BUBBL
Biomedical Ultrasonics, Biotherapy & Biopharmaceuticals Laboratory
www.ibme.ox.ac.uk/bubbl

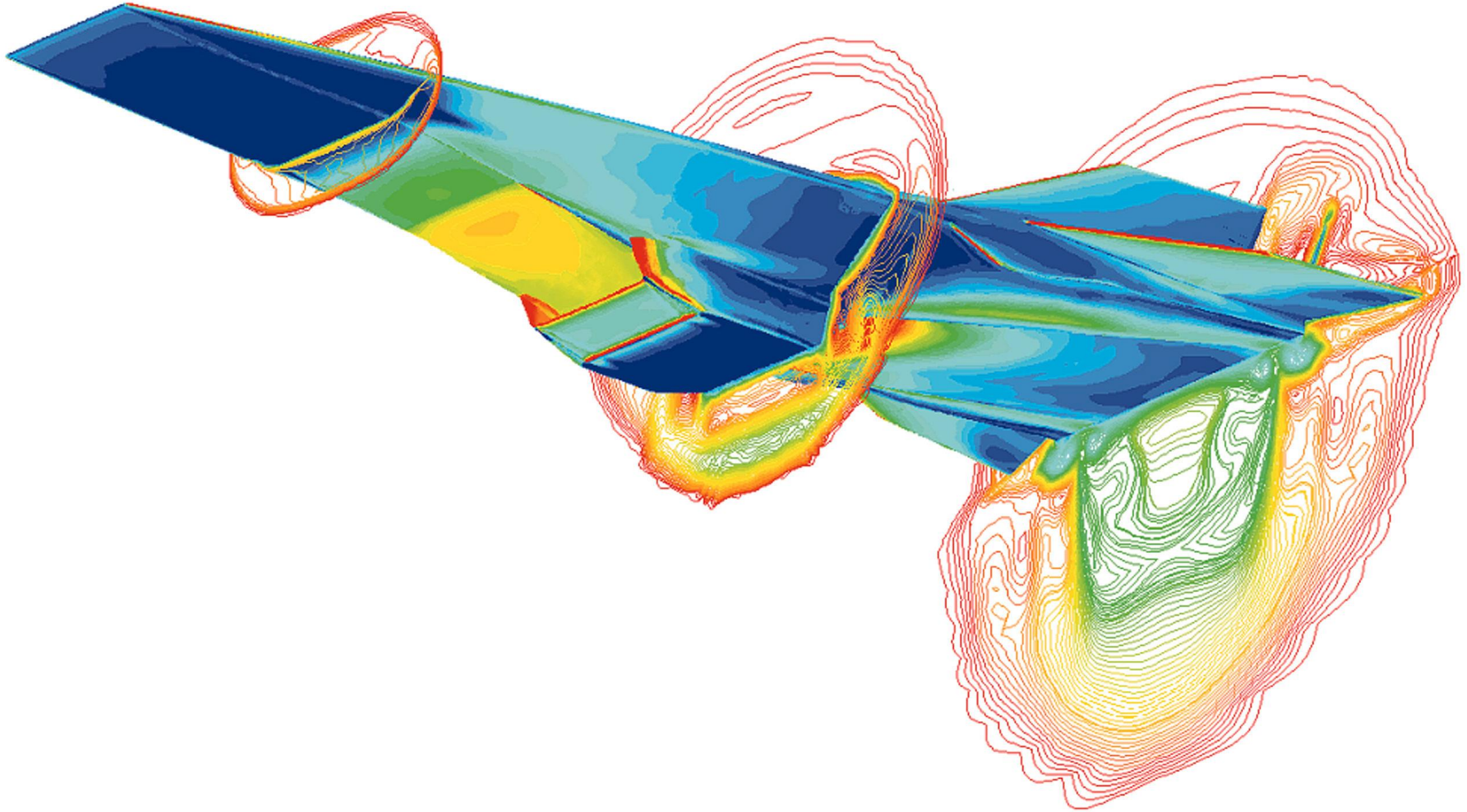
UNIVERSITY OF OXFORD

Theracoustics:
how sound and bubbles can cure our troubles

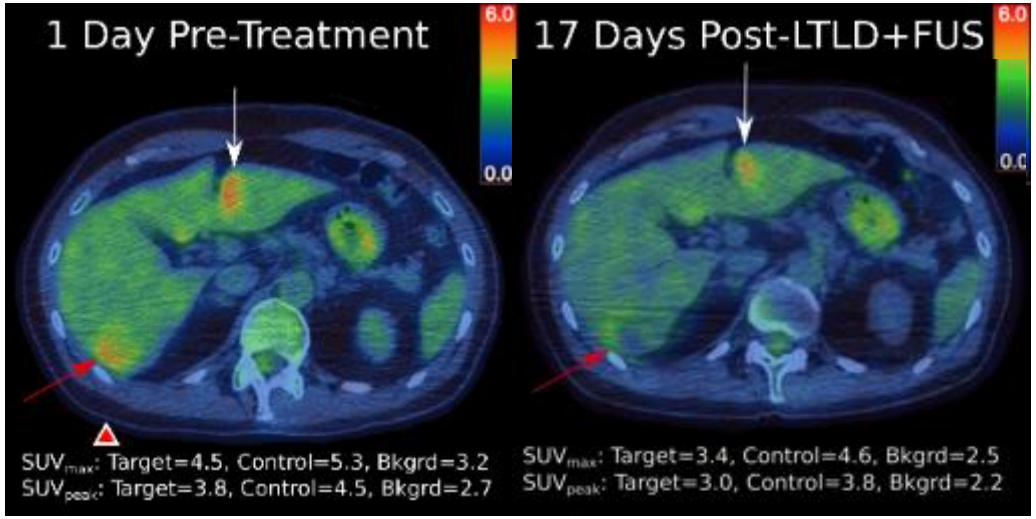
Professor Constantin-C. Coussios
Director, **Institute of Biomedical Engineering**, University of Oxford
CTO & Founder, OrganOx Ltd., OxSonics Ltd. and OrthoSon Ltd.

Sheffield, 7th January 2019

I set out to study this (with J.E. Ffowcs Williams) in 1998…



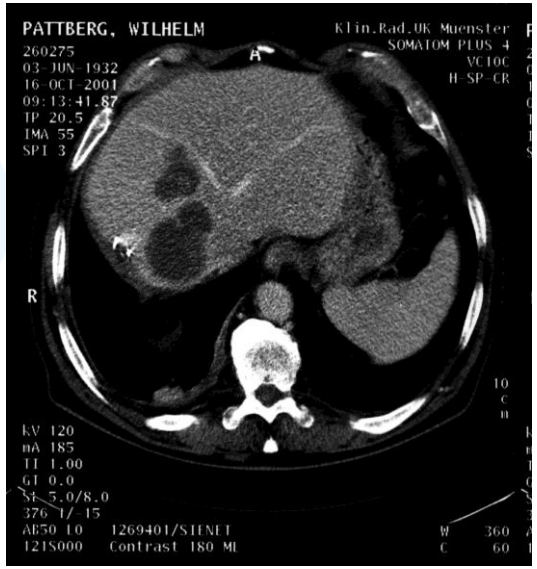
… and ended up working on this over the next 20 years…



ORTHOSON

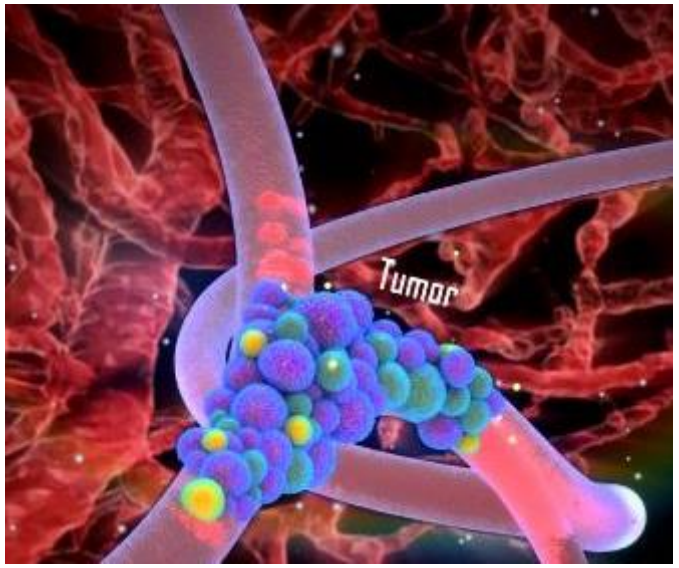
OxSonics

Towards Acoustics-Led Medicine: Surgery, Oncology, Orthopaedics,…



Surgical Ablation

Primary Liver Cancer: 15,000 cases pa in Europe
Primary Kidney: 40,000 cases pa in Europe
Colorectal Cancer 144,000 cases pa in Europe
Pancreatic Cancer: 20,000 cases pa in Europe



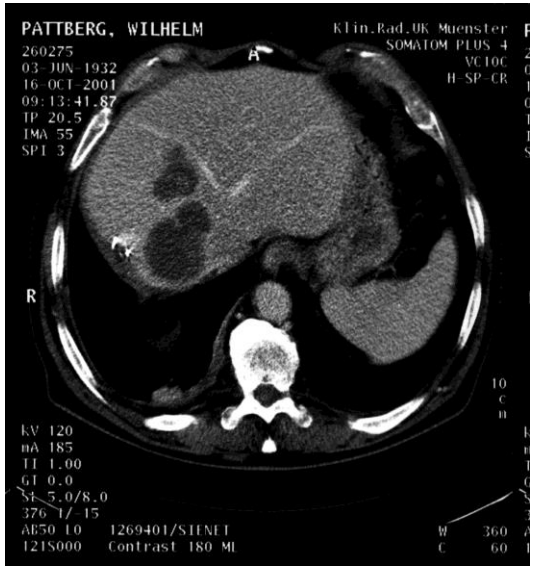
Oncological drug delivery

£8bn/year in Europe

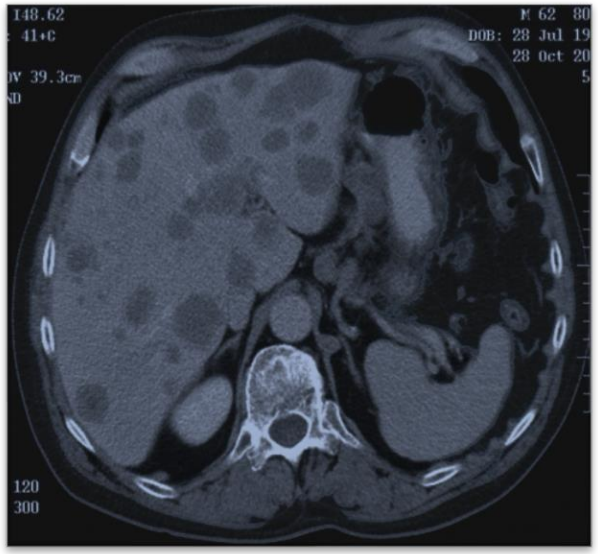
Lower Back Pain

>70% of adults

Part I:
Non-Invasive Surgery

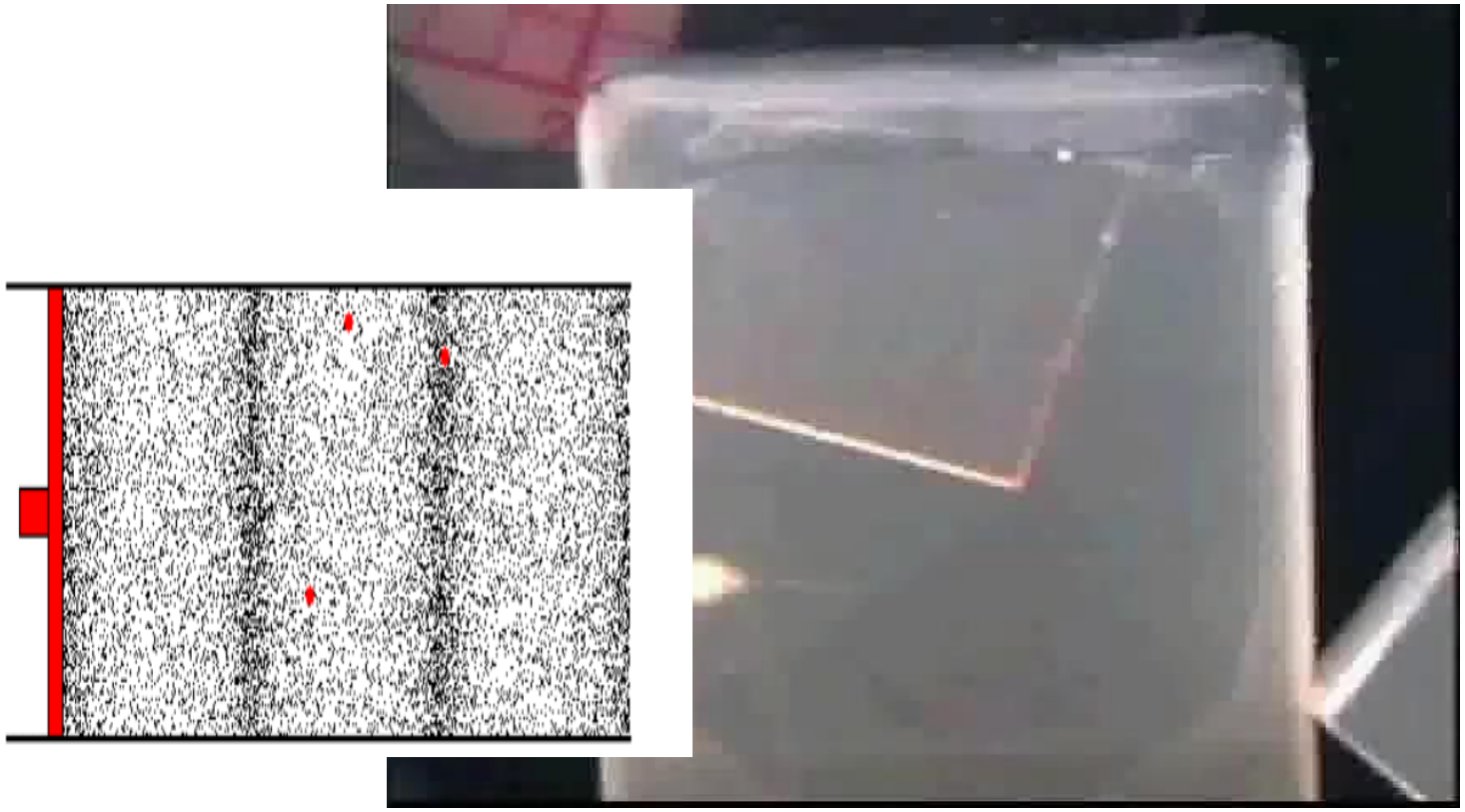


Surgery
(only feasible in 10-25% cases)



