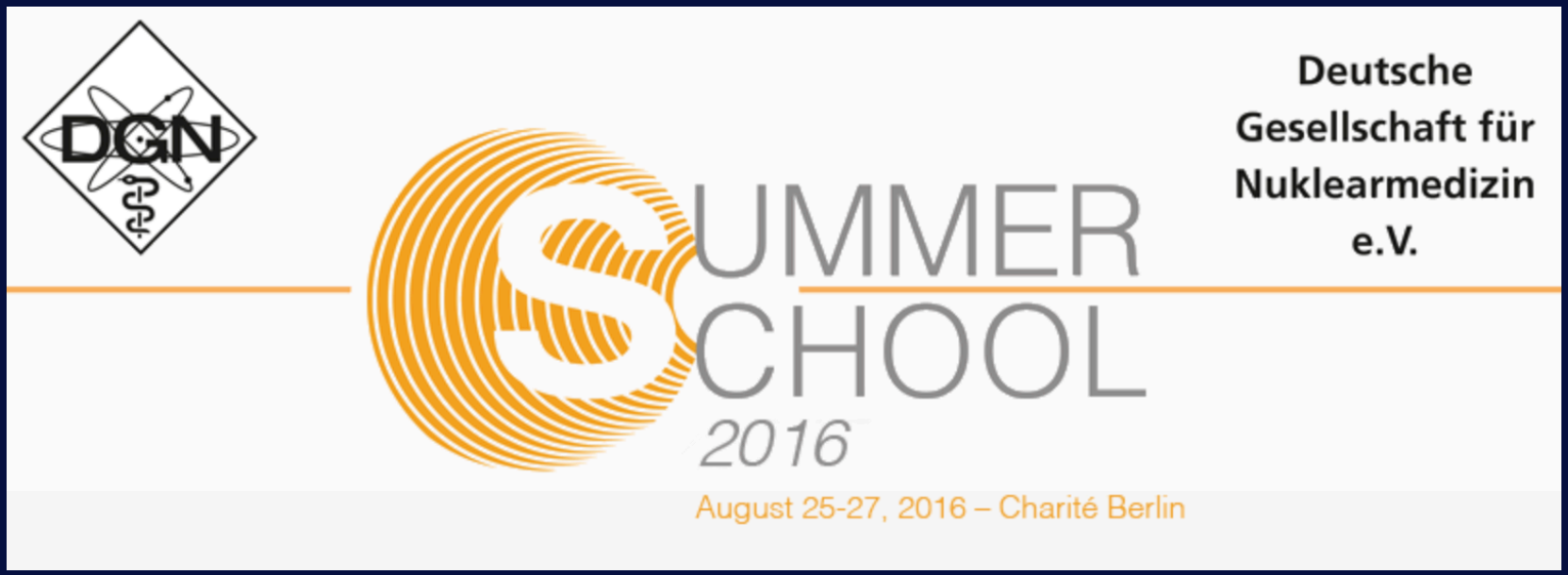
Ultrasound (Optical) and Photoacoustic Imaging



Twan Lammers

Ultrasound imaging

- Very extensively used
- Fast, cheap, transportable (bed-side)
- No radiation hazard, highly biocompatible
- Real-time imaging information
- Highly sensitive to contrast agents
- Limitations: Air, Bone

Public Hospitals in Lyon (2012)

– 9 MRI

– 11 scanners

Specific rooms

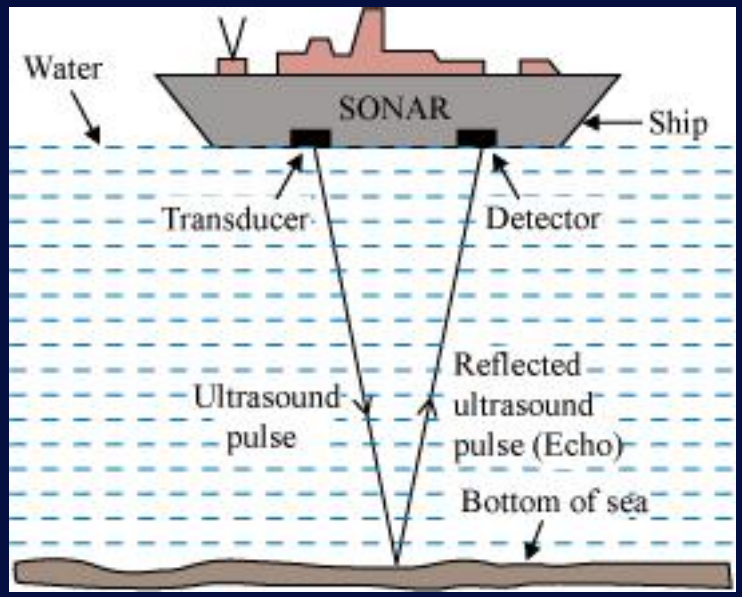
– 8 gamma (scintillation) cameras

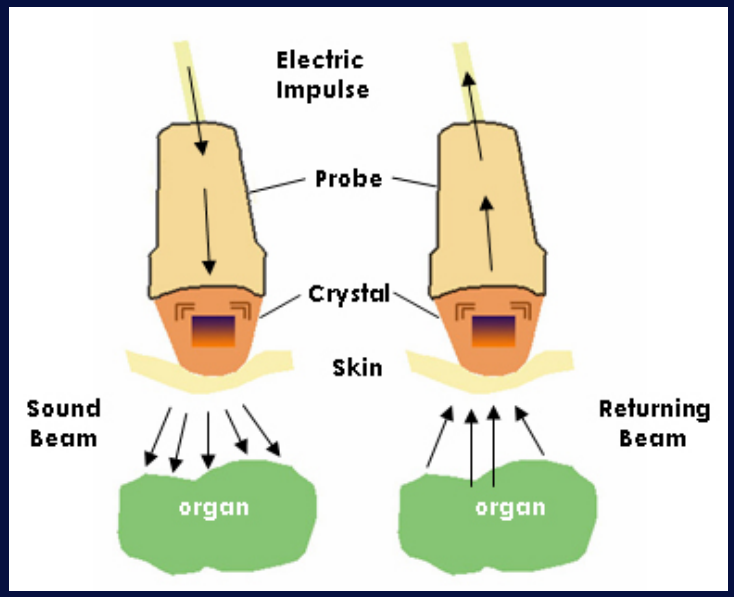
– 1 PET (Positron Emission Tomographic)

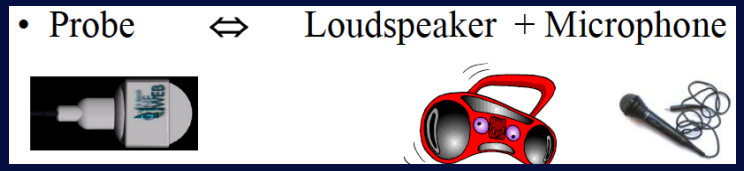
– More than 100 ultrasound scanners

Ultrasound imaging

principle







Anatomical US Imaging

"to see tissues" => generally performed <u>without</u> contrast agents

Anatomical US Imaging

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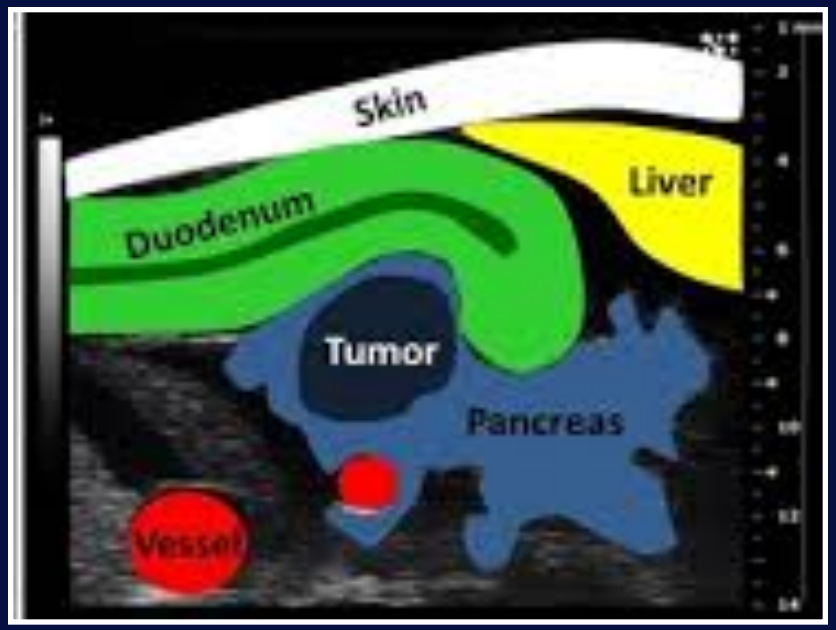

Anatomical US Imaging

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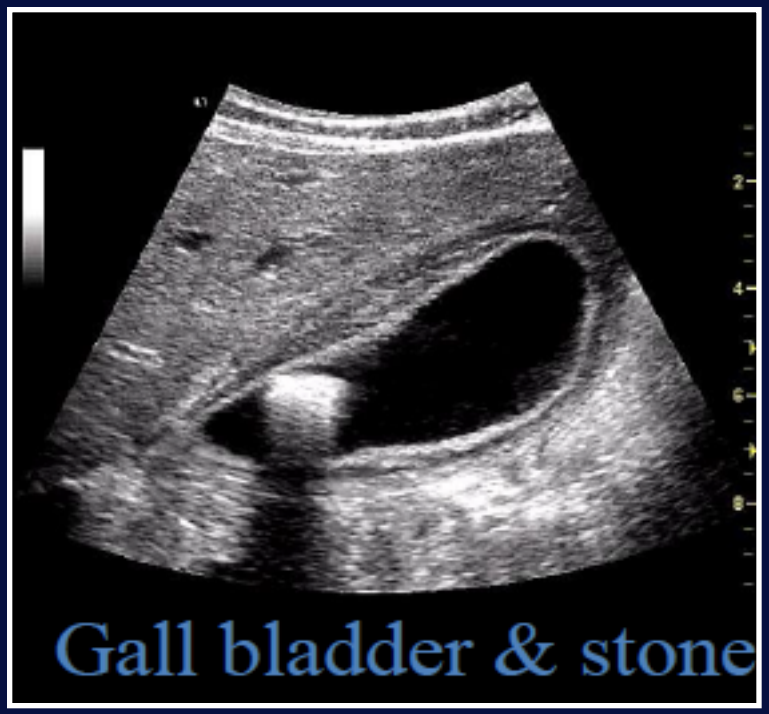
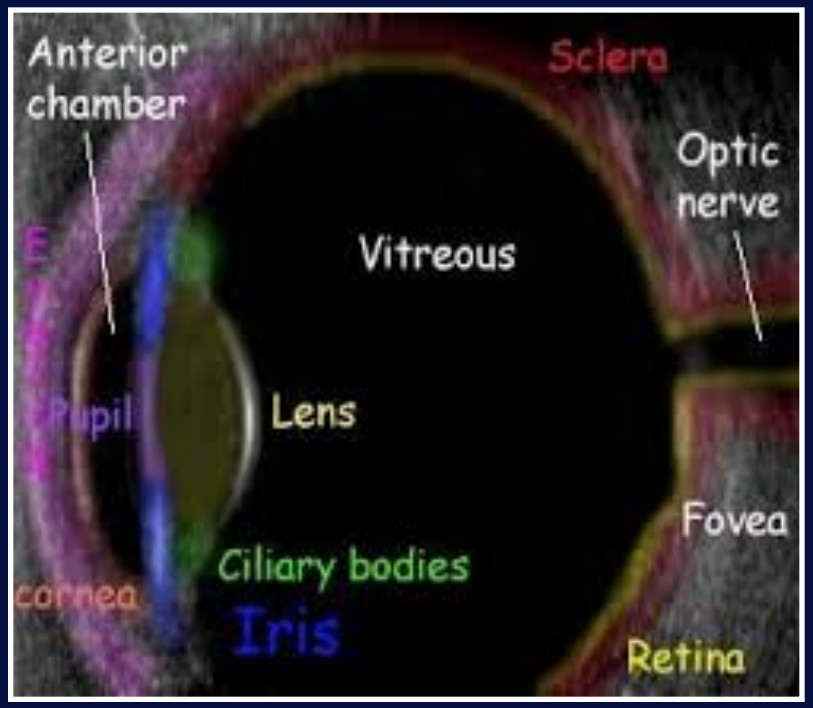
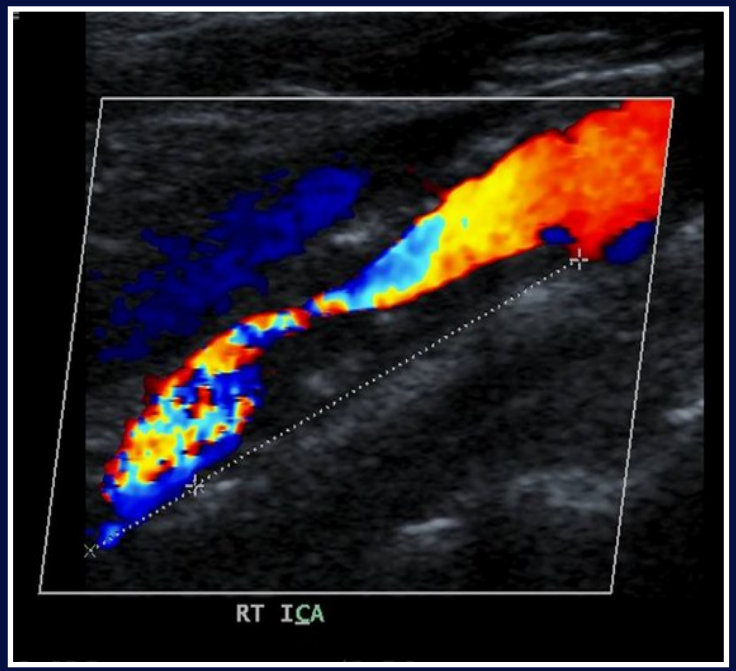


