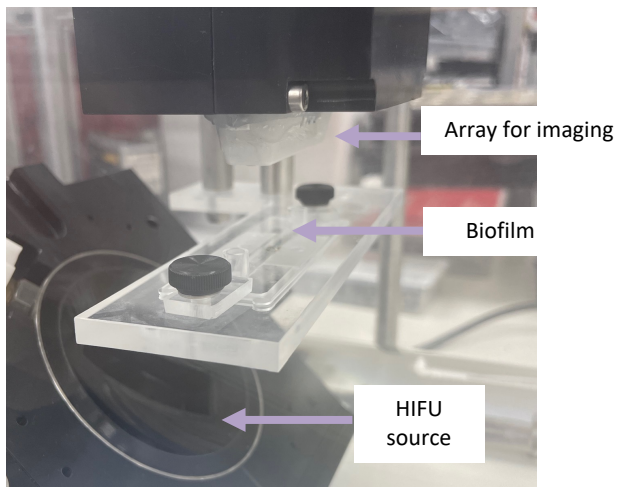


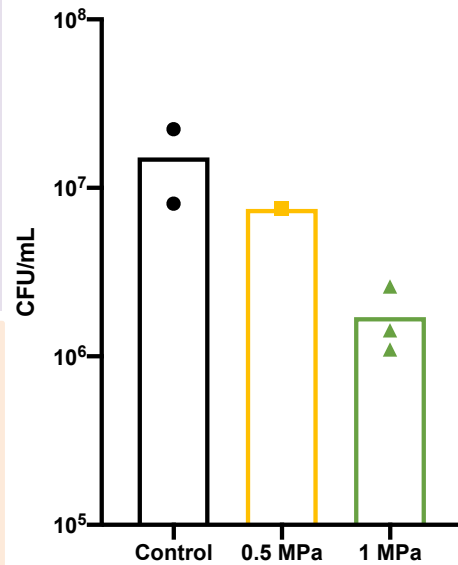
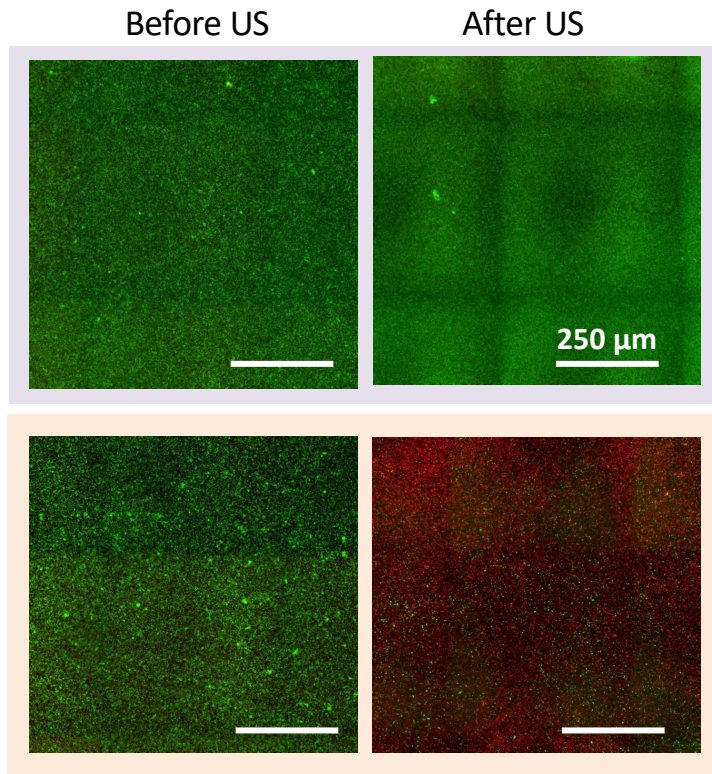
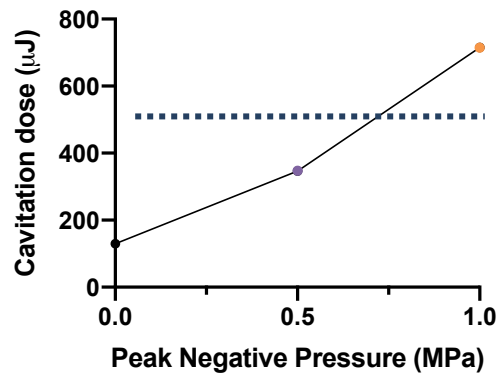
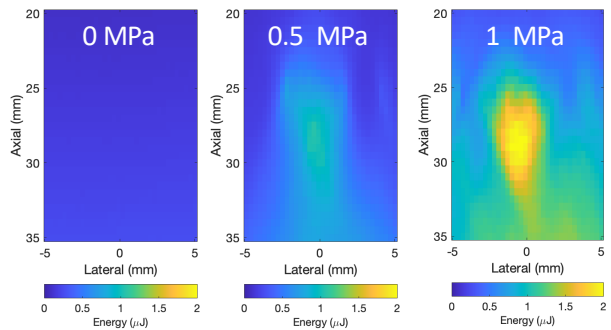
(iii) Drug-free
Treatments



- Methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from osteomyelitis
- Seeded at $OD_{600} = 0.2$ and cultured statically for 48 hours on collagen I
- **Live/dead** stained with Syto-9/Propidium iodide before and after ultrasound exposure







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Funders

The Royal Academy of Engineering
Engineering and Physical Sciences Research Council



Institute of Engineering And Technology



Cancer Research UK

The Leverhulme Trust



The MS Society