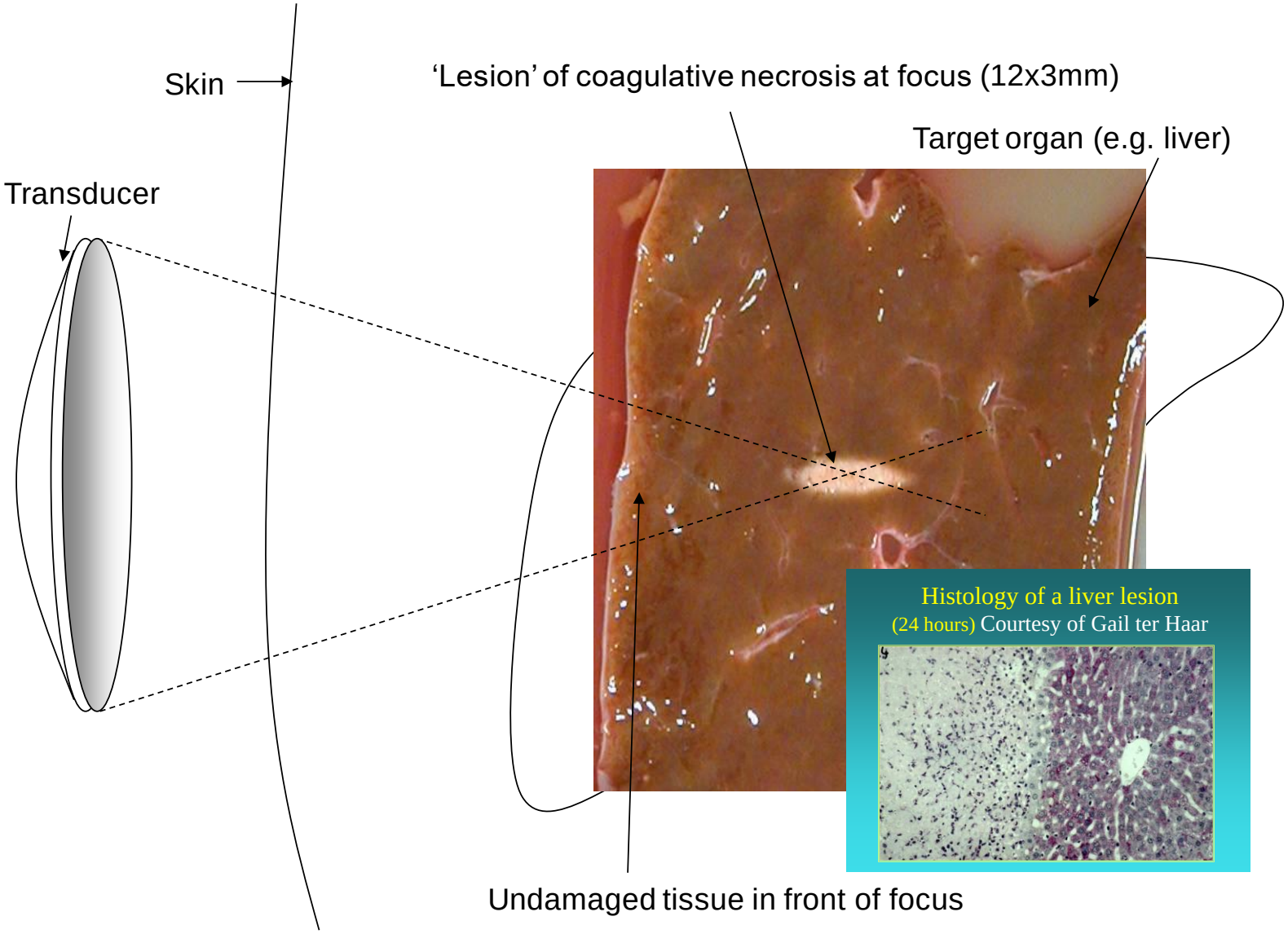
Drug delivery / chemotherapy
(20-50% response, 12-month survival)

Therapeutic Focused Ultrasound: Thermal Effects



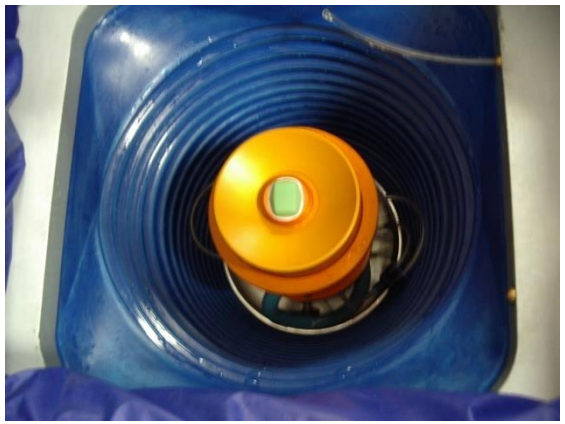
[Thermal Denaturation Video: Prof. Larry Crum, CIMU, Univ. of Washington]

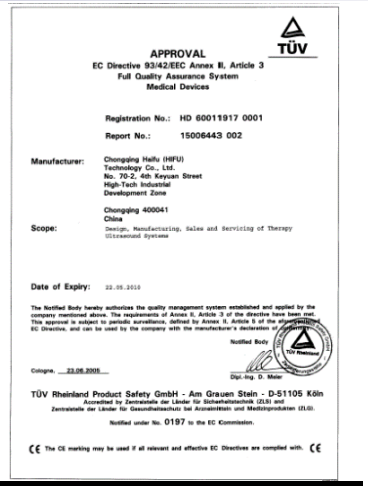
High-Intensity Focussed Ultrasound (HIFU)



J. Kennedy, *Nat. Cancer Reviews,* 2005.

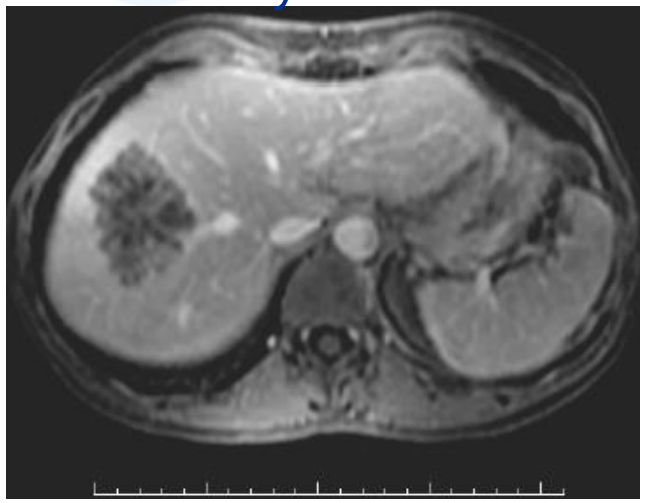
HIFU in the Clinic (Churchill Hospital-Oxford)



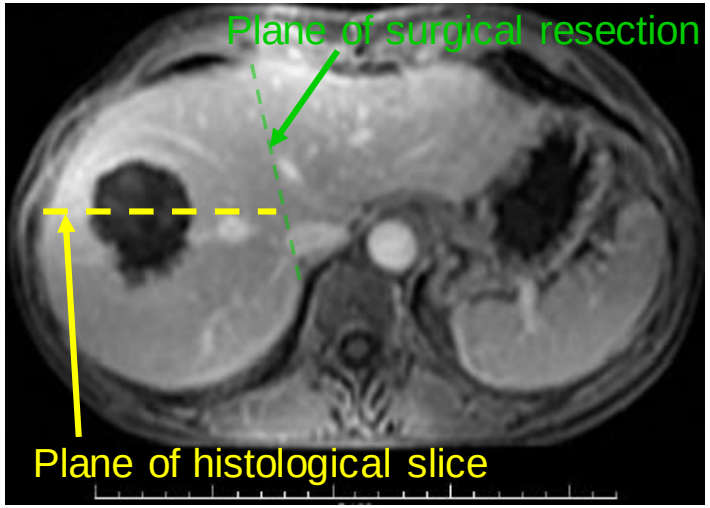


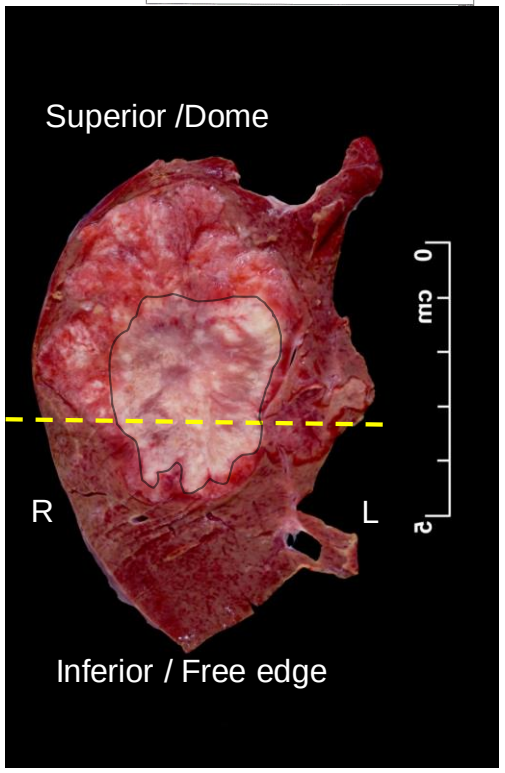
JC 200 - Chongqing

2 days Pre-HIFU

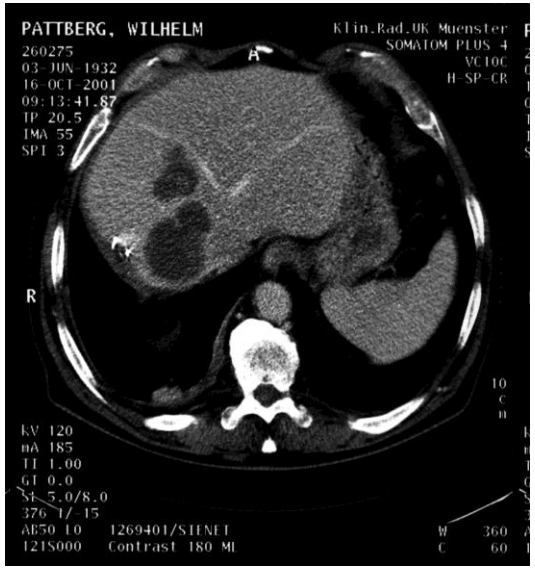


1 day post-HIFU





Part II:
Oncological Drug Delivery



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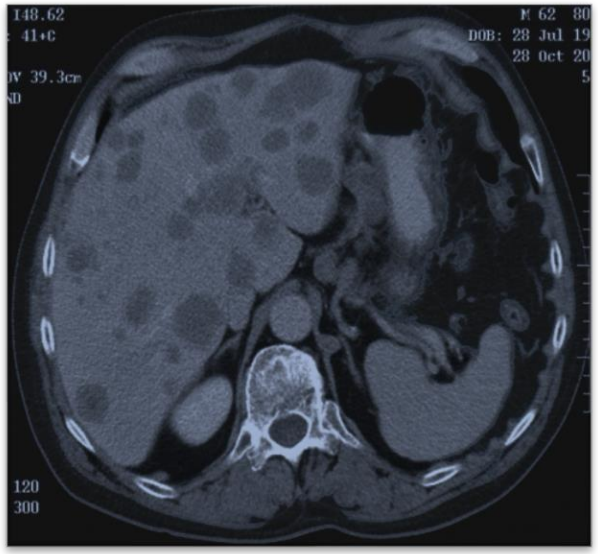


Drug delivery / chemotherapy
(20-50% response, 12-month survival)

Drug Delivery for Cancer

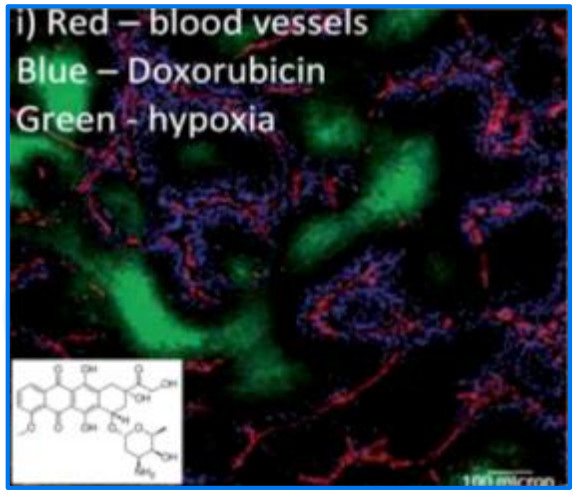
"Among 68 cancer drug indications approved by the EMA in the period 2009-13, and with a median of 5.4 years' follow-up,

only 35 (51%) were associated with significant improvement in survival or quality of life over alternative treatment options, placebo, or as add-on treatment.

For 33 (49%), uncertainty remains over whether the drugs extend survival or improve quality of life."

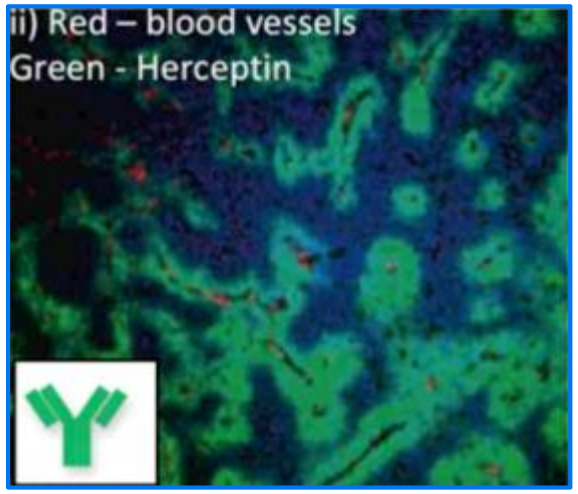
Davis et al., BMJ 2017;359:j4530

A Common Problem Across All Cancer Drug Classes



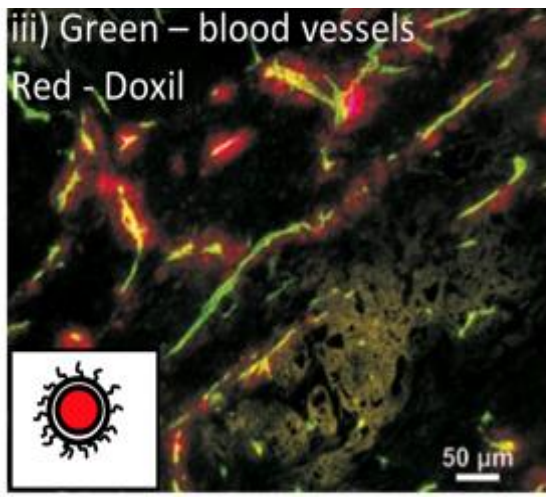
CHEMO-THERAPEUTICS

<1nm



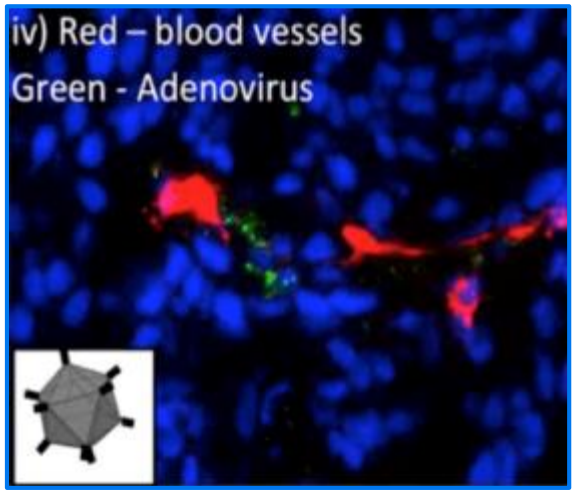
ANTIBODIES / IMMUNO-ONCOLOGY

15nm



LIPOSOMES / POLYMERIC VEHICLES

90-140nm

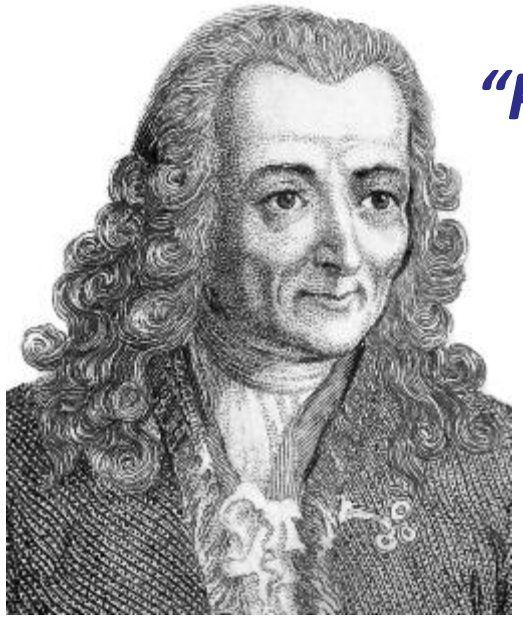


ONCOLYTIC VIRUSES / IMMUNO-ONCOLOGY

100-300nm

➢Typically, **0.5-1.4%** of the administered drug dose reaches the target tumour

Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, et al. 2016. Analysis of nanoparticle delivery to tumours. Nature Reviews Materials 1:16014



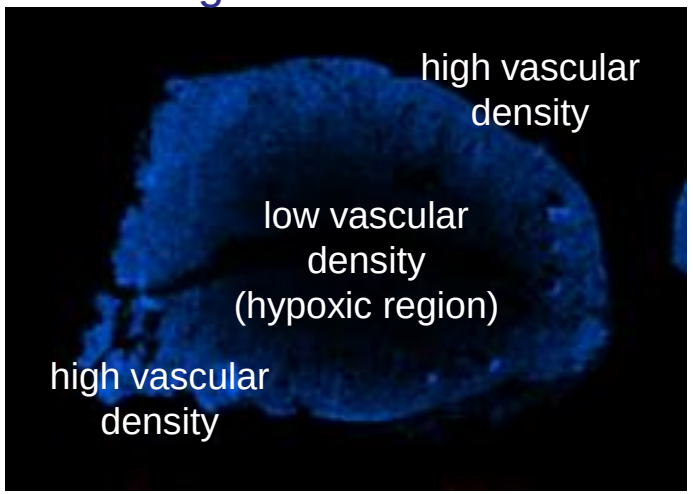
"Physicians pour drugs of which they know little, to cure diseases of which they know less, into humans of which they know nothing."