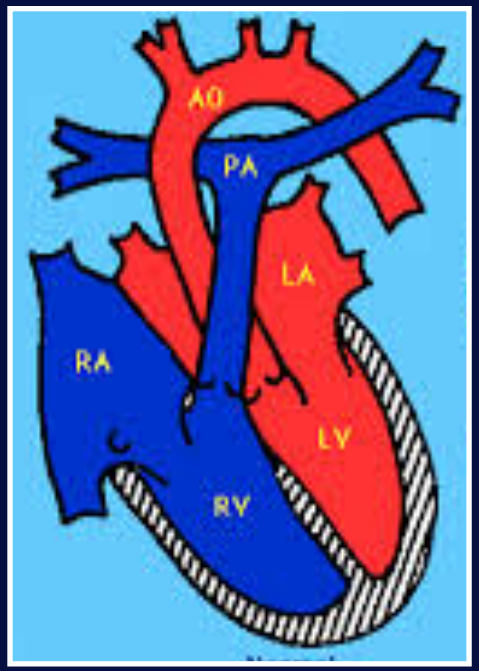


Functional US Imaging

"to see tissues how (well) tissues work"

=> can be performed without and with contrast agents





Functional US Imaging

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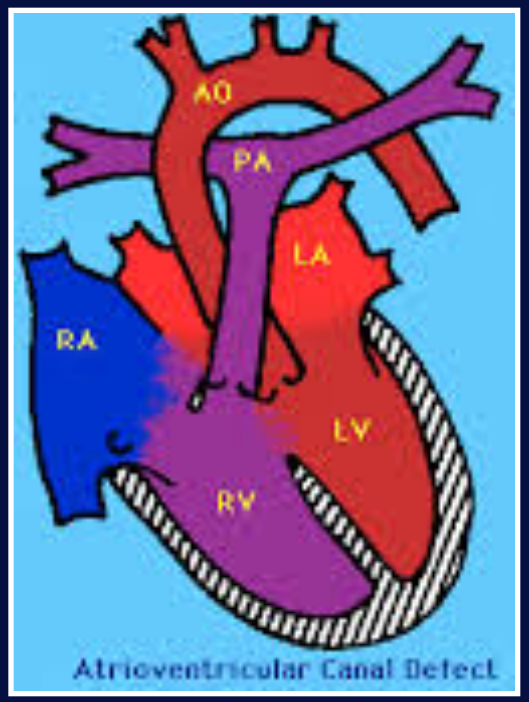
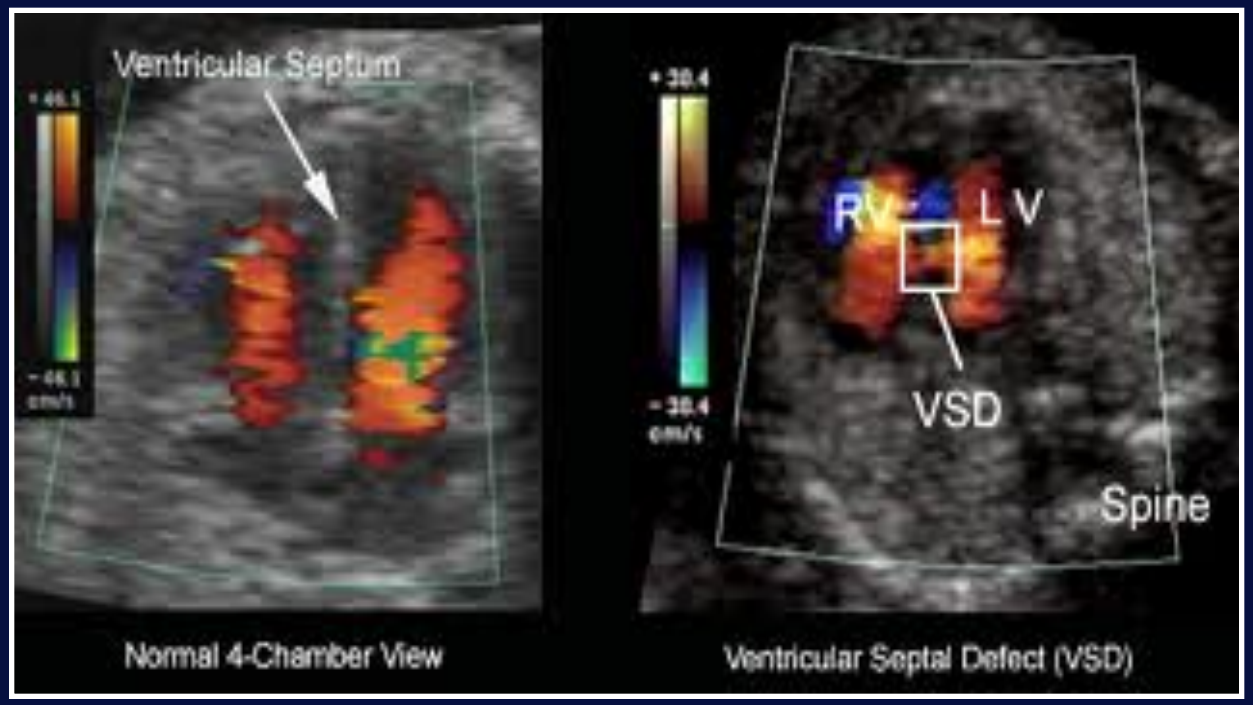


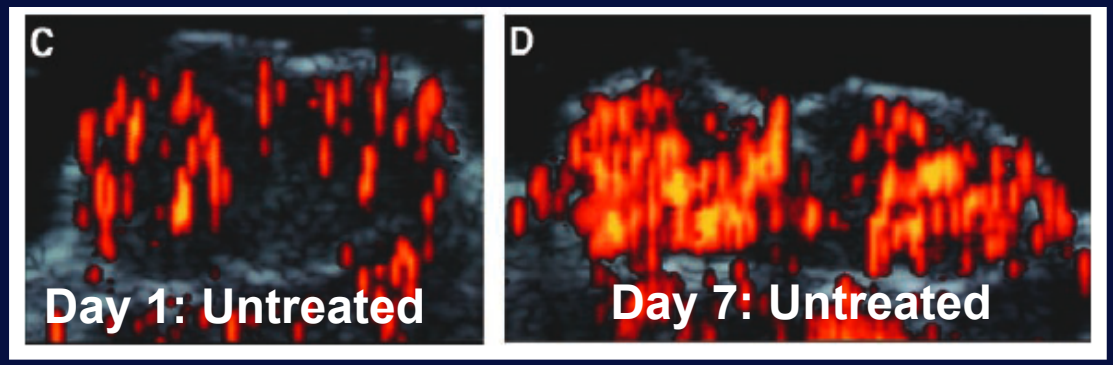


Functional US Imaging

"to see tissues how well tissues work"

=> with contrast agents (MicroBubbles)

"to see tissues how well treatments work"



Molecular US Imaging

"to see molecular processes"

=> can only be performed with contrast agents

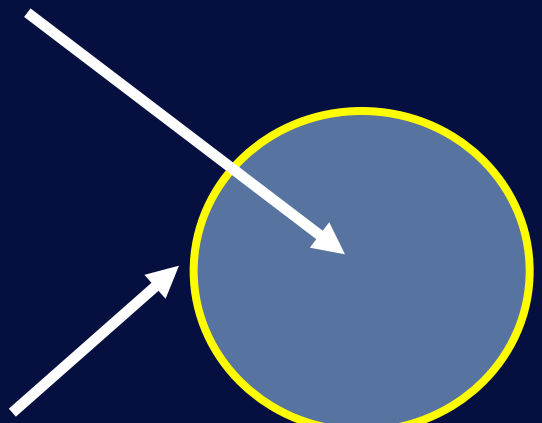
i.e. with ligand-targeted microbubbles

Microbubbles

Diameter ~1-5 μm

Intravascular contrast agents

Gas-filled core, e.g. air, SF_6



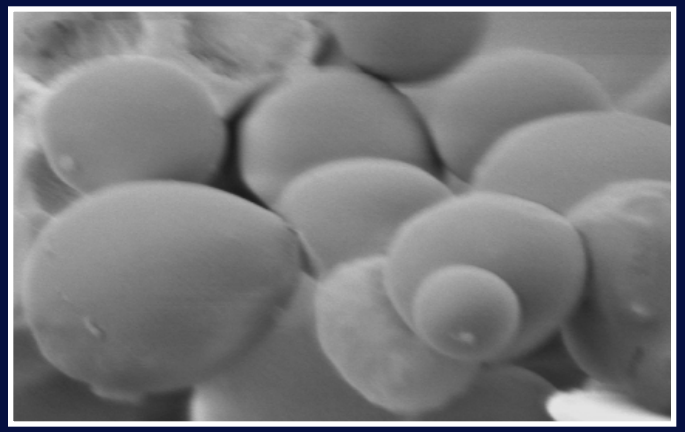
Stabilized shell,

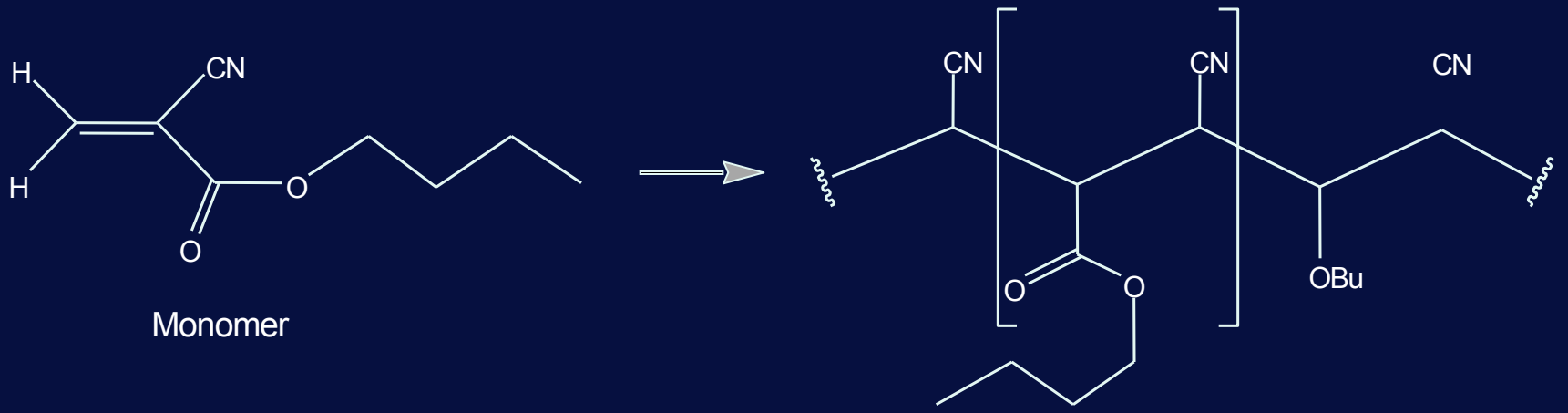
e.g. lipids, proteins, polymers, sugars

Name	Gas	Shell
Biosphere	Air	Polymer
BY963	Air	Lipid
EchoGen	Dodecafluoropentane	Surfactant
Echovist	Air	Galactose
Definity	SF6	Lipid
Imagent	SF6	Surfactant
Levovist	Air	Palmitinic acid/ Galactose
Optison	Perfluoropropane	Albumin
Sonavist	Air	Polymer
Sonovue	SF6	Lipid
Sonazoid	Perfluorcarbon	Lipid