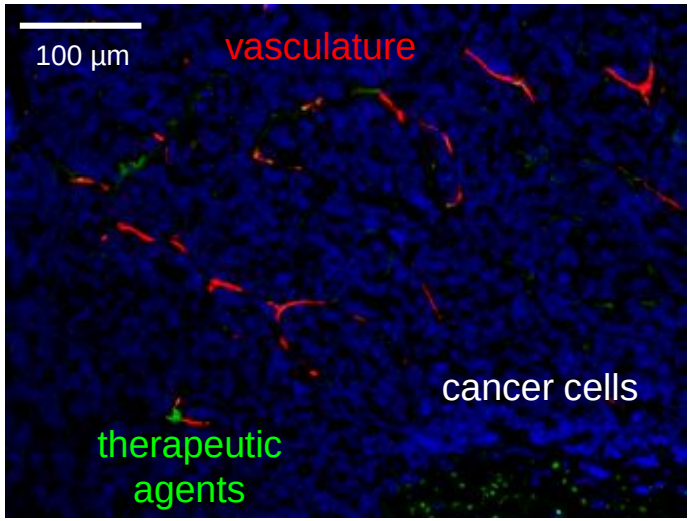
François Voltaire (1694 – 1778)

Tumour Physiology as a Barrier to Drug Delivery

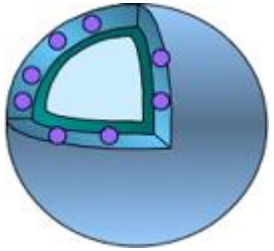
- Size selectivity of the tumour endothelium (**100-600 nm**)
- Elevated intratumoral pressure (~ 20 mm Hg)
- Highly irregular tumour vasculature
- Increased distance between nearest blood vessel and farthest cell (~ 200 µm in tumours vs 90 µm in tissue)

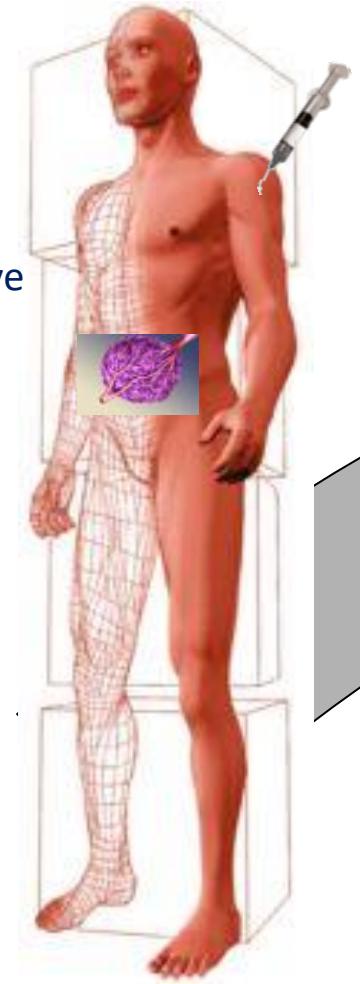
Irregular Vasculature



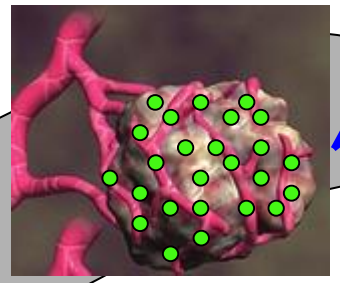


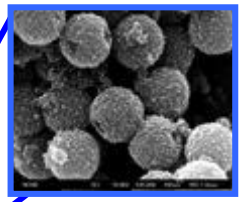
Manufacturing of Stimulus Responsive Nano & Micro Particles



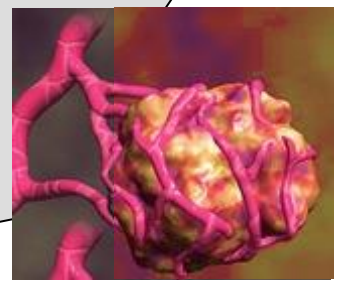


Active or Passive Accumulation

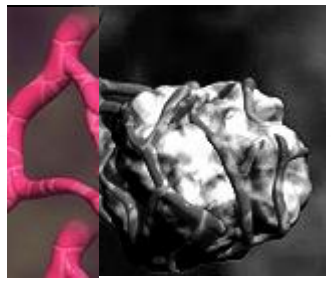




Triggered Release (with Monitoring)

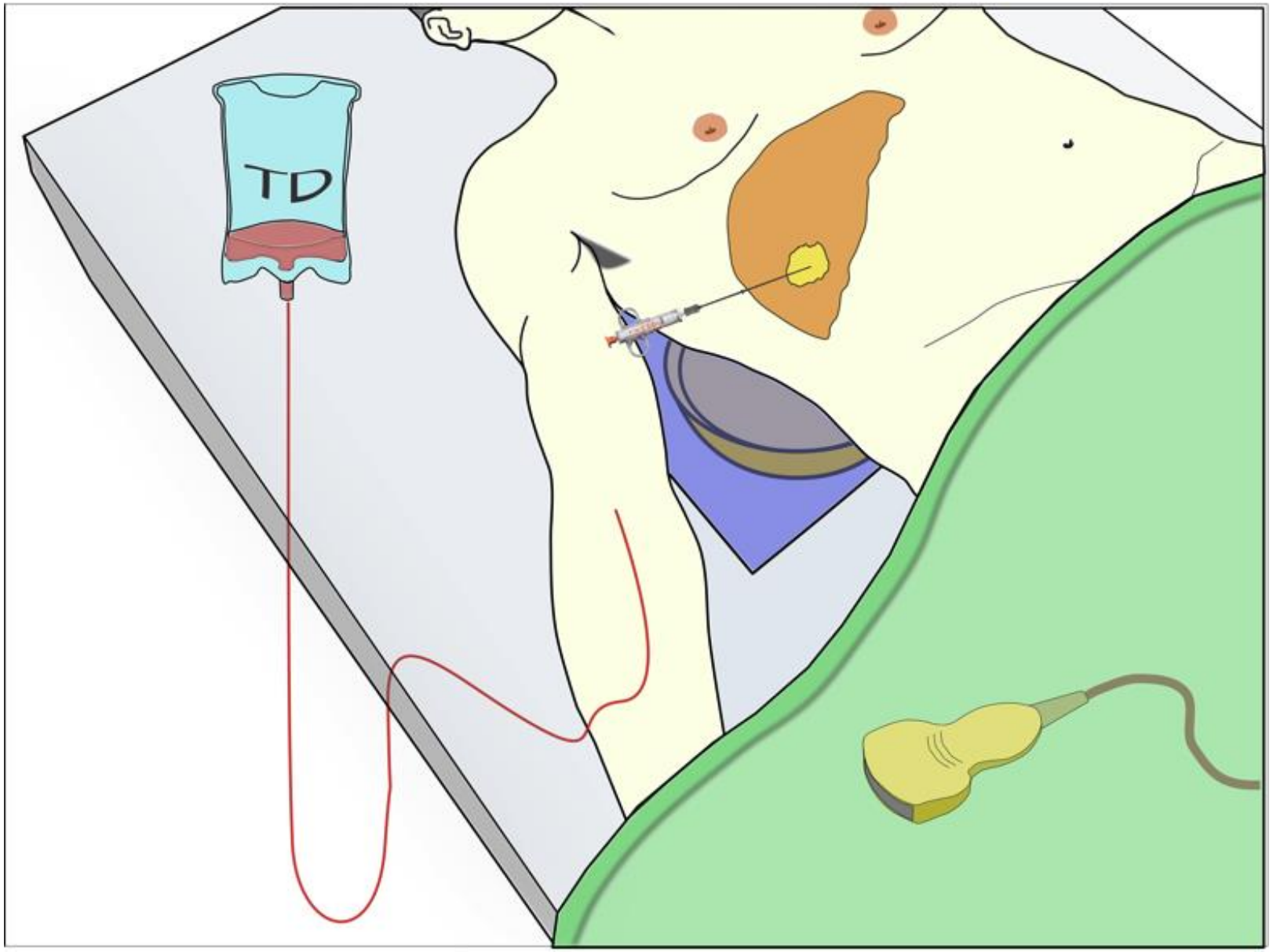


Enhanced Extravasation (with Monitoring)



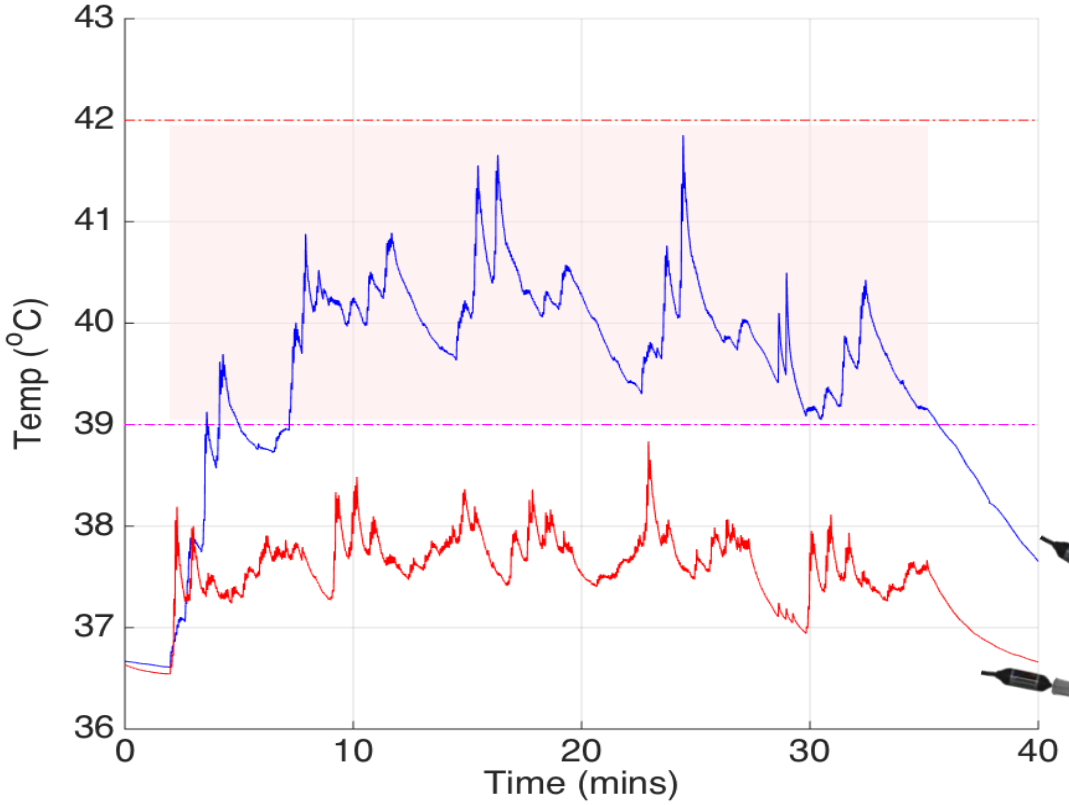
Therapy

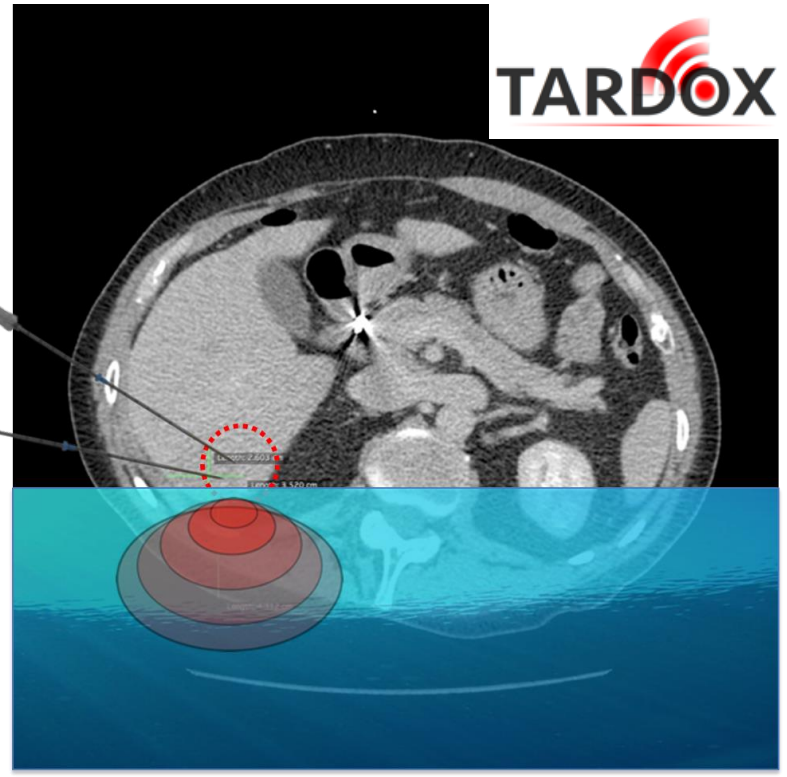
TarDox Clinical Trial



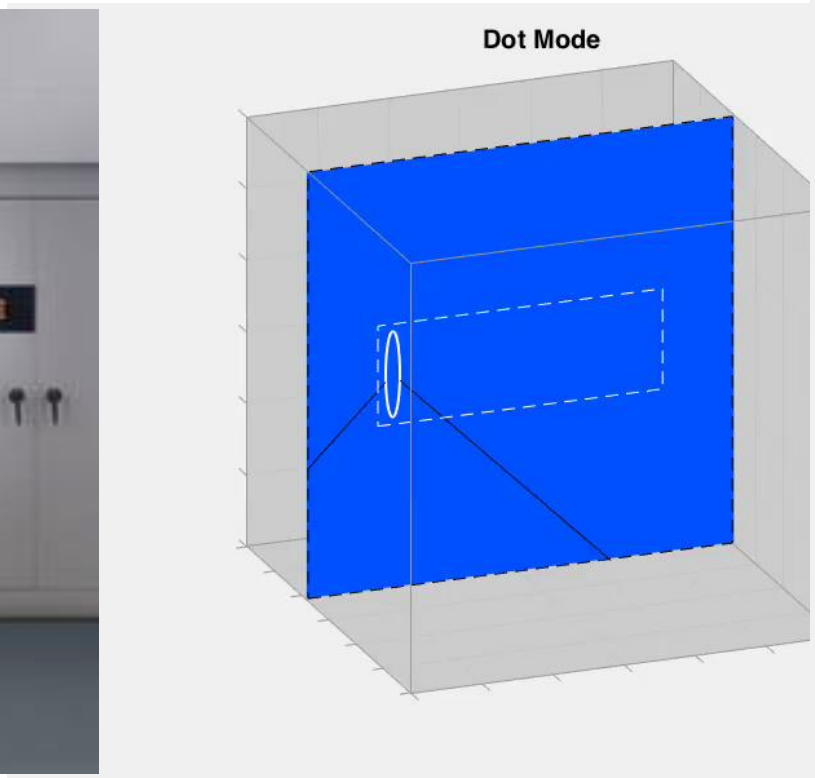
P.C. Lyon, C-C. Coussios, et al. “Clinical Trial Protocol for TarDox: A Phase I Study to Investigate the Feasibility of Targeted Release of Lyso-thermosensitive Liposomal Doxorubicin (ThermoDox®) Using Focused Ultrasound in Patients with Liver Tumours”, J. Therapeutic Ultrasound – in press (2017).

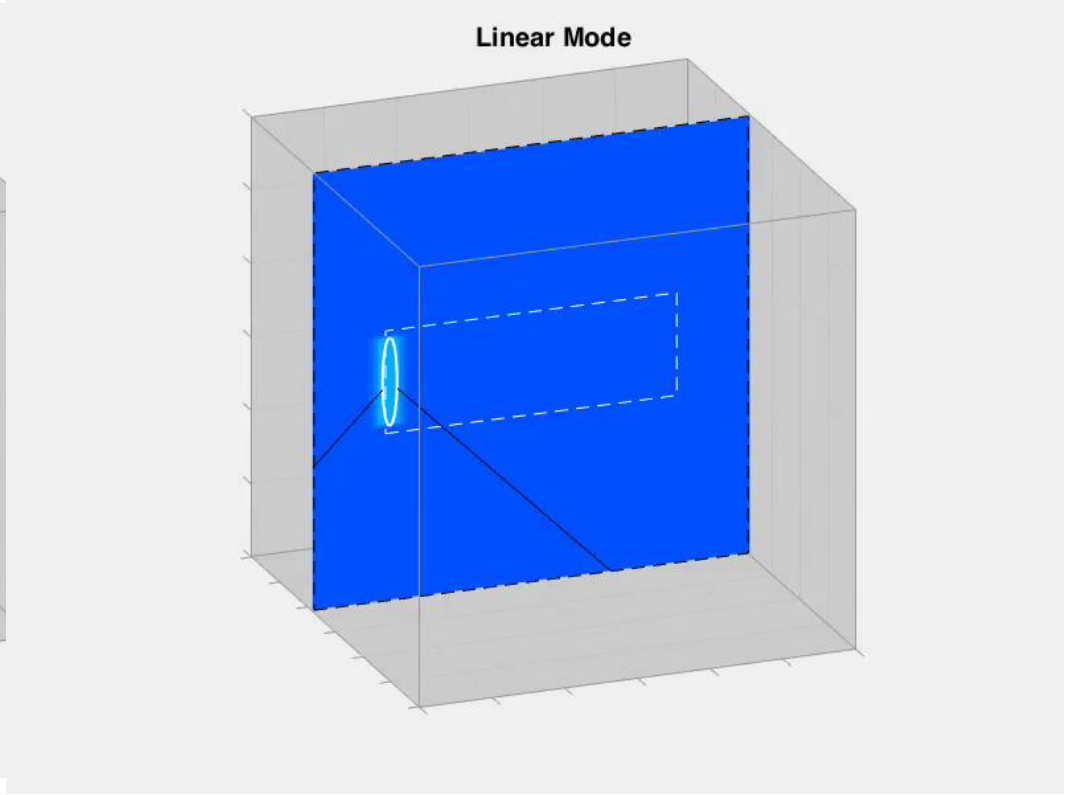
Extracorporeal FUS for Targeted Volumetric Hyperthermia

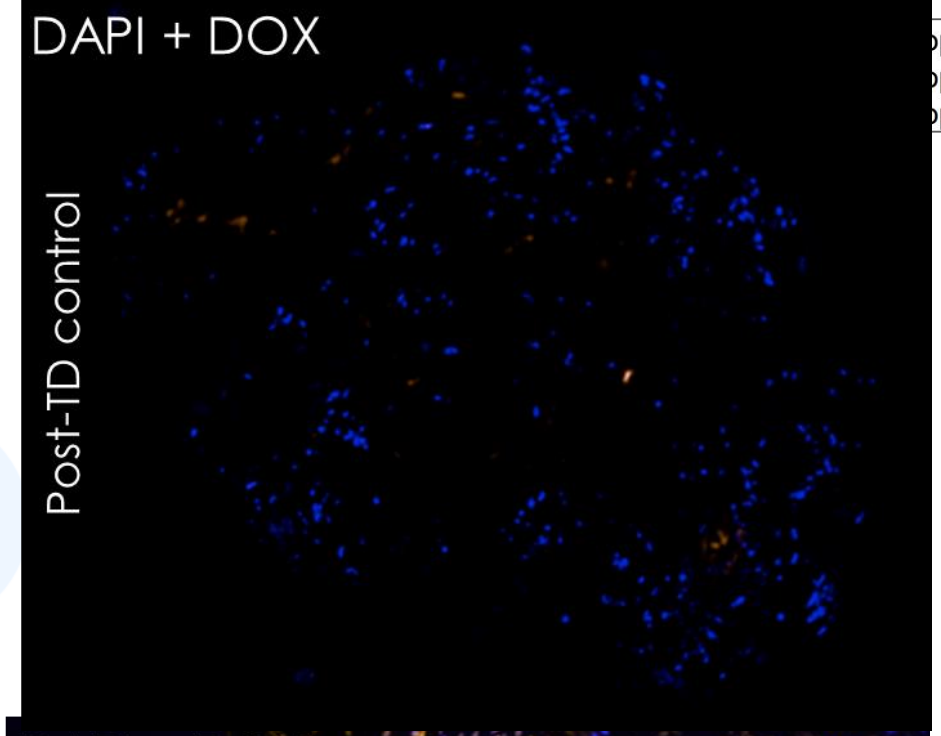


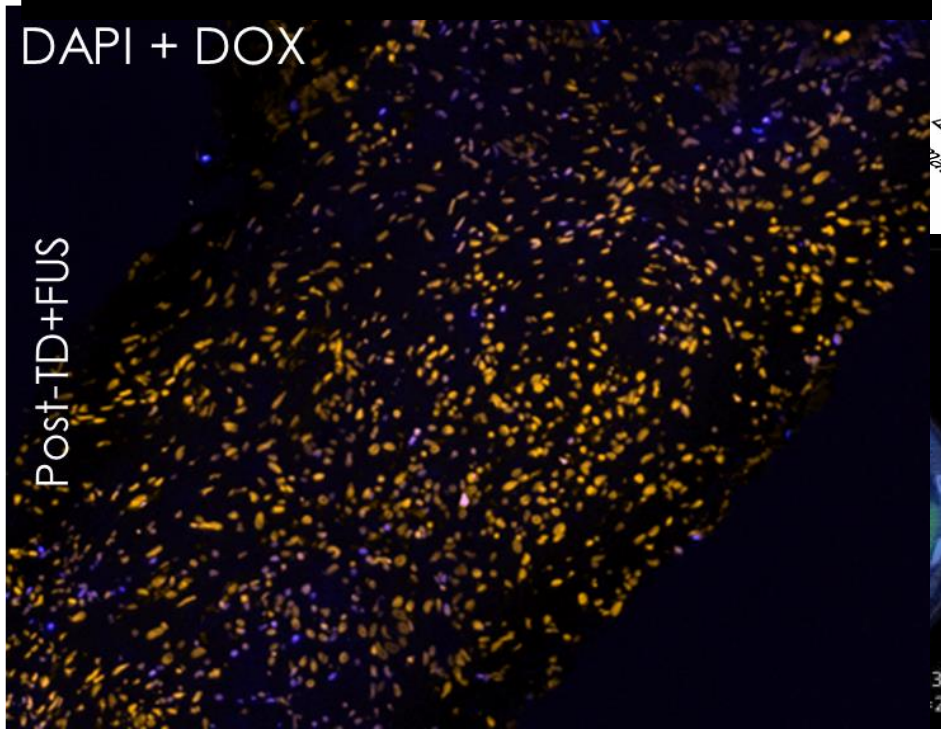


Extracorporeal FUS for Targeted Volumetric Hyperthermia






DAPI + DOX
Post-TD control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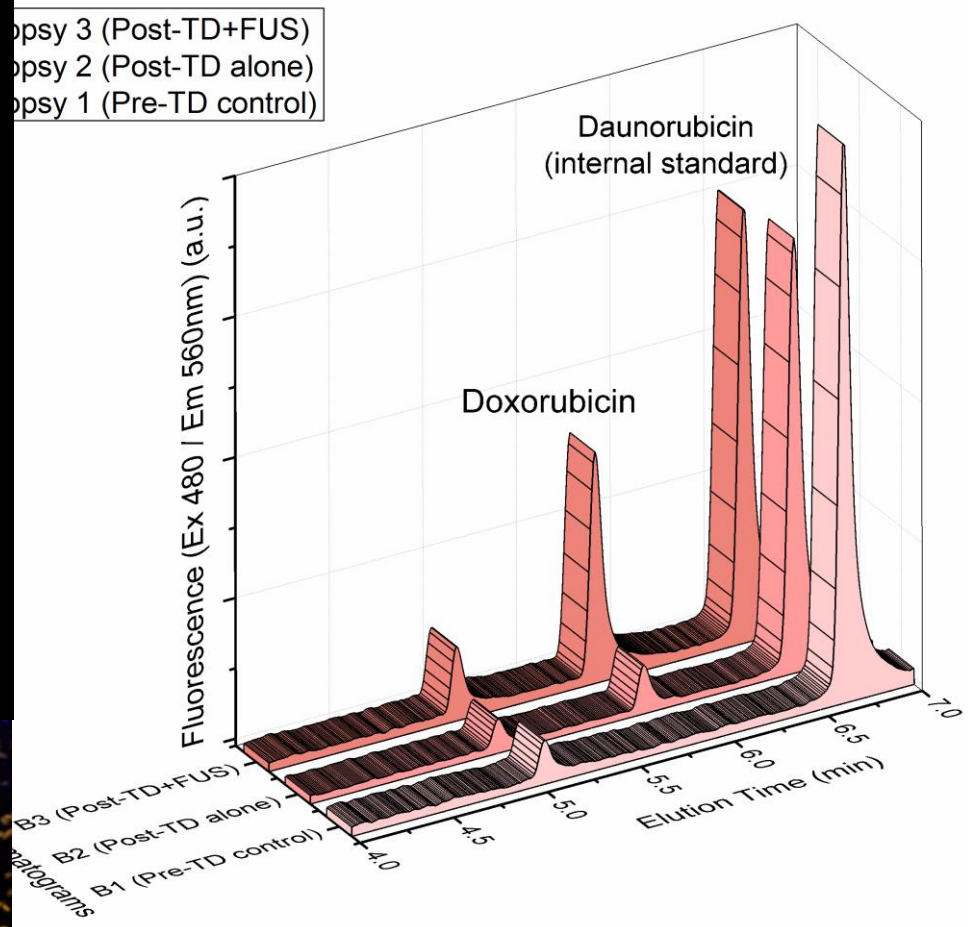
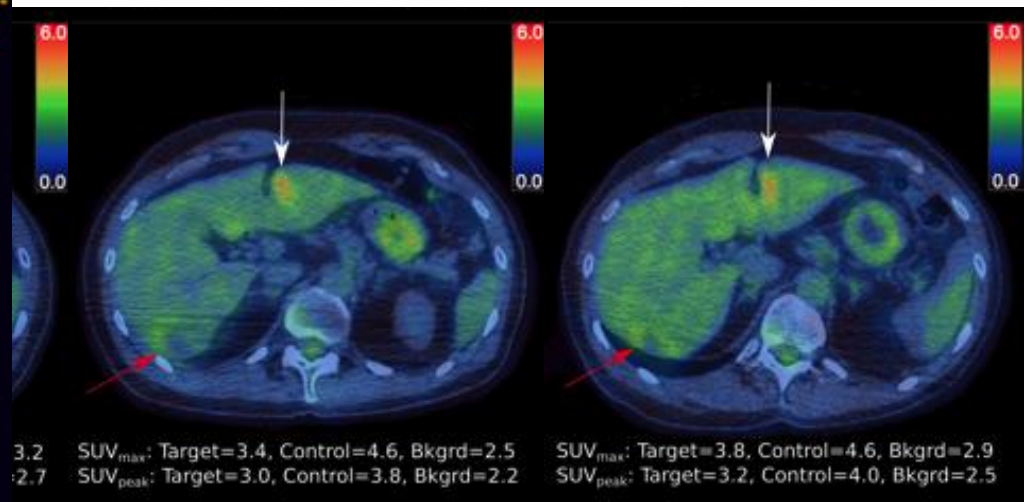

psy 3 (Post-TD+FUS)
psy 2 (Post-TD alone)
psy 1 (Pre-TD control)
Daunorubicin
(internal standard)
Doxorubicin
Fluorescence (Ex 480 I Em 560nm) (a.u.)
B3 (Post-TD+FUS)
B2 (Post-TD alone)
B1 (Pre-TD control)
atograms
4.0
4.5
5.0
5.5
6.0
6.5
7.0
Elution Time (min)


6.0
0.0
SUVmax: Target=3.4, Control=4.6, Bkgrd=2.5
SUVpeak: Target=3.0, Control=3.8, Bkgrd=2.2
SUVmax: Target=3.8, Control=4.6, Bkgrd=2.9
SUVpeak: Target=3.2, Control=4.0, Bkgrd=2.5

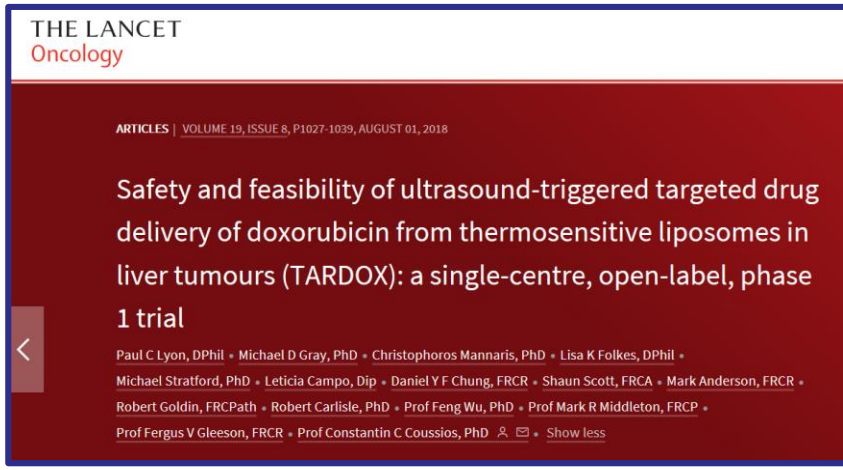
Thermally Triggered Release & Drug Delivery by Ultrasound

In first 10 patients (4 without thermistor), using a clinical USgFUS system

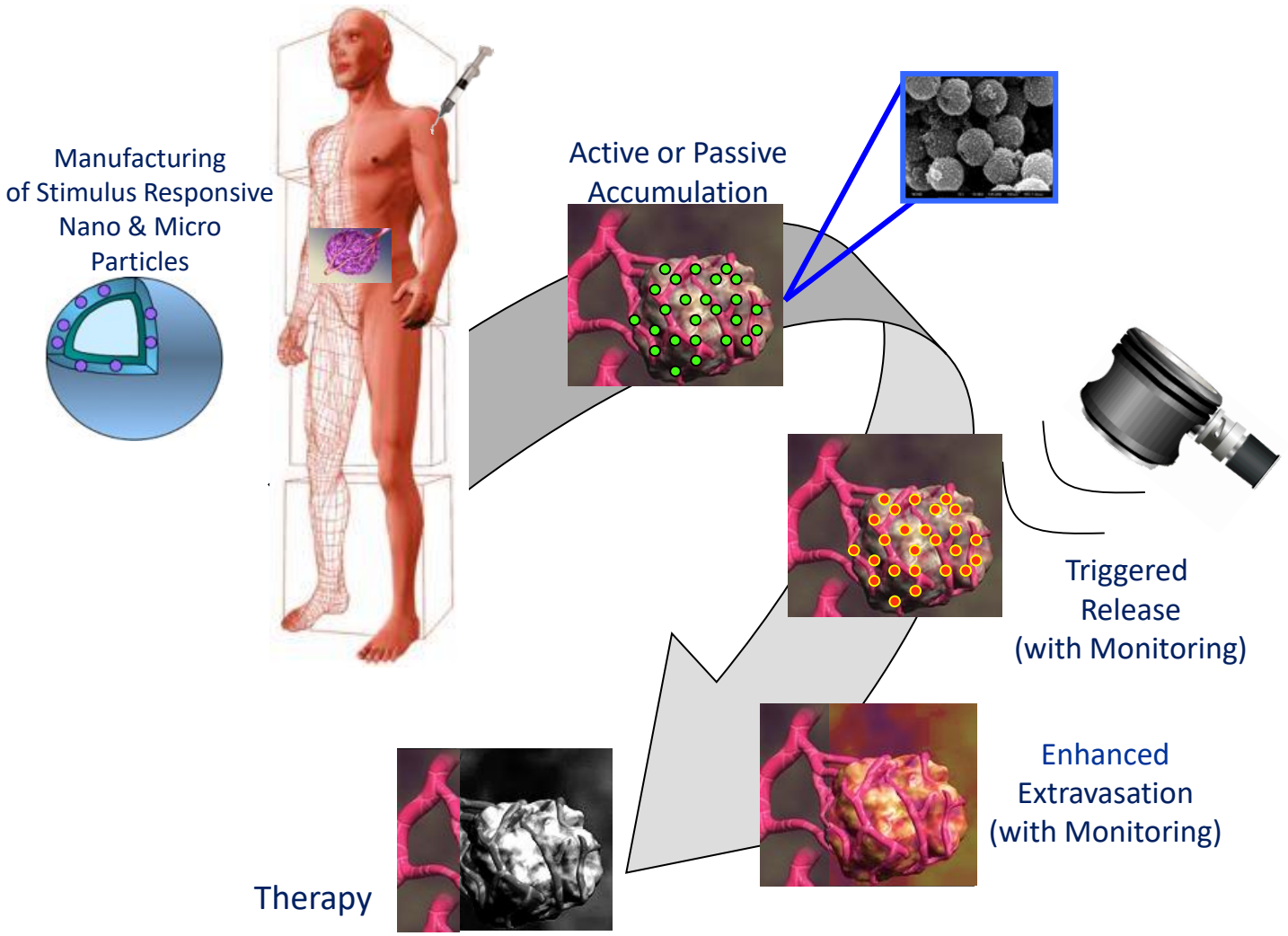
- Mild hyperthermia > 39.5 C successfully sustained for 23-79 minutes over volumes of 14-73cc in 5/6 patients with CEM43<15 minutes.
- Mean intratumoural dox concentration increase of 3.7x achieved following FUS exposure, with 7/10 patients demonstrating at least a 2x increase.
- Notable therapeutic response (PET/CT) observed in 6/10 patients even after a single cycle of chemo.