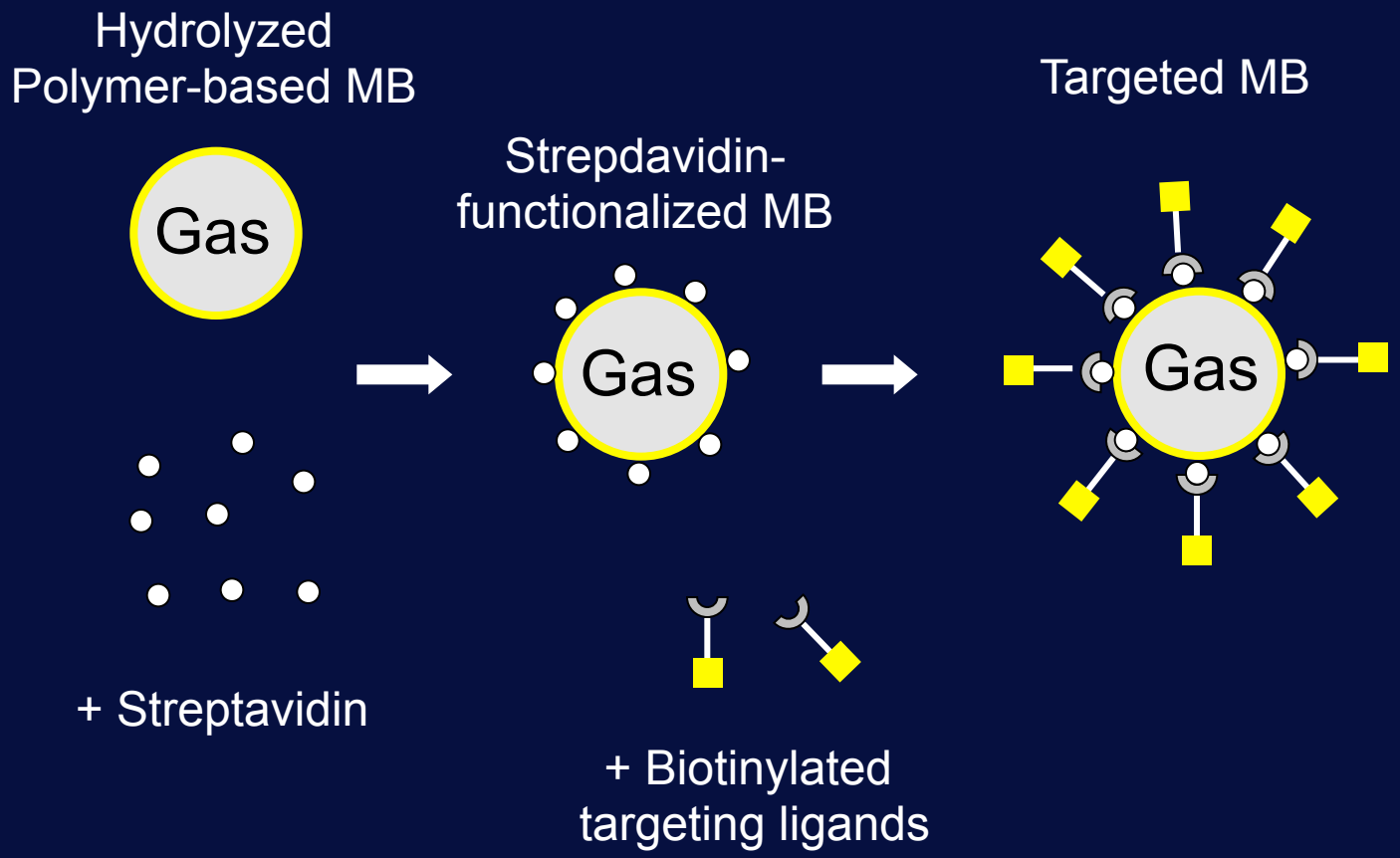
Polymer-based Microbubbles

polymerization of n-butyl-cyanoacrylate : (surgical) super glue : PBCA MB



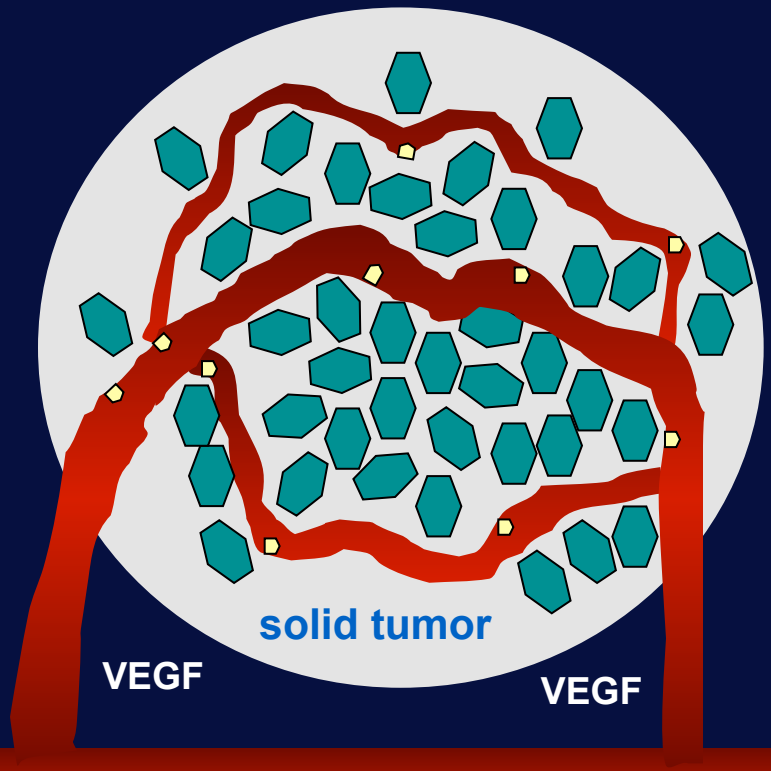


Ligand-Targeted Microbubbles



Molecular US Imaging using Targeted MB

angiogenic blood vessels in tumors express high levels of disease-associated marker molecules, e.g. VEGF-R2

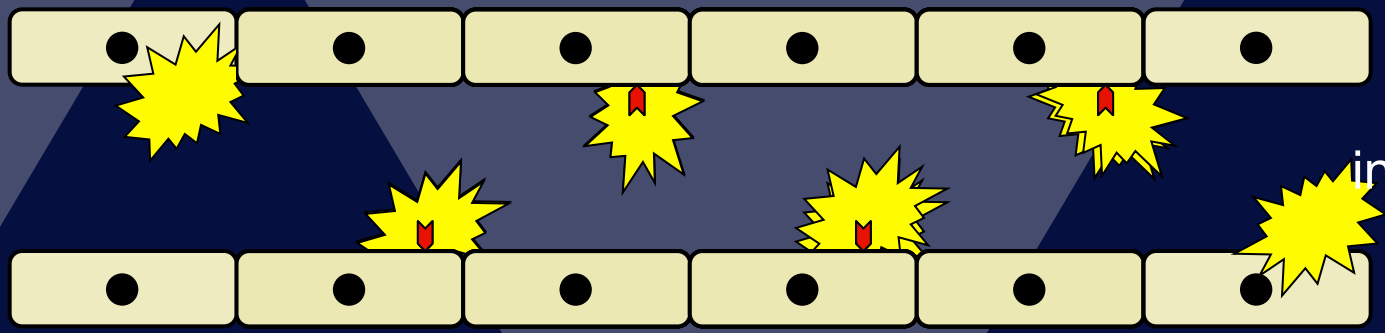


mature blood vessel

Molecular US Imaging using Targeted MB

SPAQ : Sensitive Particle Acoustic Quantification

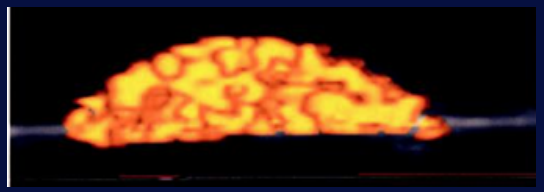
=> to quantitatively assess angiogenic marker expression by (tumor) endothelial cells



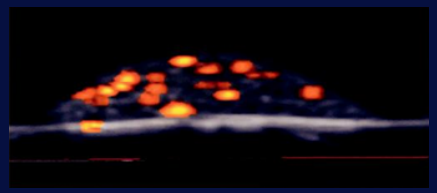
intravascular

extravascular

Standard US

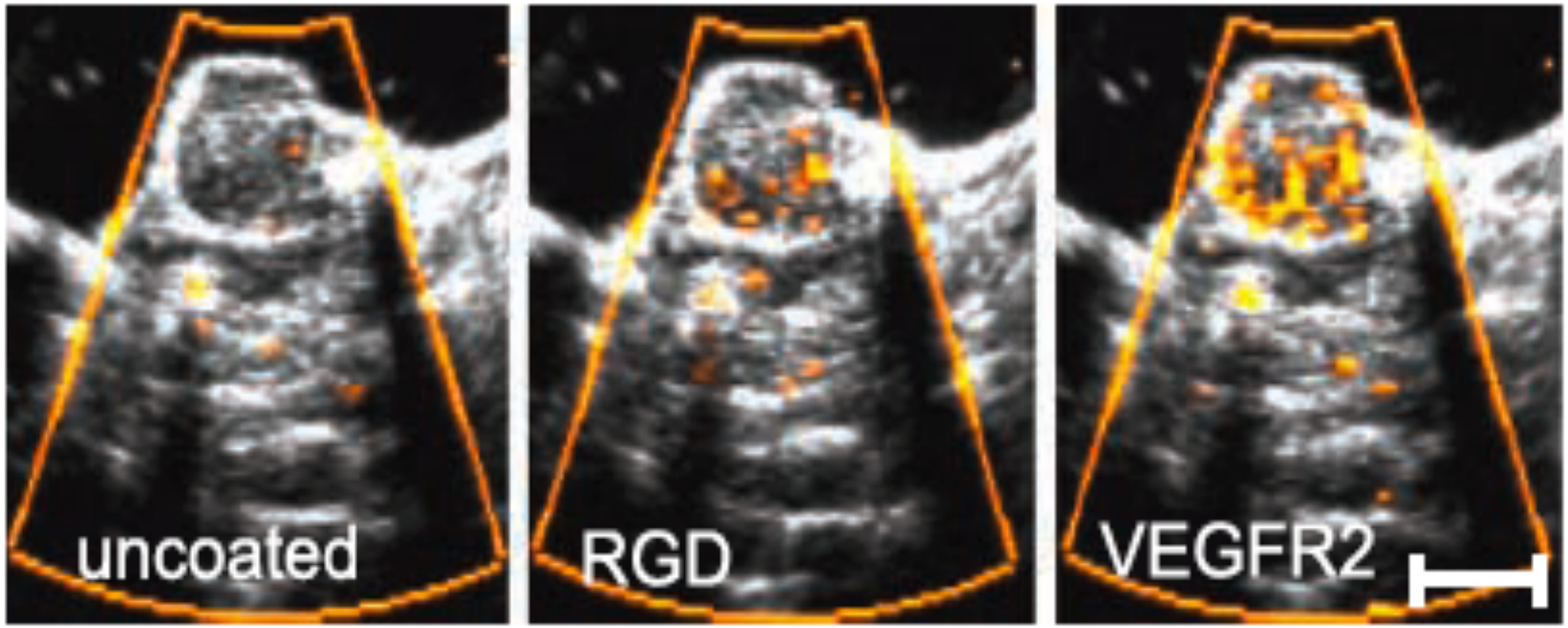


SPAQ



Molecular US Imaging using Targeted MB

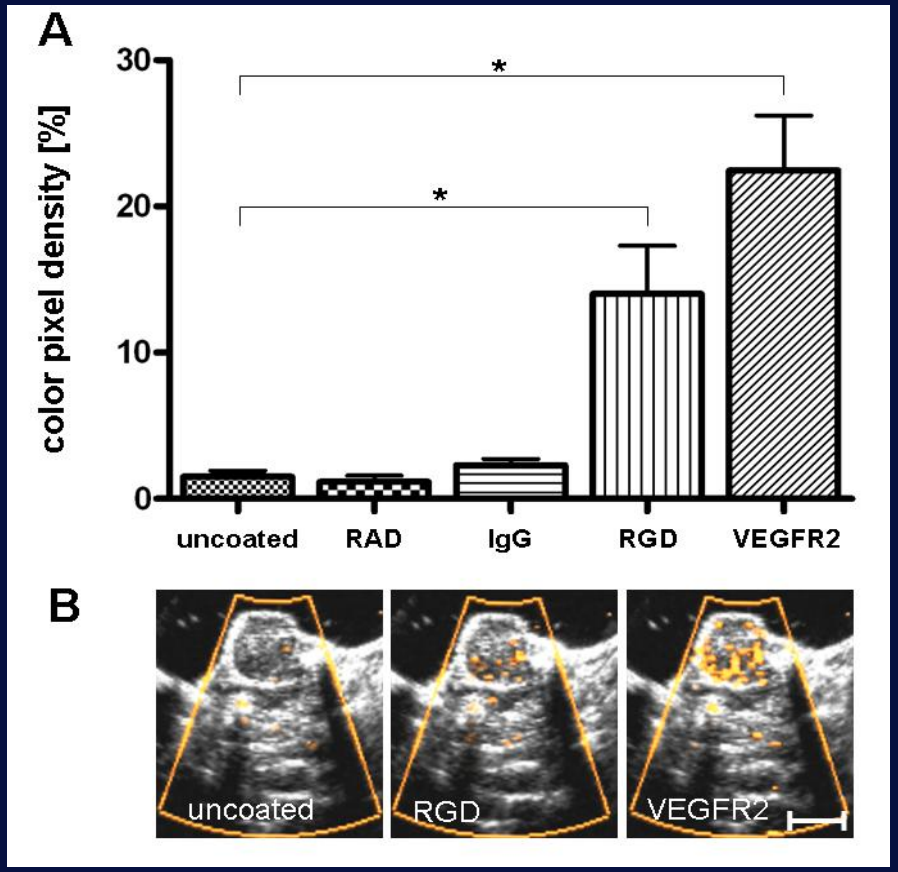
=> quantitative assessment of MB binding to tumor blood vessel markers

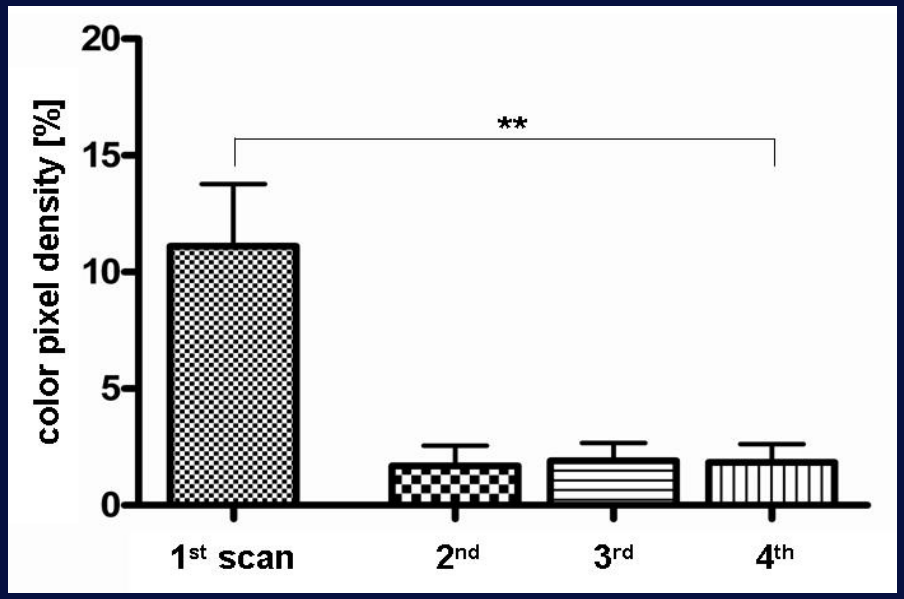


Palmowski et al, Mol Cancer Ther (2008)

Molecular US Imaging using Targeted MB

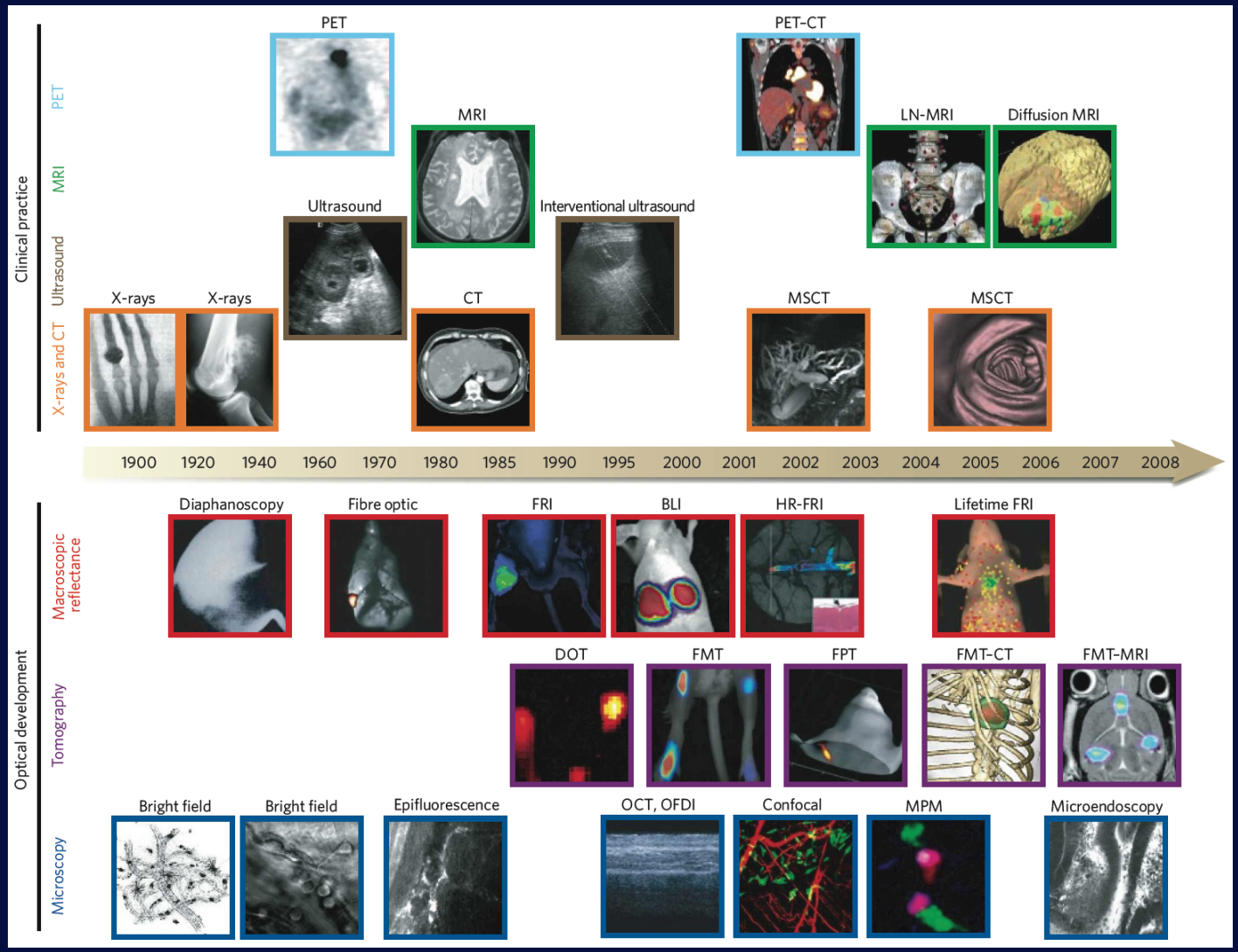
- Efficient binding of VEGFR2- and RGD-MB, no binding of control MB
  - 1 SPAQ-scan destroys almost all stationary MB





Palmowski et al, Mol Cancer Ther (2008)

Optical imaging



Weissleder and Pittet, Nature (2008)

Optical imaging

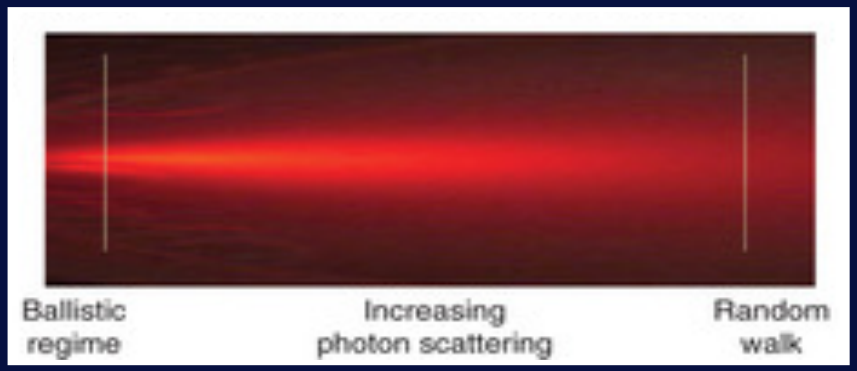
in vivo imaging using light

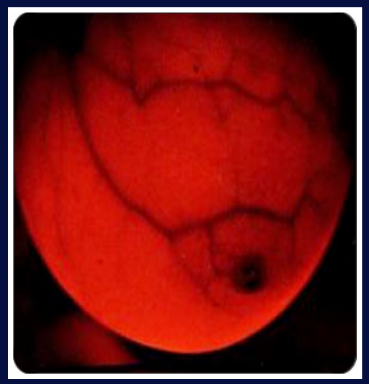
Advantages

- Cheap
- Versatile
- High throughput
- Widely used preclinically
- Many model systems available
- Translational potential

Disadvantages

- Scattering
- Absorption
- Surface-dominated
- Poor penetration depth
- No anatomical information
- Difficult quantification