'Big picture' challenges:

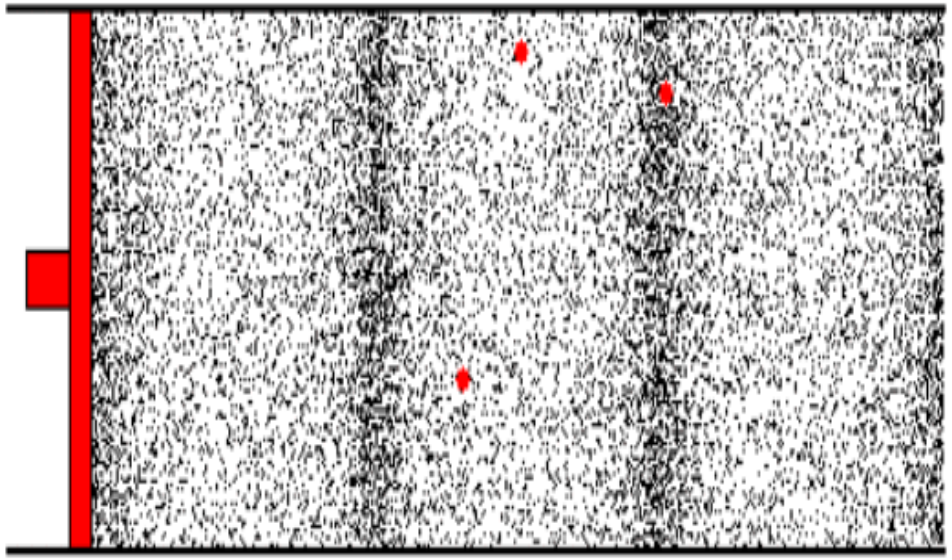
- Liposomal delivery requires drug re-formulation
- Thermal delivery may not be suitable for certain types of biologics
- Using current systems, FUS-hyperthermia is difficult to scale up to thousands of patients in each hospital.

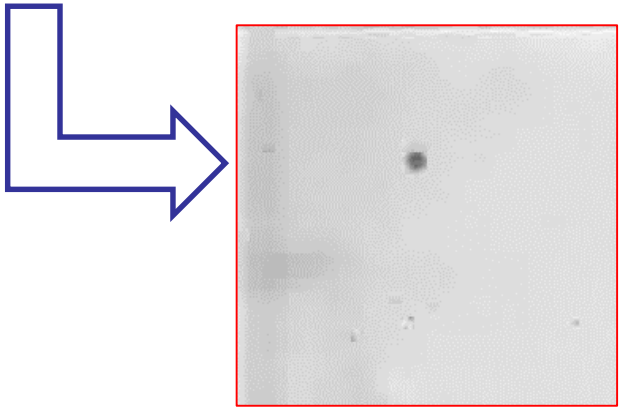


Avoiding Drug Reformulation

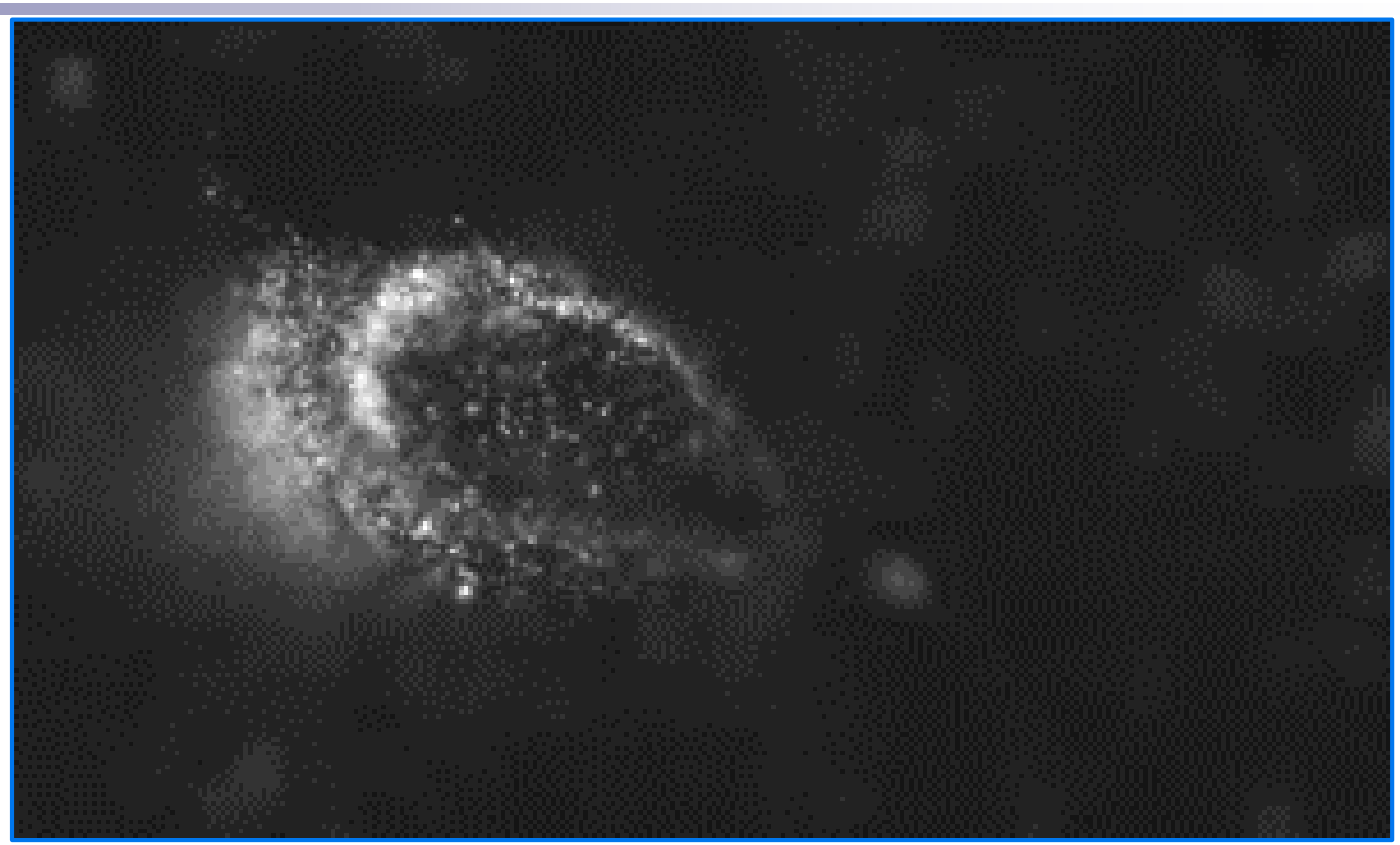


The Ultrasonic Pump: Cavitation-Mediated Drug Transport





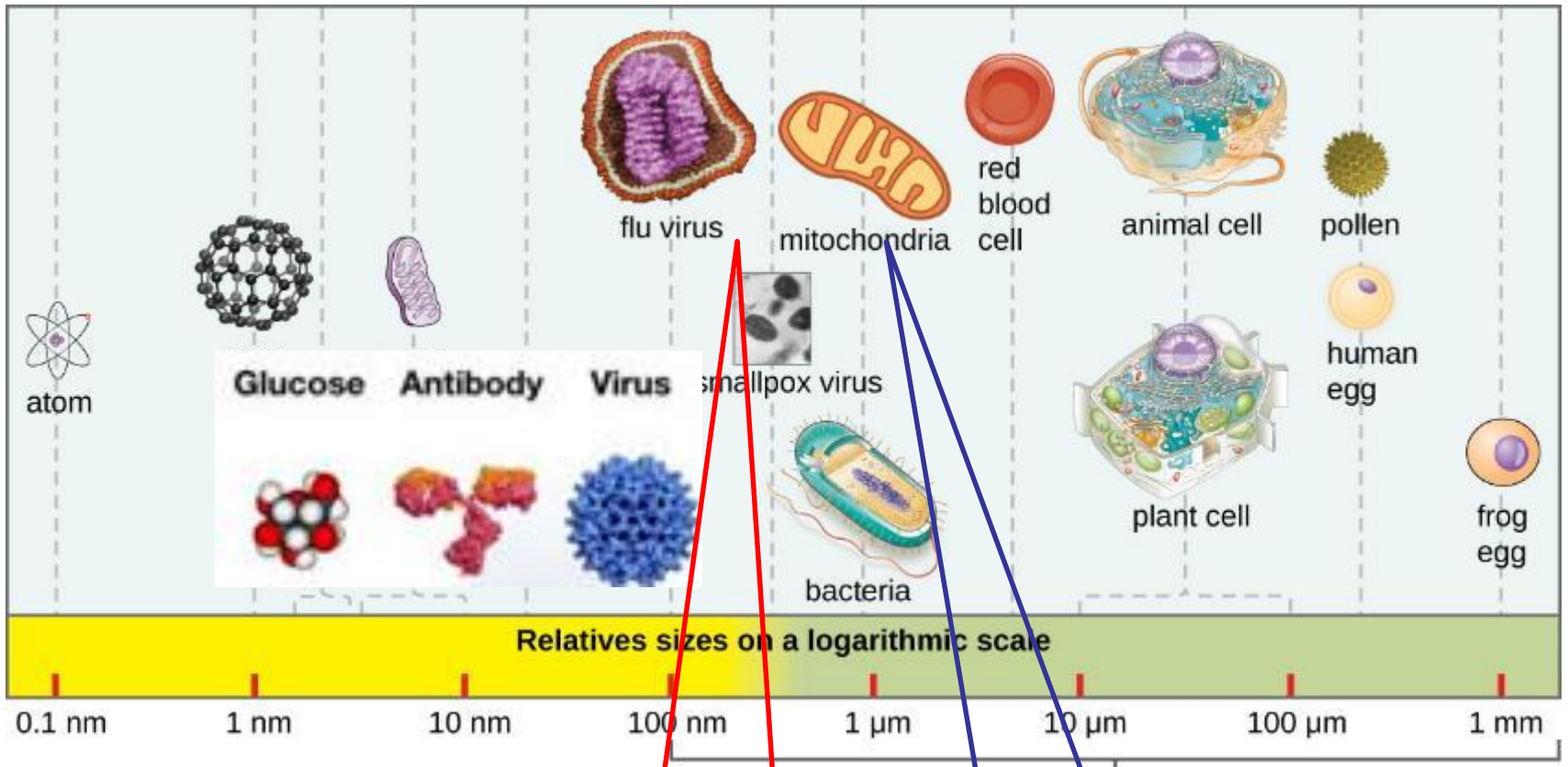
Timescales of Microseconds



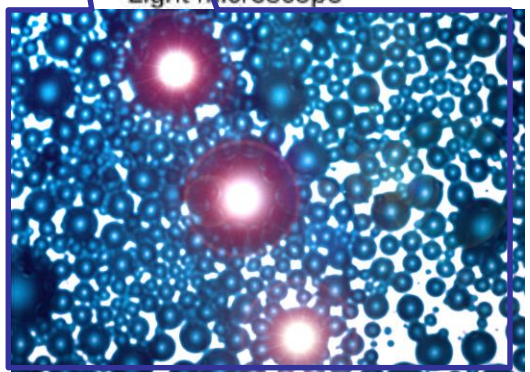
Timescales of Seconds (Real Time) and Length scales of mm

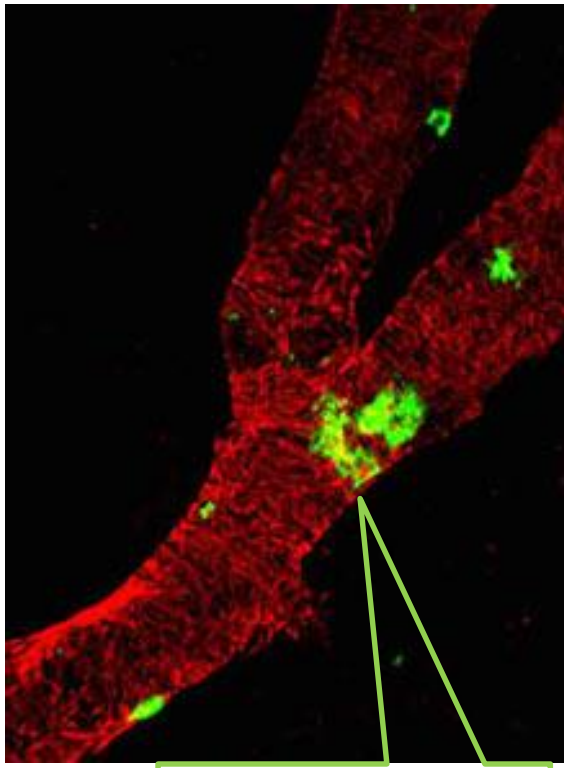
Coussios C. and Roy R., “Applications of Acoustics and Cavitation to Non-Invasive Therapy and Drug Delivery” *Annual Review of Fluid Mechanics* 40: 395-420 (2008).

Clinical Challenges : Matching Biological Length Scales



Need for acoustic cavitation nucleation agents in the size range 100-500 nm

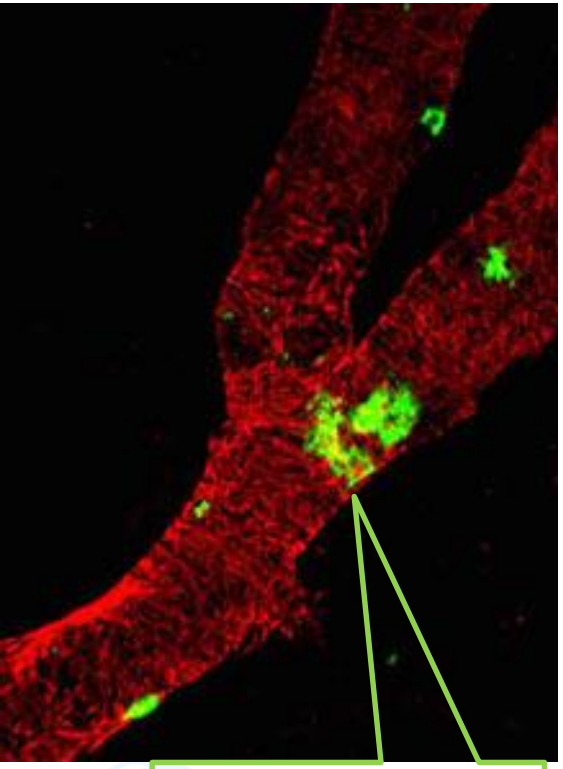




Coussens *et al.*, 2017

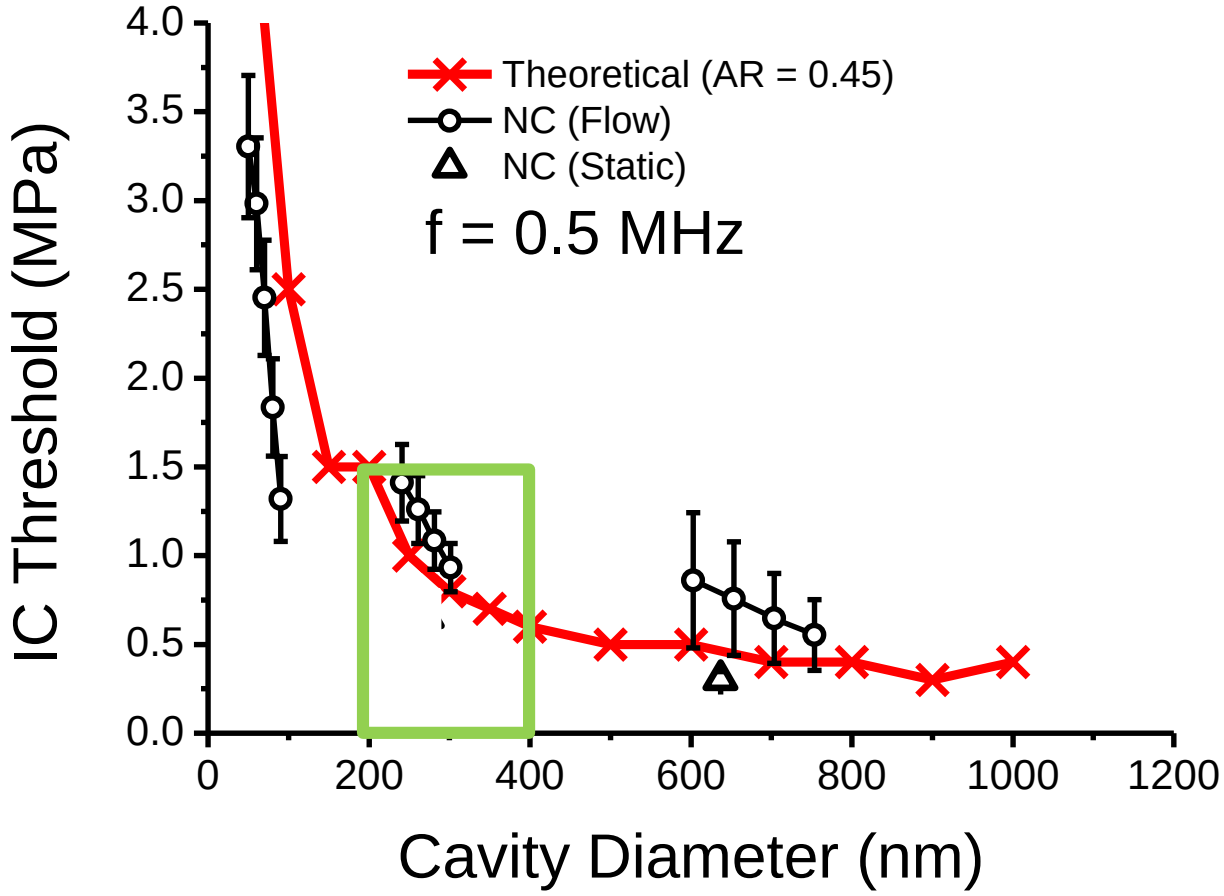
Leaky vasculature
100-1000 nm

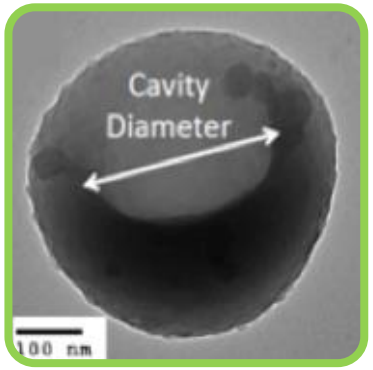
Matching the Engineering to the Biological Length Scales

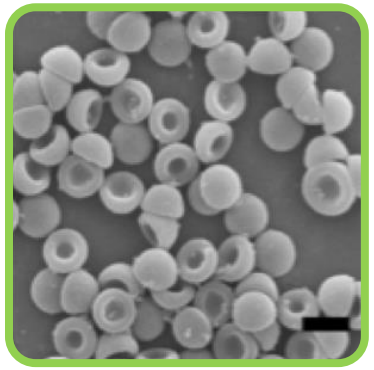


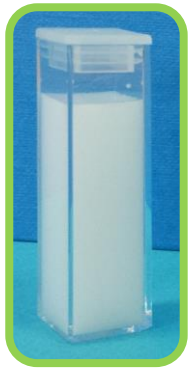
Leaky vasculature
100-600 nm

Coussens *et al., 2017*







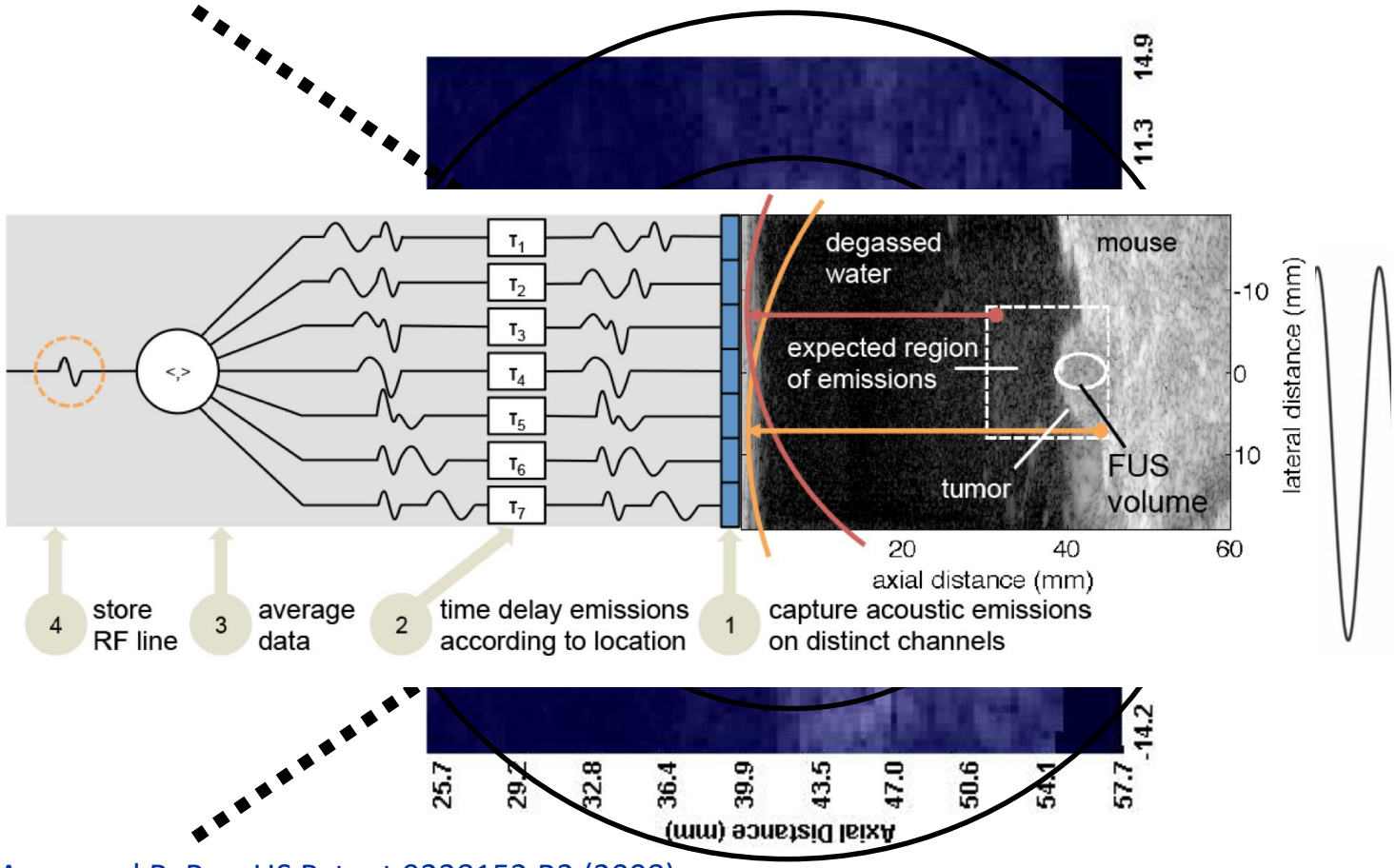


[1] J.J. Kwan …, E Stride and C. C. Coussios, "Ultrasound-Propelled Nanocups for Drug Delivery," Small 11(39):5305-5314 (2015).
[2] J.J. Kwan, ..., E. Stride, and C. Coussios, "Ultrasound-induced inertial cavitation from gas-stabilizing nanoparticles," Physical Review E 92(2) (2015)
[3] J. Kwan, R Myers, A. Shah and C Coussios, "Cavitation-Inducing Polymeric Nanoparticles", EP3071183 A1 (2014).

Treatment Monitoring: Passive Acoustic Mapping of Cavitation

0.5-1.5 MHz focussed ultrasound source array

5-15 MHz ultrasound array receiver

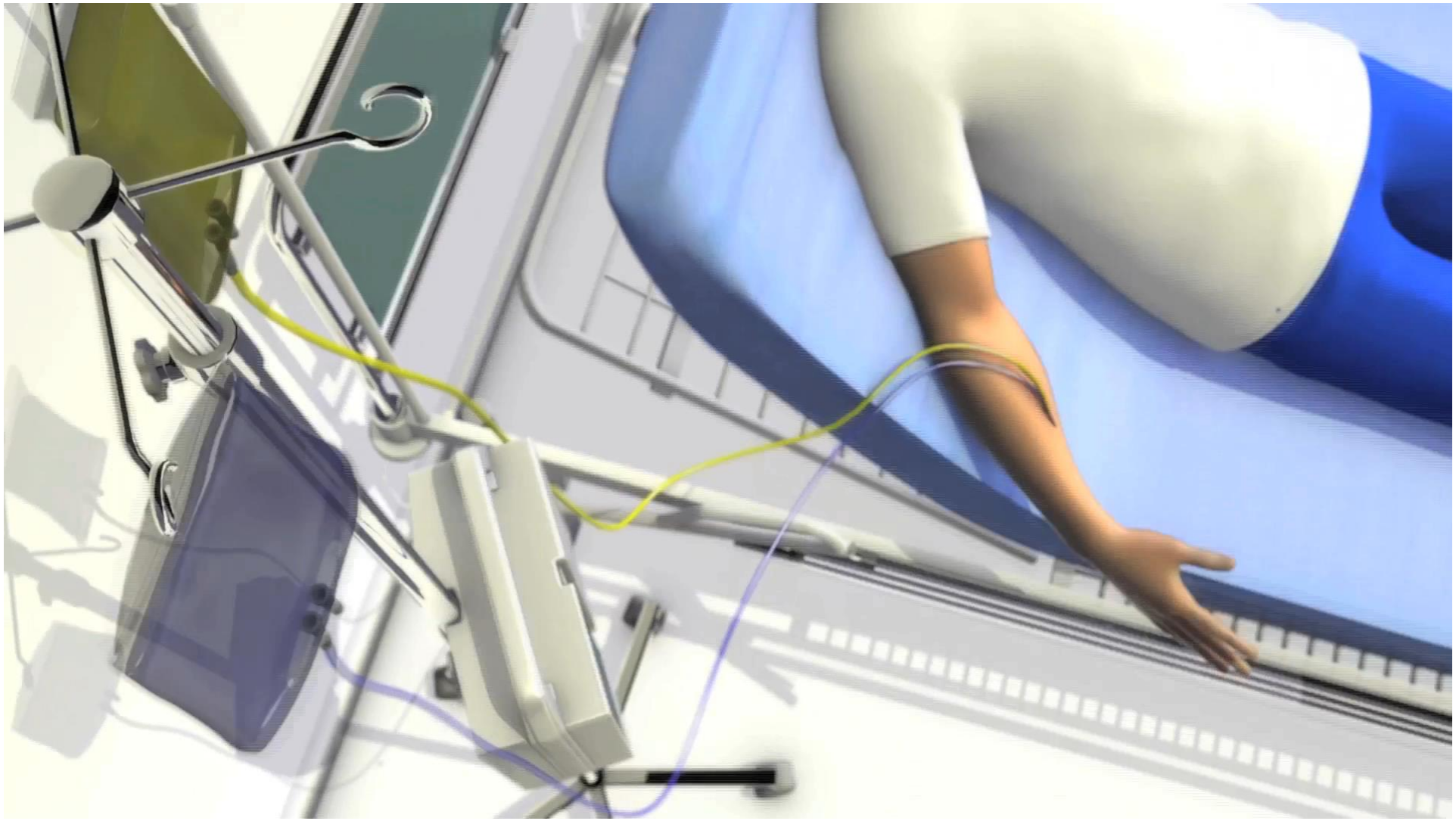


[1] C. Coussios, M .Gyöngy, M. Arora and R. Roy, US Patent 9238152 B2 (2008).

[2] M. Gyöngy and C. Coussios, "Passive spatial mapping of inertial cavitation during HIFU exposure", IEEE Trans on Biom.Eng, 57(1): 48 - 56 (2010).

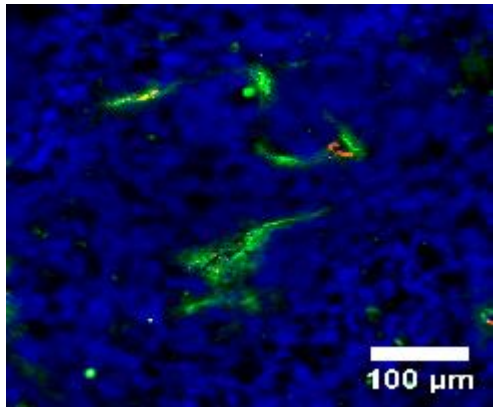
[3] C. Coviello, R. Kozick and C.-C. Coussios, “Passive acoustic mapping utilizing optimal beamforming in ultrasound therapy monitoring,” J. Acoustc. Soc. Am. 137(5): 2573-2585 (2015).