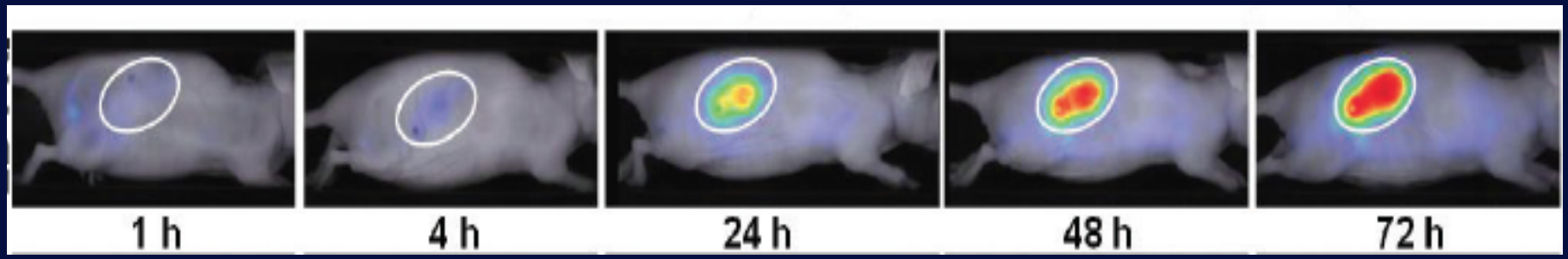
Ntziachristos, Nature Methods (2010)

Optical imaging

- RAMAN : RAMAN Spectroscopy
- OCT : Optical Coherence Tomography
- BLI : Bioluminescence Imaging
- FRI : Fluorescence Reflectance Imaging
- FMT : Fluorescence Molecular Tomography
- MEFT : Mesoscopic EpiFluorence Tomography
- TPLSM : Two-Photon Laser Scanning Microscopy
- …

Fluorescence Reflectance Imaging (FRI)

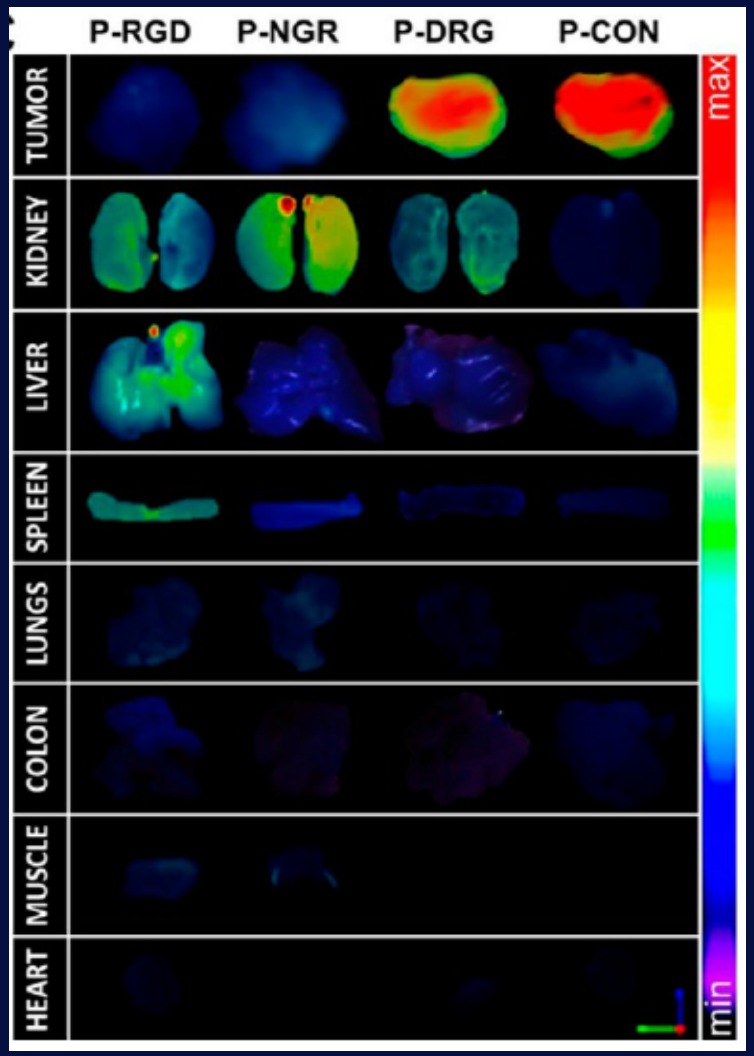
biodistribution and tumor accumulation of NIRF-labeled polymeric drug carriers



=> exemplifies poor penetration depth of FRI ; not only accumulation in tumors...

Kunjachan et al, ACS Nano (2013)

Fluorescence Reflectance Imaging (FRI)



ex vivo FRI of the biodistribution of

NIRF-labeled polymeric drug carriers

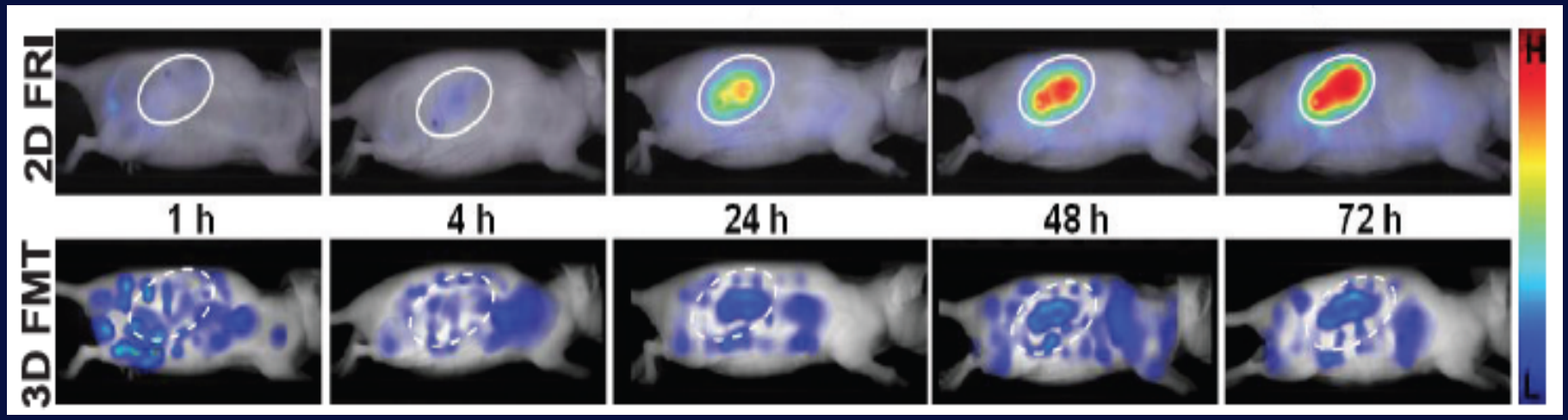
besides poor penetration depth =>

also significant absorption by highly vascularized tissues

Kunjachan et al, Nano Lett (2014)

Fluorescence Molecular Tomography (FMT)

biodistribution and tumor accumulation of NIRF-labeled polymeric drug carriers

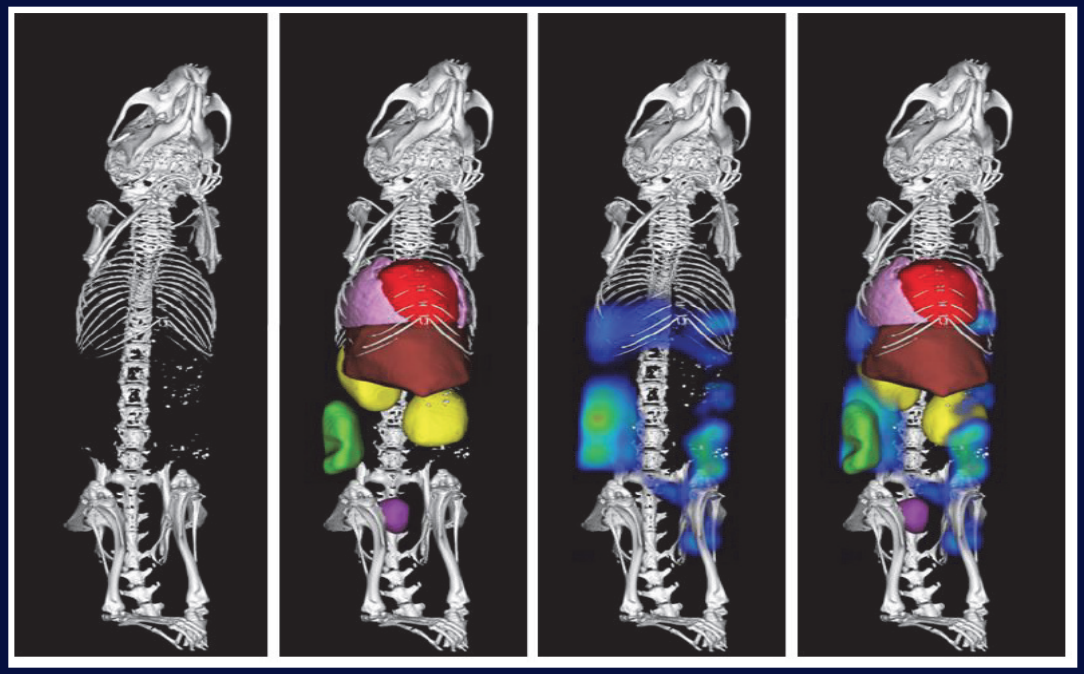


FMT : better penetration, but poor spatial resolution and no anatomical information

Kunjachan et al, ACS Nano (2013)

FMT

biodistribution and tumor accumulation of NIRF-labeled polymeric drug carriers

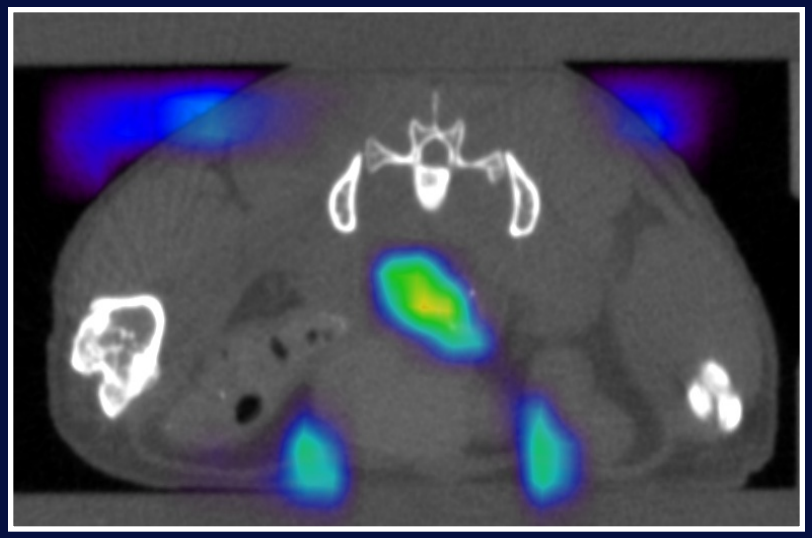


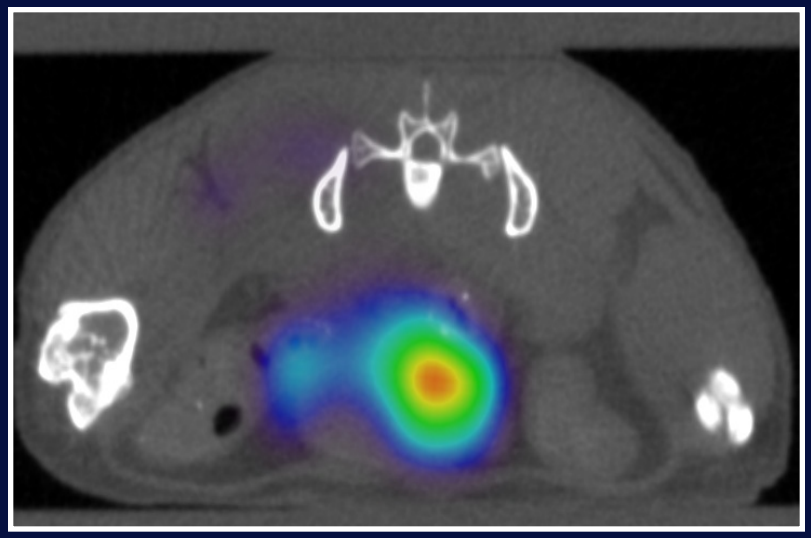
Hybrid CT-FMT => CT-based anatomical information + FMT-based molecular information