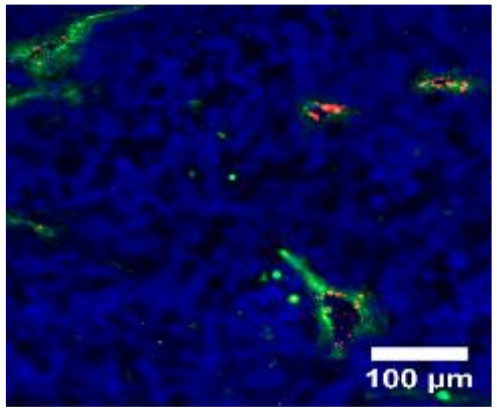
Towards Clinical Translation (CEeDD Clinical Trial)

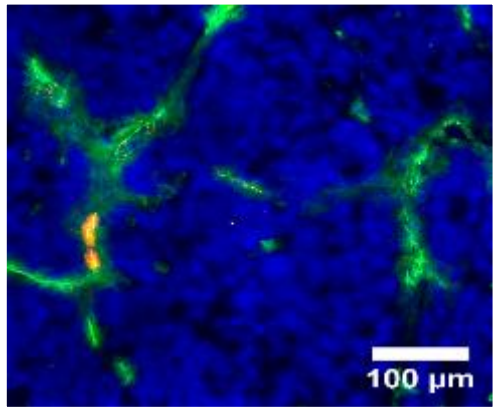


Conquering the Whole Tumour with US-Mediated Transport

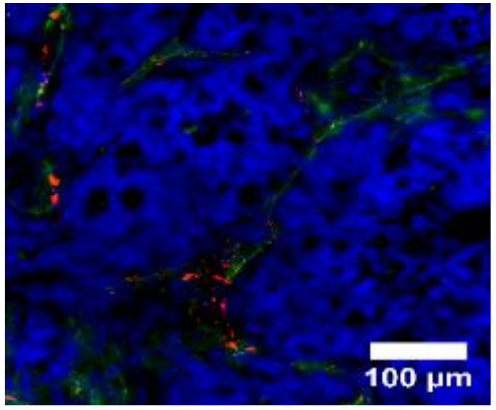
Without ultrasound

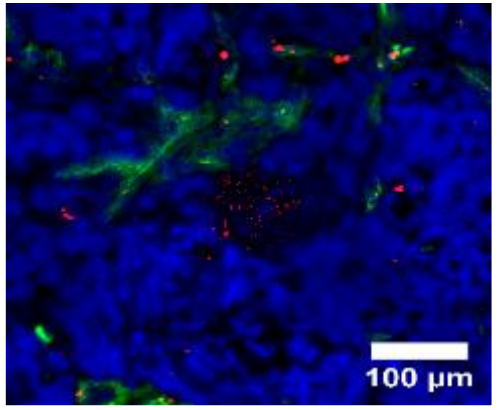


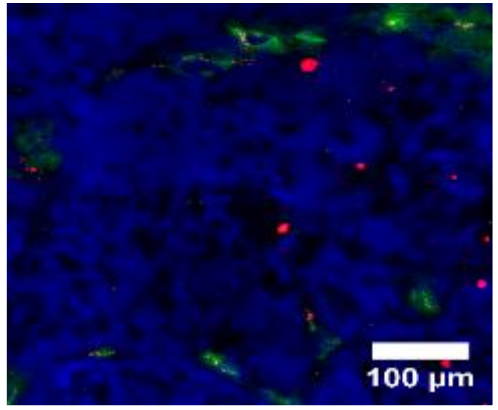




With ultrasound

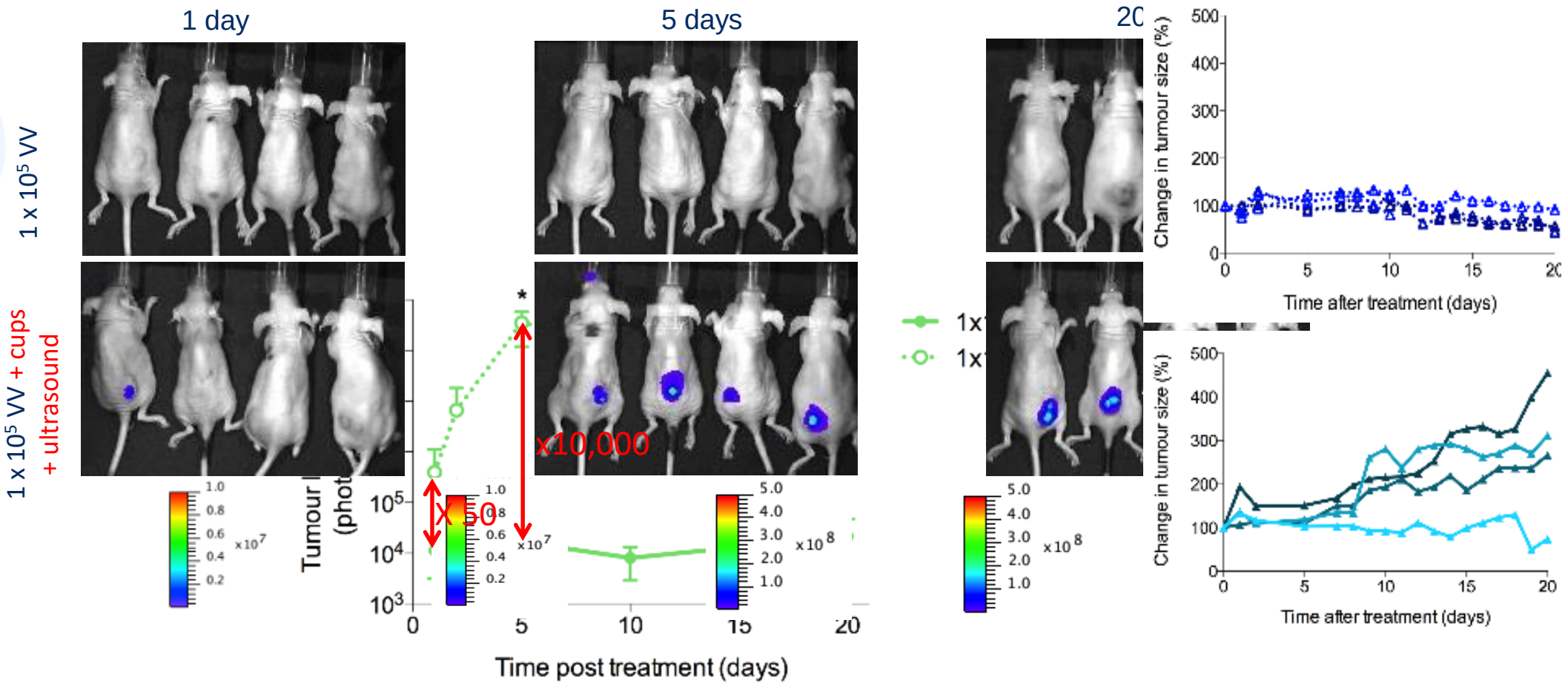






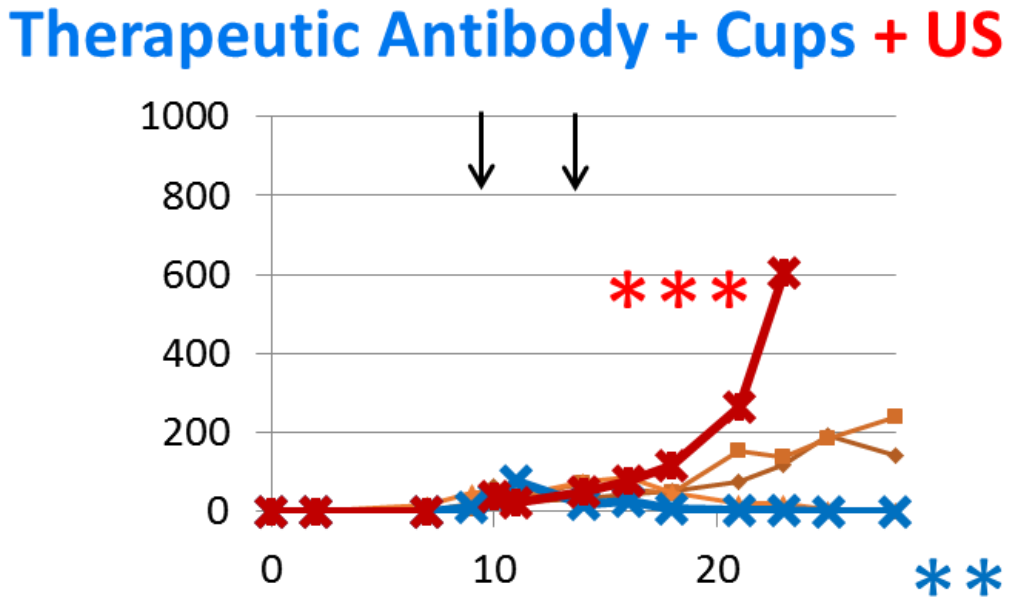
Blood vessels **Polymeric cups** **Cancer Cell**

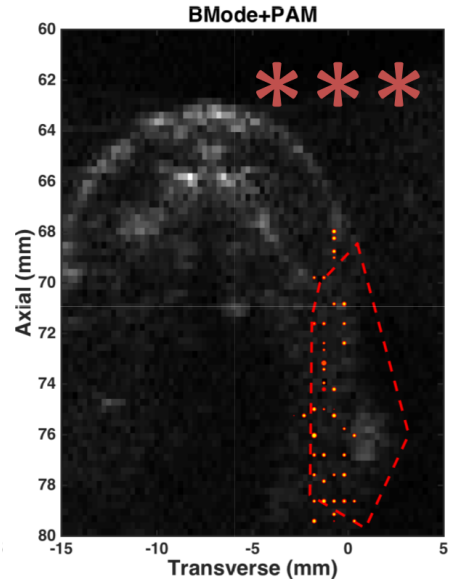
Improving Delivery of Novel Oncology Drugs into Tumours

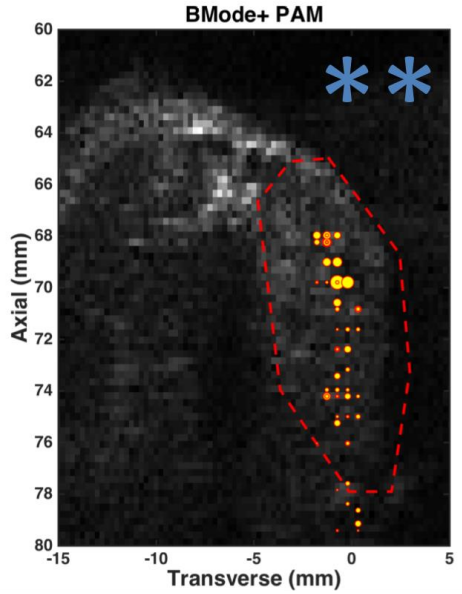


Myers, R., Kwan,J., Coviello, C., Carlisle, R. & Coussios, C. C. et al., (2016*)* Polymeric cups for cavitation mediated delivery of oncolytic vaccinia virus. Molecular Therapy

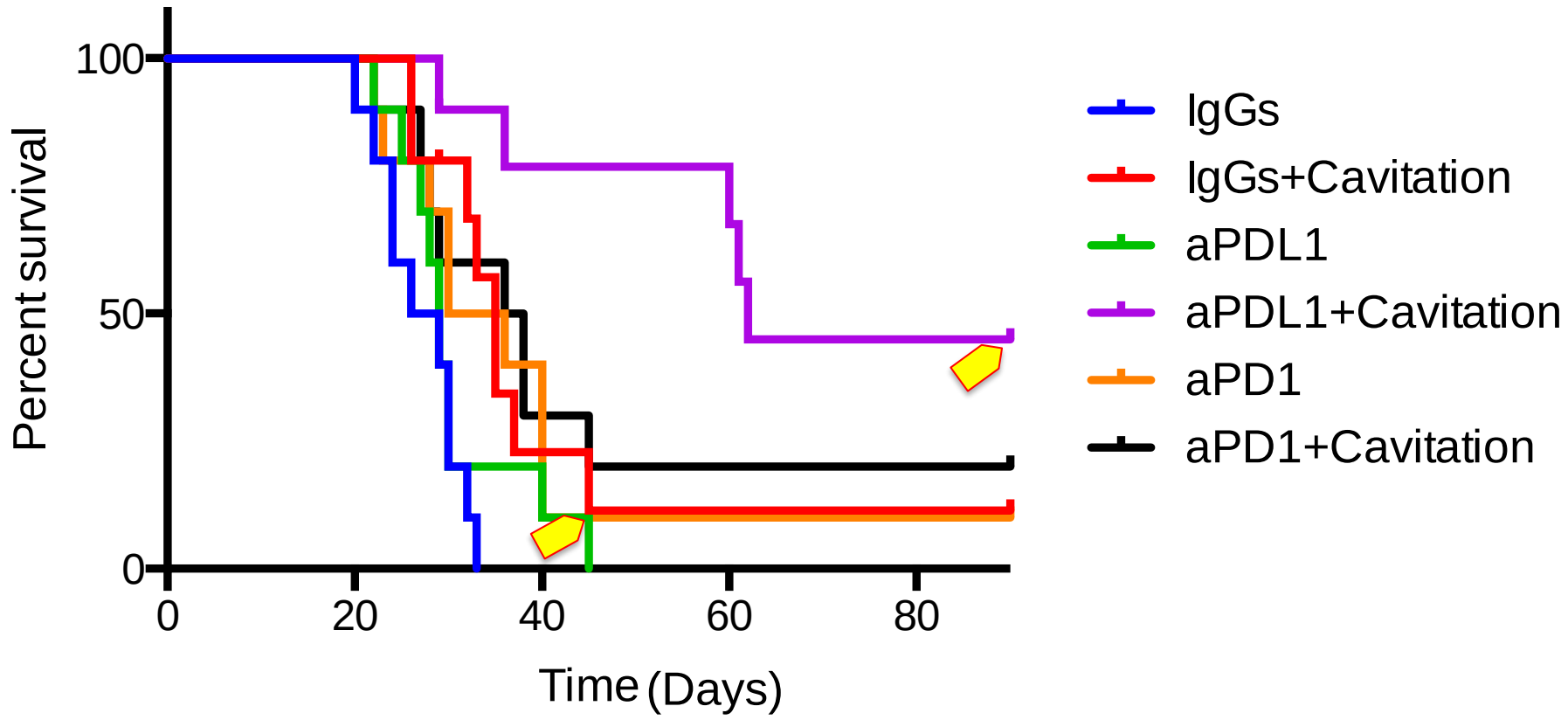
The Value of Real-Time Mapping of Drug Delivery





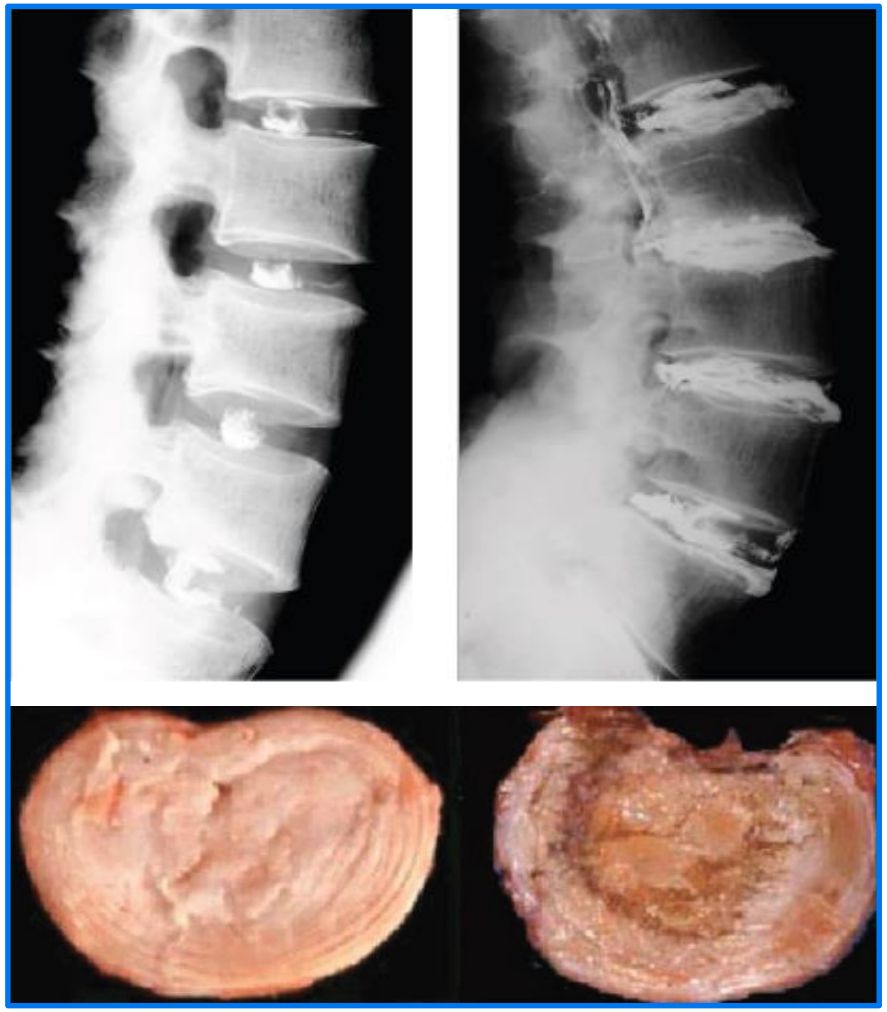


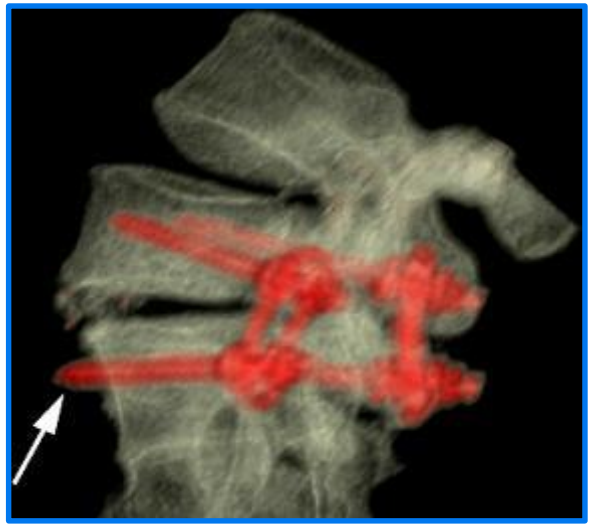
Enhanced Anti-PD-L1 Therapy in CT-26/Balbc (IV)