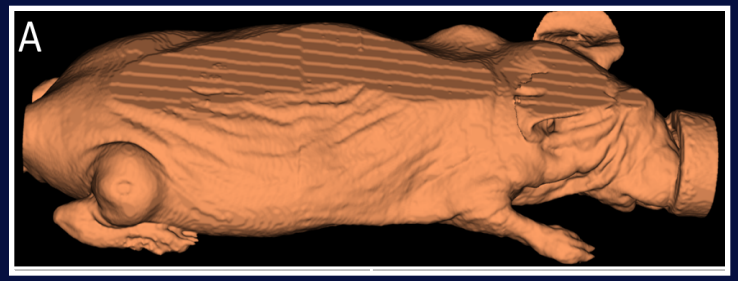
Kunjachan et al, ACS Nano (2013)

FMT

CT-based volumetric reconstruction => kidney clearance a low MW probe





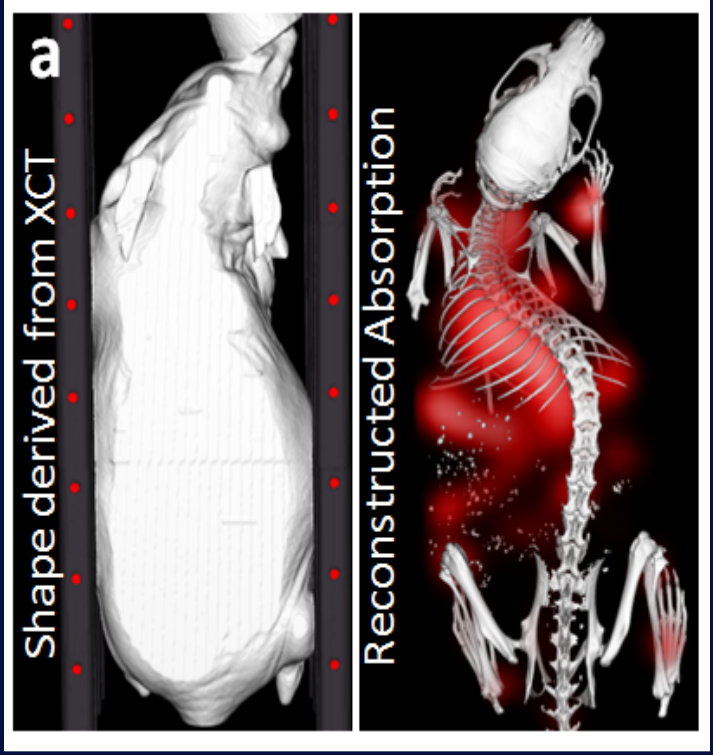


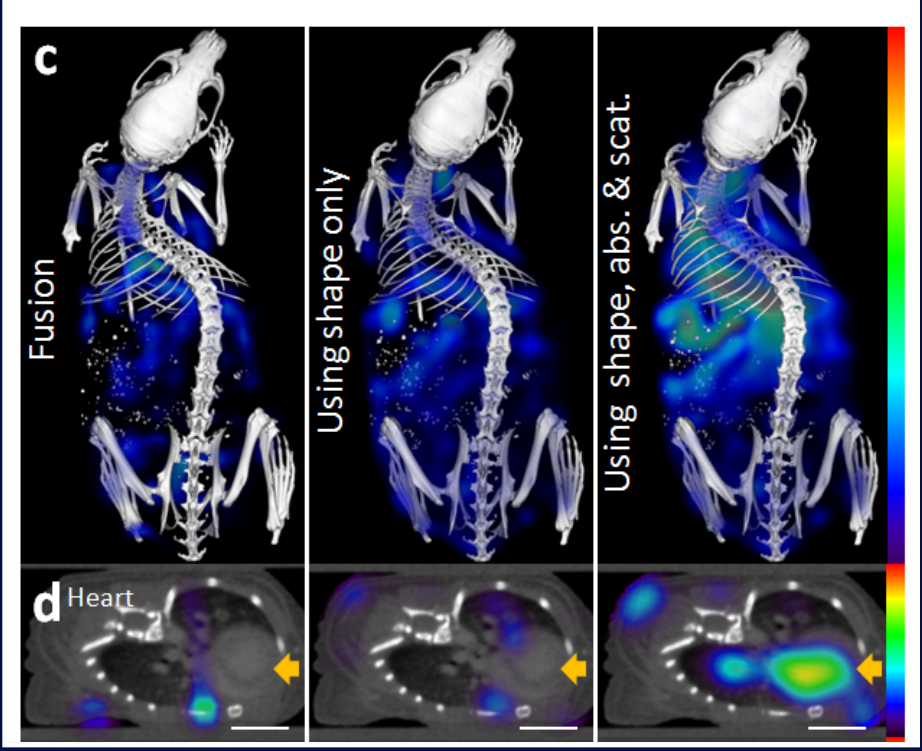
Gremse et al, Theranostics (2014)

FMT

CT-based volumetric reconstruction + FMT-based absorption reconstruction

=> to more accurately assess drug carrier accumulation in highly vascularized organs





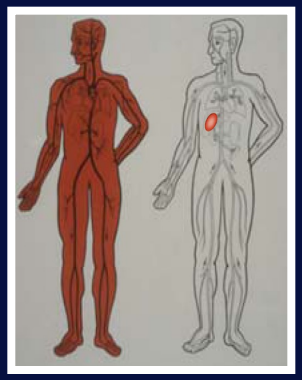
Gremse et al, Theranostics (2014)

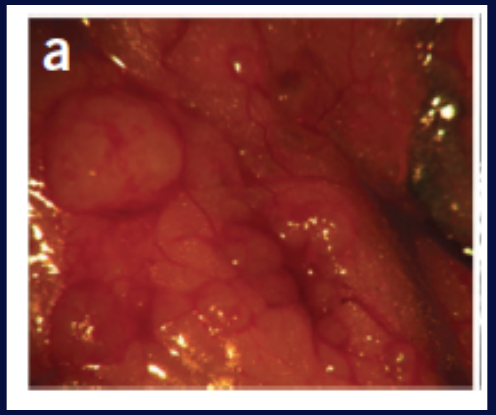
Optical imaging : Clinical translation

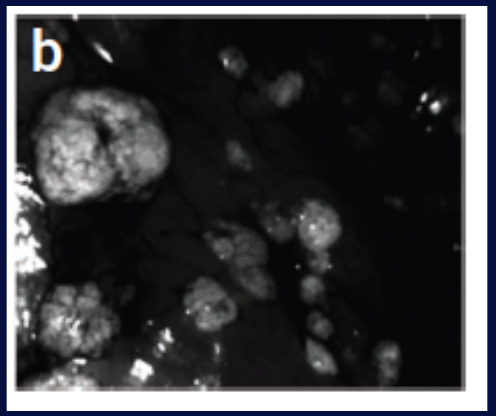
staging and treatment monitoring of rheumatoid arthritis using ICG

Optical imaging : Clinical translation

intra-operative imaging of metastatic ovarian cancer using Folate-FITC







Van Dam et al, Nature Medicine (2011)

Photoacoustic imaging (PAI)

Photoacoustic imaging (PAI)

- Generation of ultrasound signals upon exposure to laser light
- Detected pressure amplitude is proportional to light absorption
- PAI combines high contrast agent sensitivity and specificity of OI with high resolution and high penetration depth of US

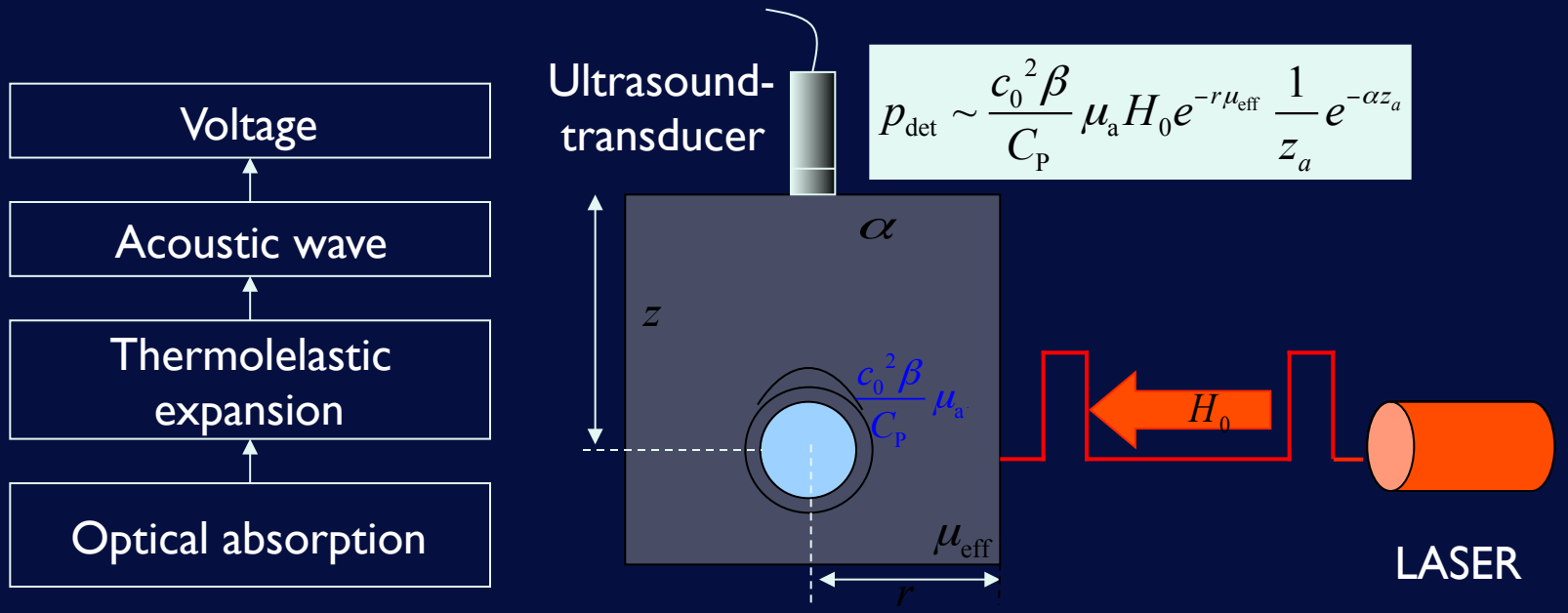


Image courtesy : Georg Schmitz (Bochum)

Photoacoustic imaging

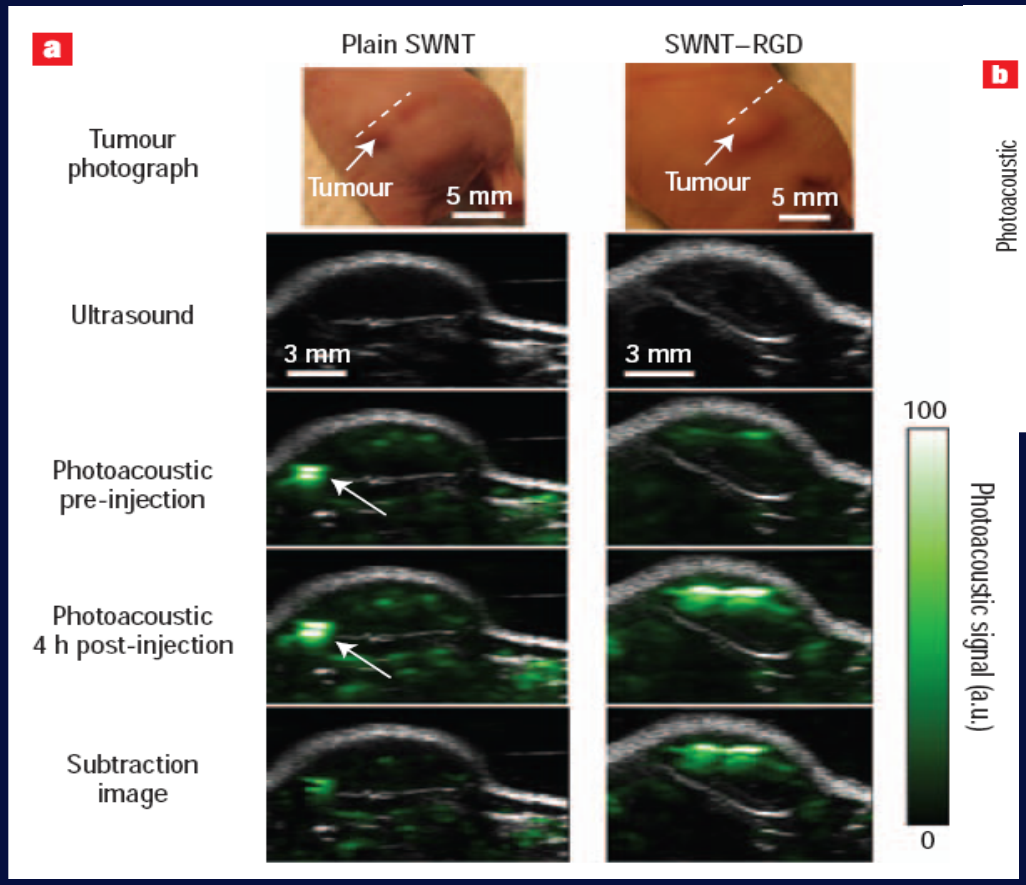
- Contrast agents
  - Gold nanoparticles
  - Carbon nanotubes
  - “Fluorescent“ dyes (ICG, methylene blue)
  - “Fluorescent“ proteins (reporter gene imaging)

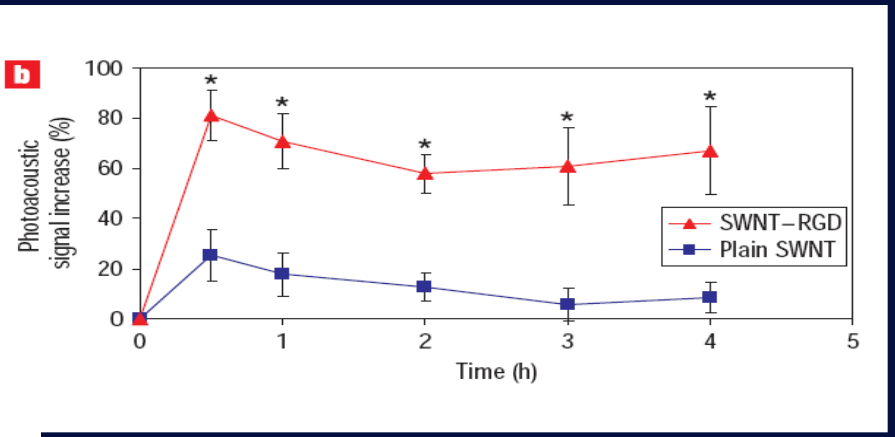
- Endogenous contrast, e.g. hemoglobin, oxygenation

- Advantages
  - More quantitative than optical imaging
  - Higher spatial resolution in depth
  - Use of various low MW contrast agents and reporter genes
  - Hypoxia and rBV determination with endogenous contrast

Molecular PAI of angiogenic markers

with contrast agents : RGD-targeted carbon nanotubes

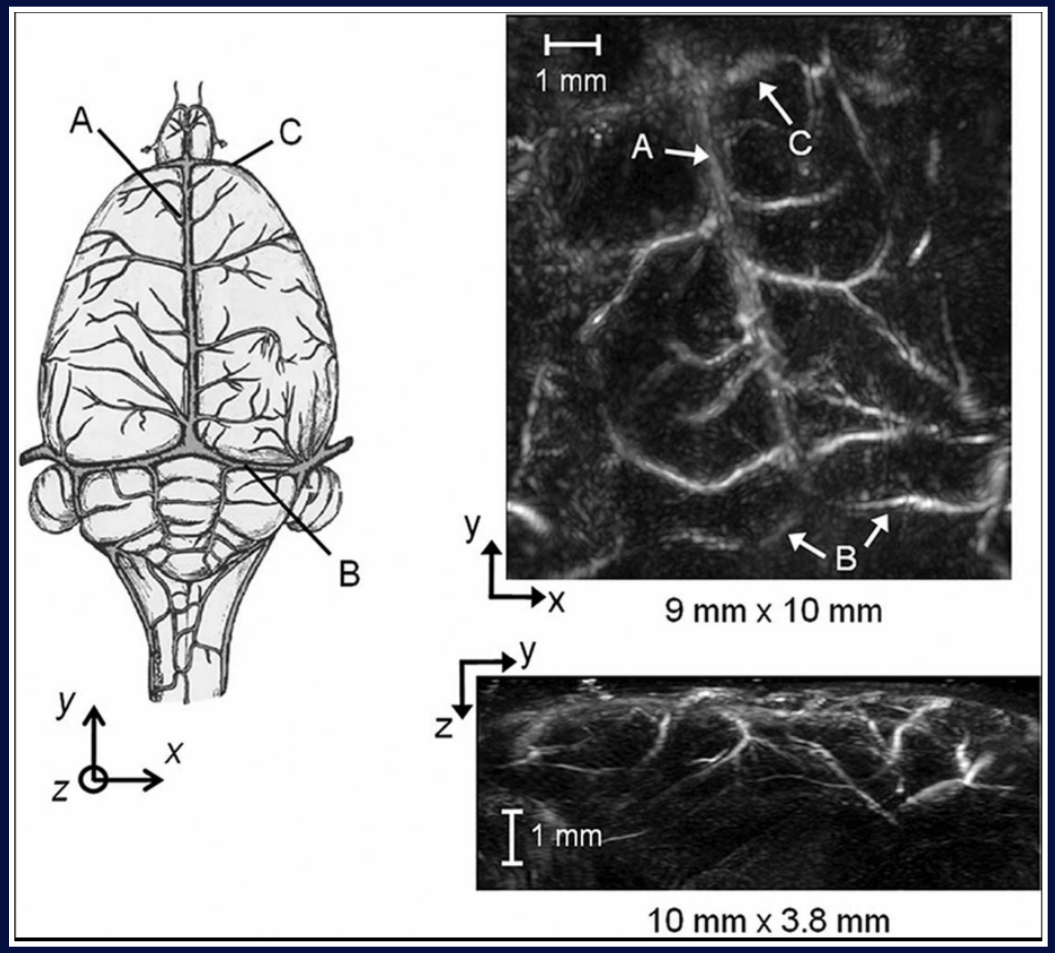




Zerda et al, Nature Nanotechnology (2008)

PAI of brain blood vessels

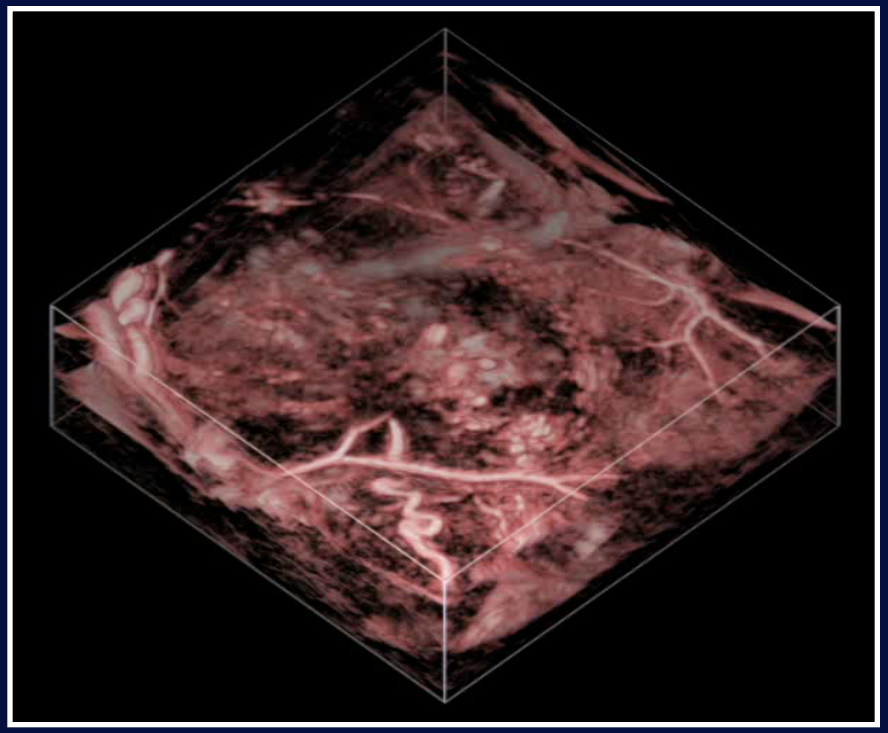
without contrast agents : using the endogenous contrast generated by hemoglobin



Laufer et al, Applied Optics (2009)

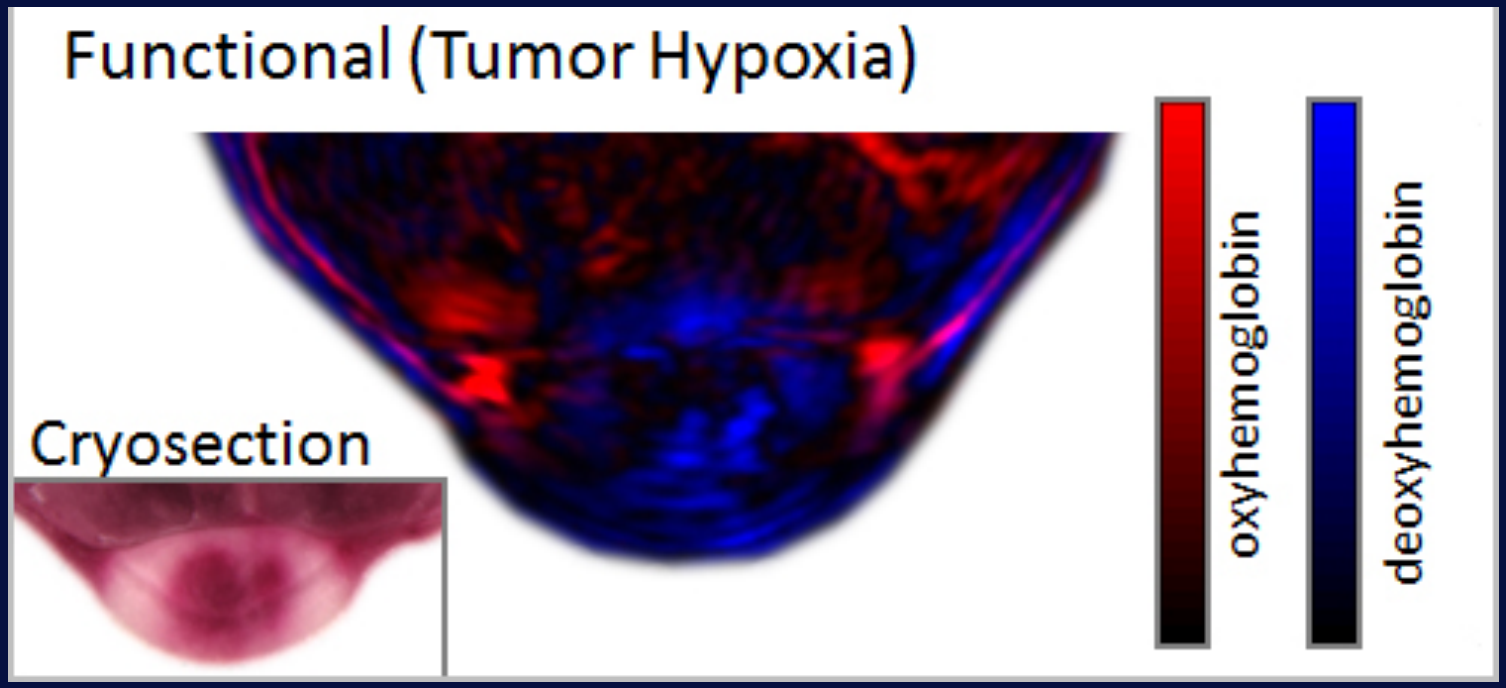
PAI of tumor blood vessels

without contrast agents : using the endogenous contrast generated by hemoglobin



PAI of tumor oxygenation

using the endogenous contrast generated by oxy/deoxy-hemoglobin



Herzog et al, Radiology (2012)