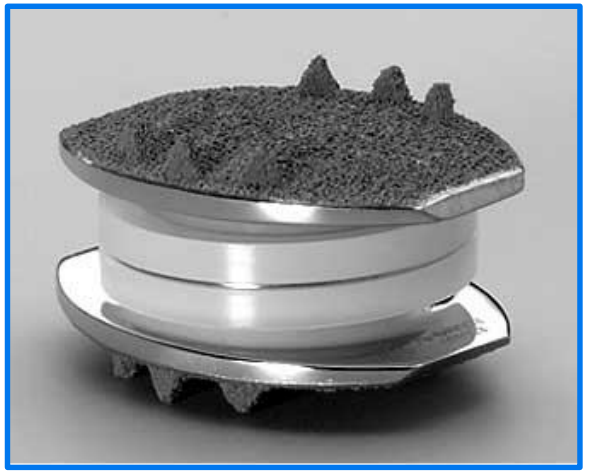


Part III:
Spinal Therapies

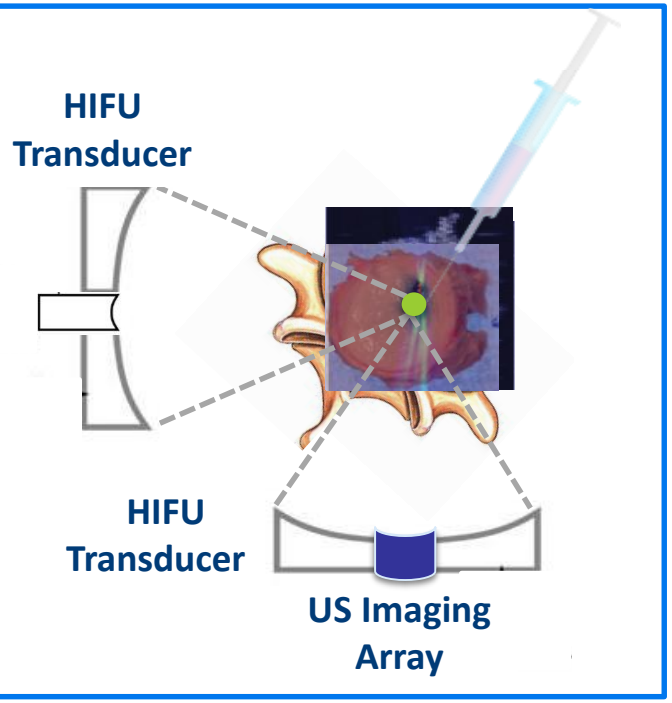
Surgery for Discogenic Back Pain

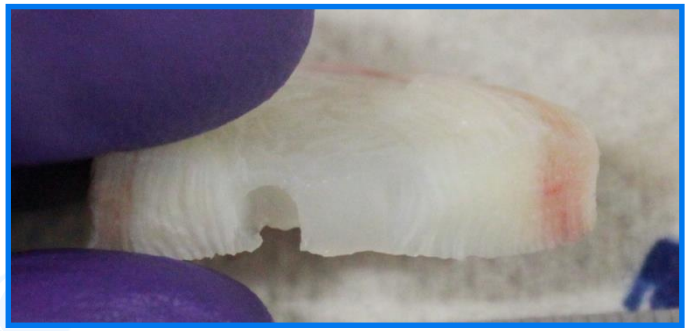


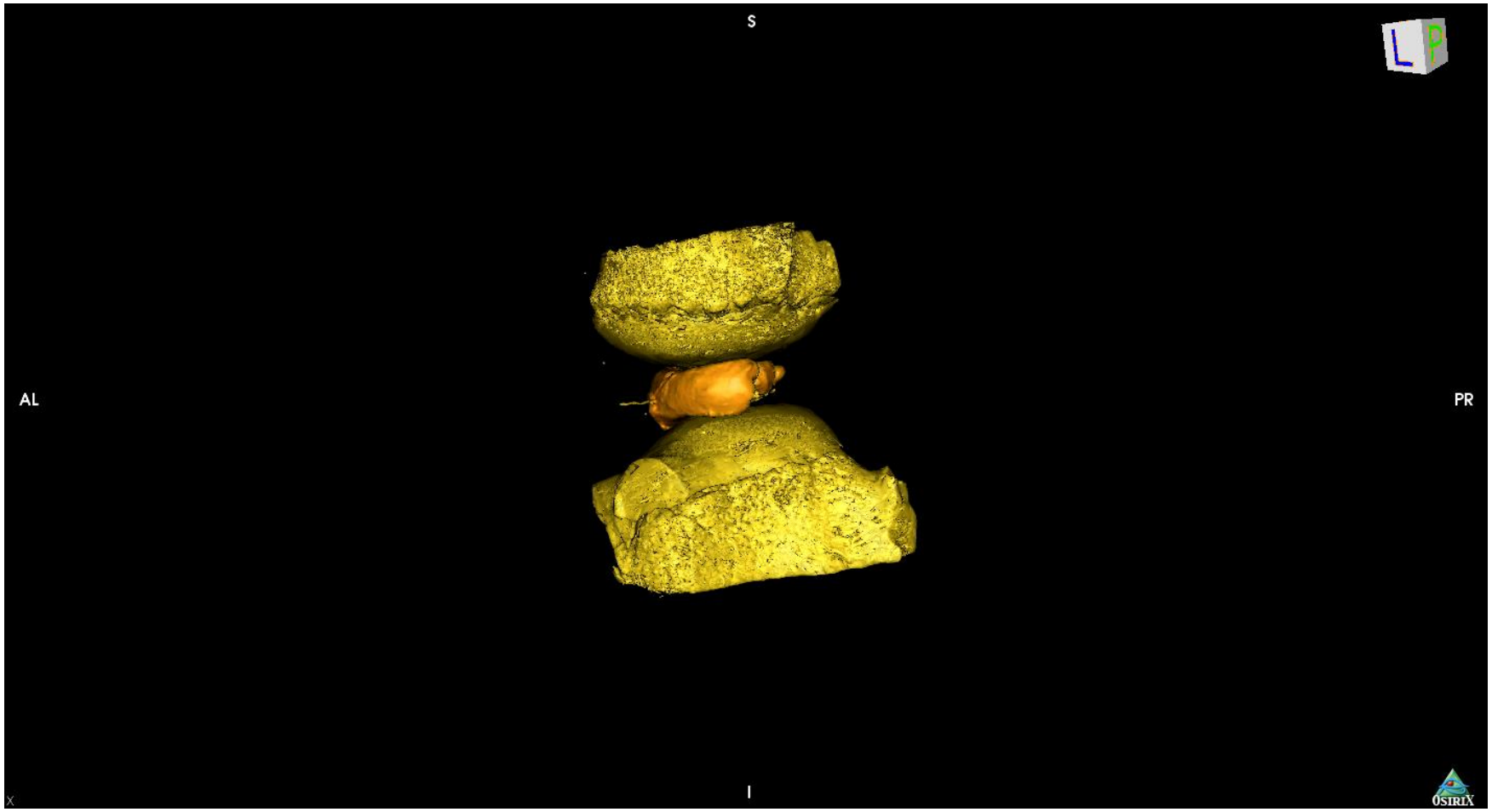




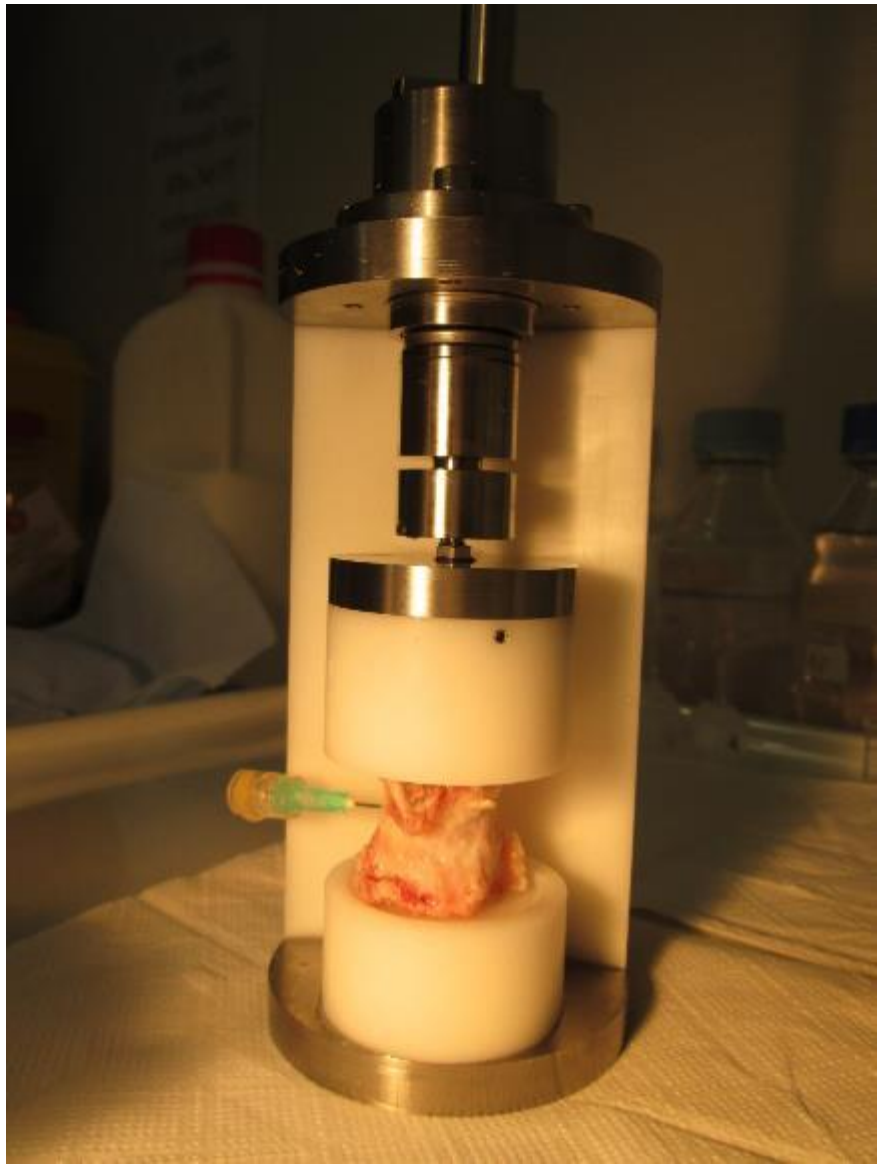
UltraSpine: Minimally Invasive Disc Replacement

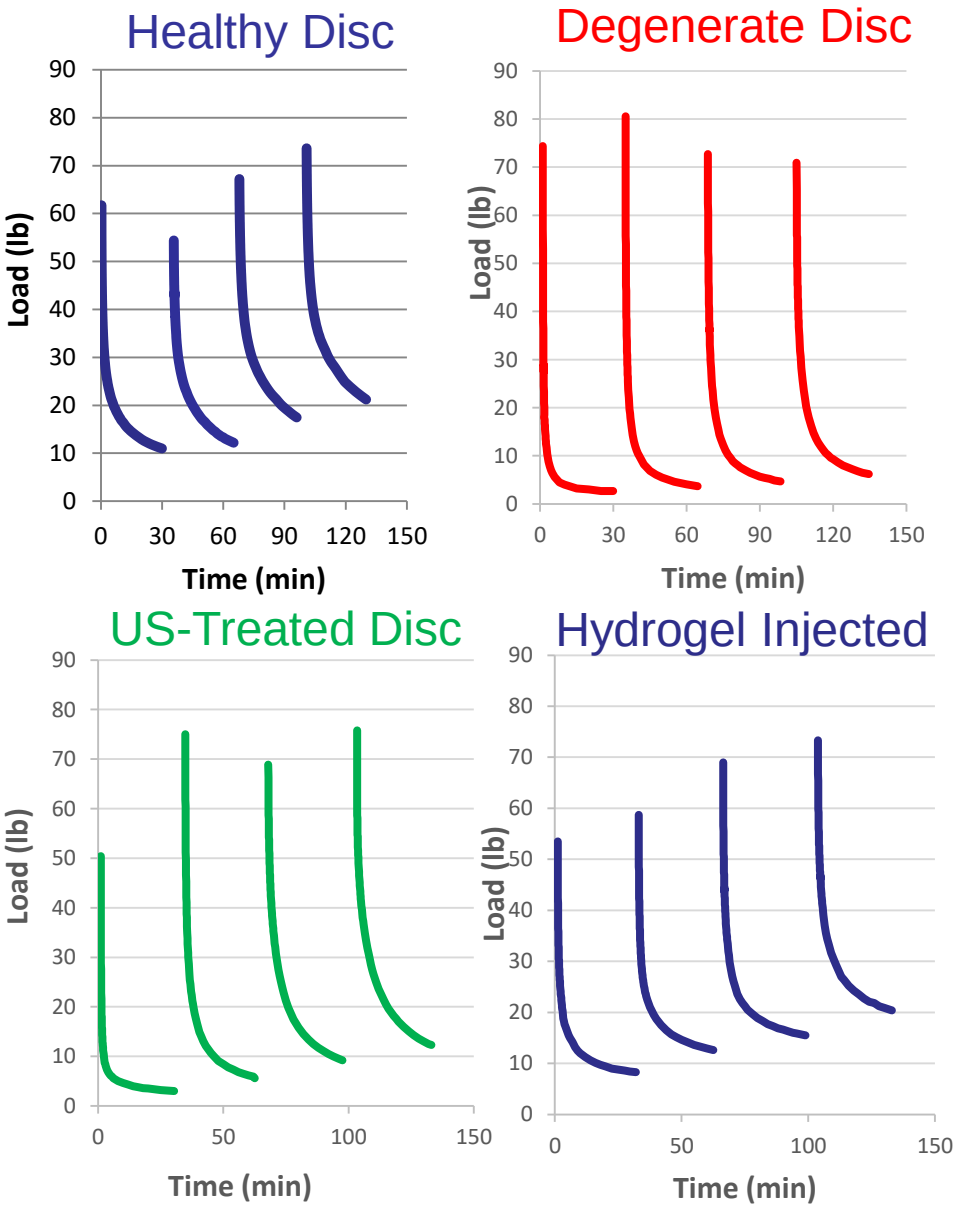


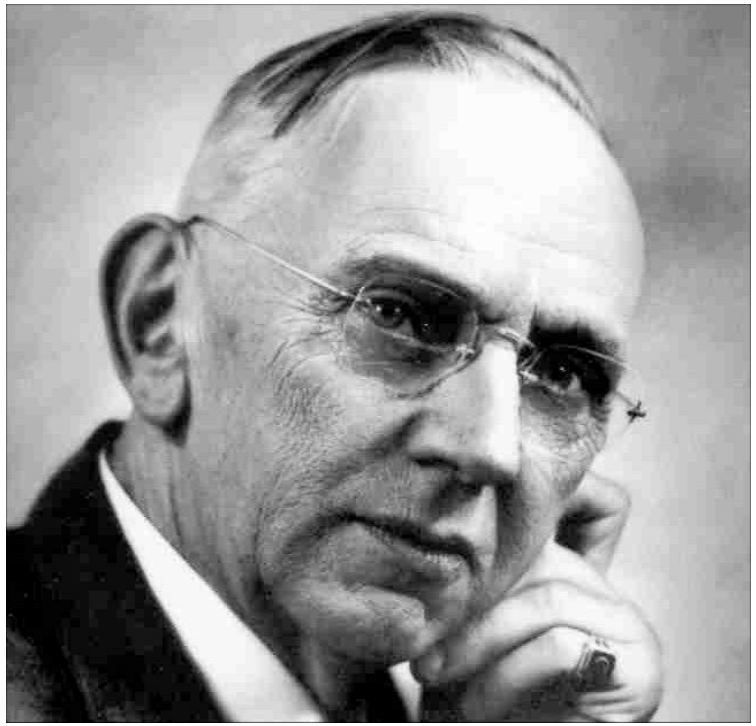




Restoring Function of Repaired Degenerate Discs







"Sound

will be the future

of medicine…"

… and it is (nano) bubbly!

Edgar Cayce (1877 – 1945)
Father of Hollistic Medicine