Assessing tumor hypoxia using PAI

real-time imaging of changes in tumor pO_2 in mice upon inhalation with 100 - 5 - 100% oxygen-containing air

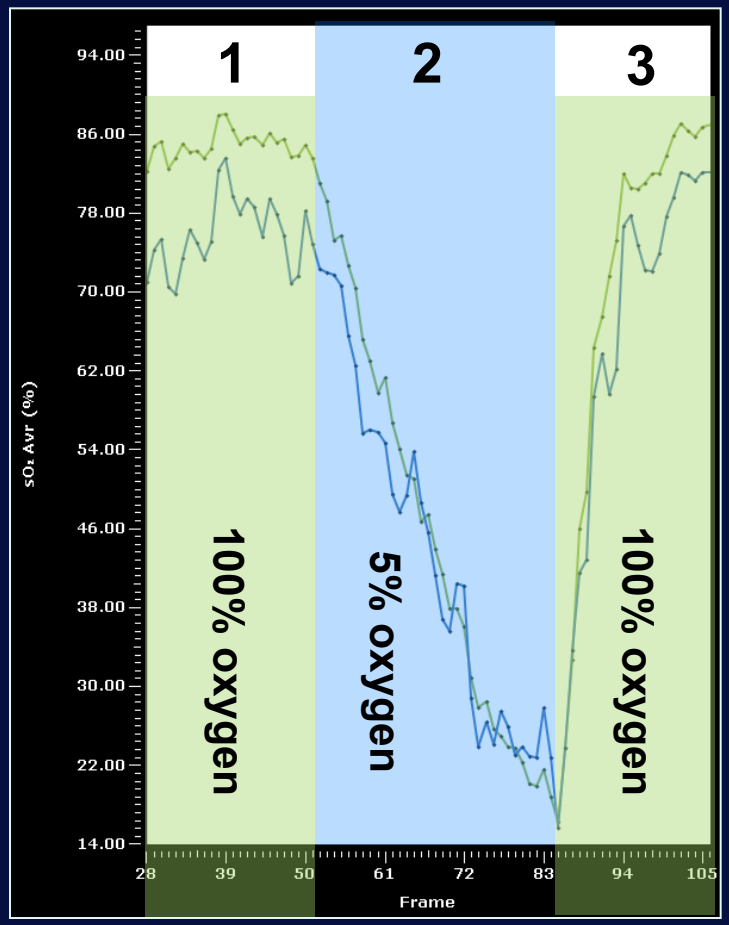
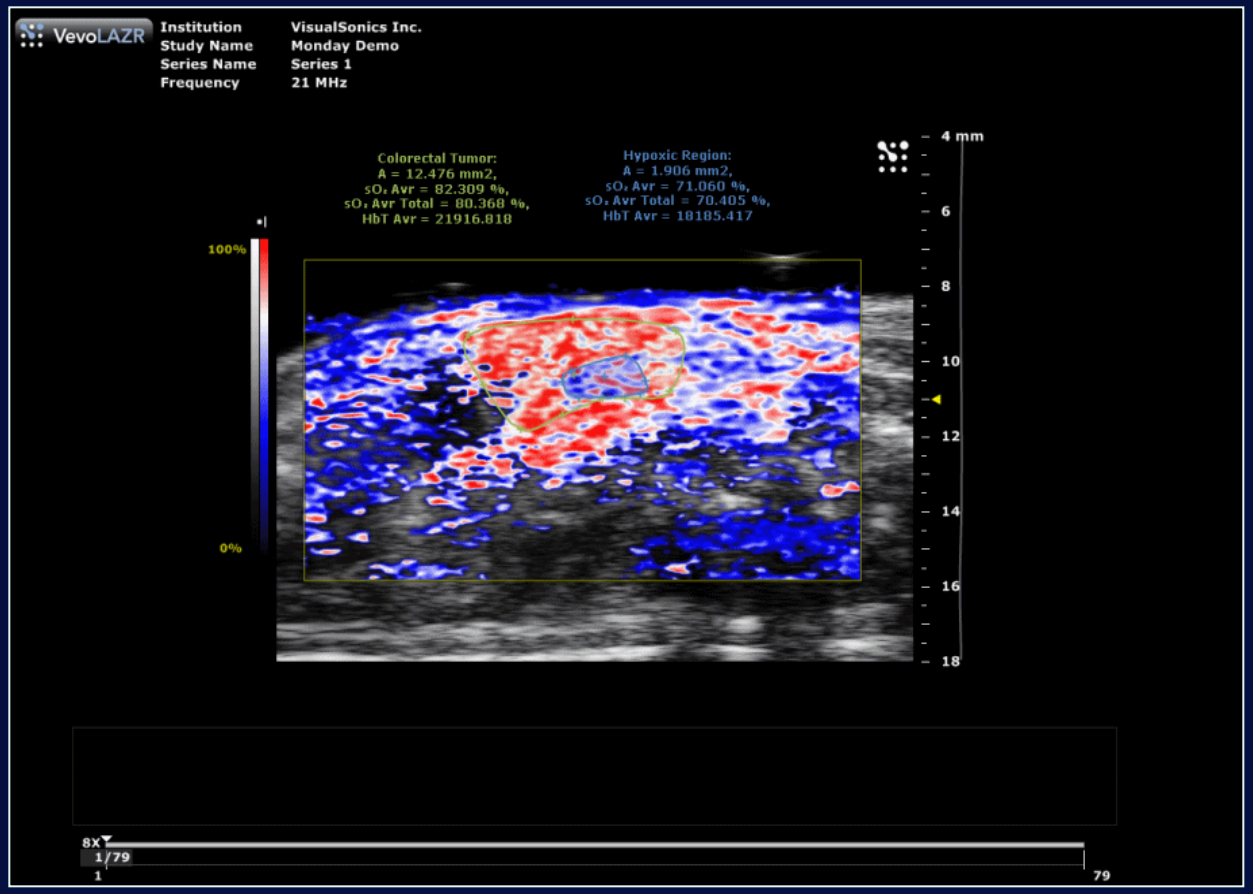
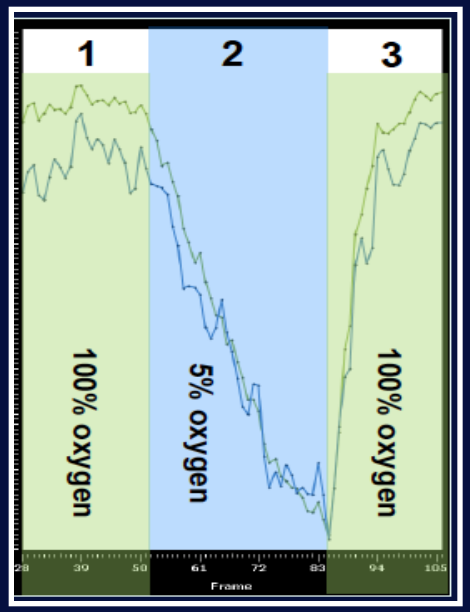


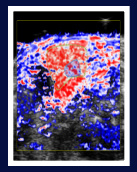
Image courtesy: VisualSonics

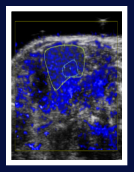
Assessing tumor hypoxia using PAI

real-time, non-invasive and quantitative imaging of tumor oxygenation









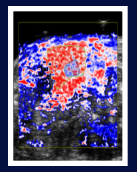


Image courtesy: VisualSonics

PAI of sentinel lymph nodes

RESEARCH ARTICLE

CANCER IMAGING

Metastatic status of sentinel lymph nodes in melanoma determined noninvasively with multispectral optoacoustic imaging

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Stoffels et al, Science Transl Med (2015)

Finding sentinel lymph nodes (ICG)

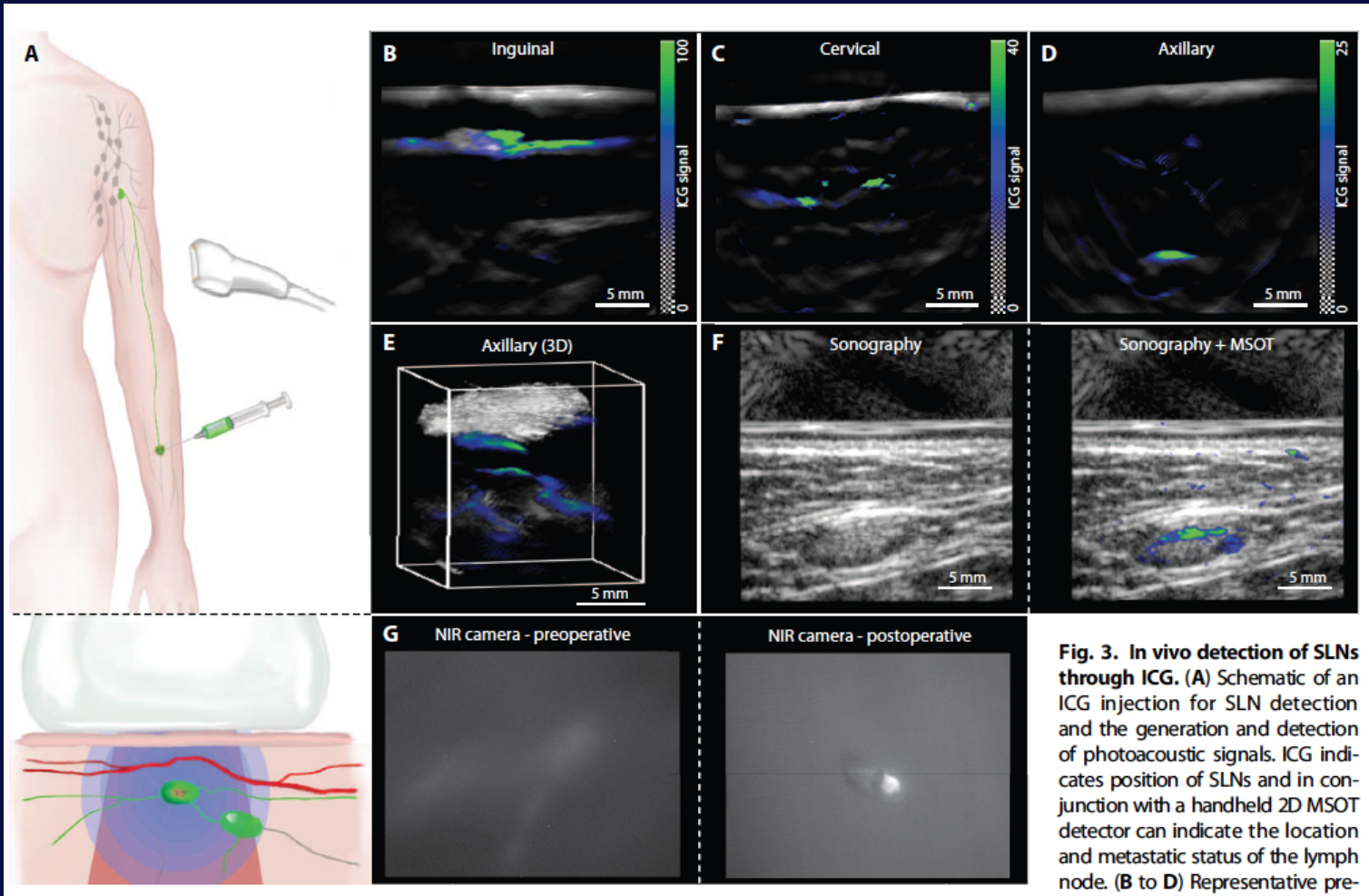
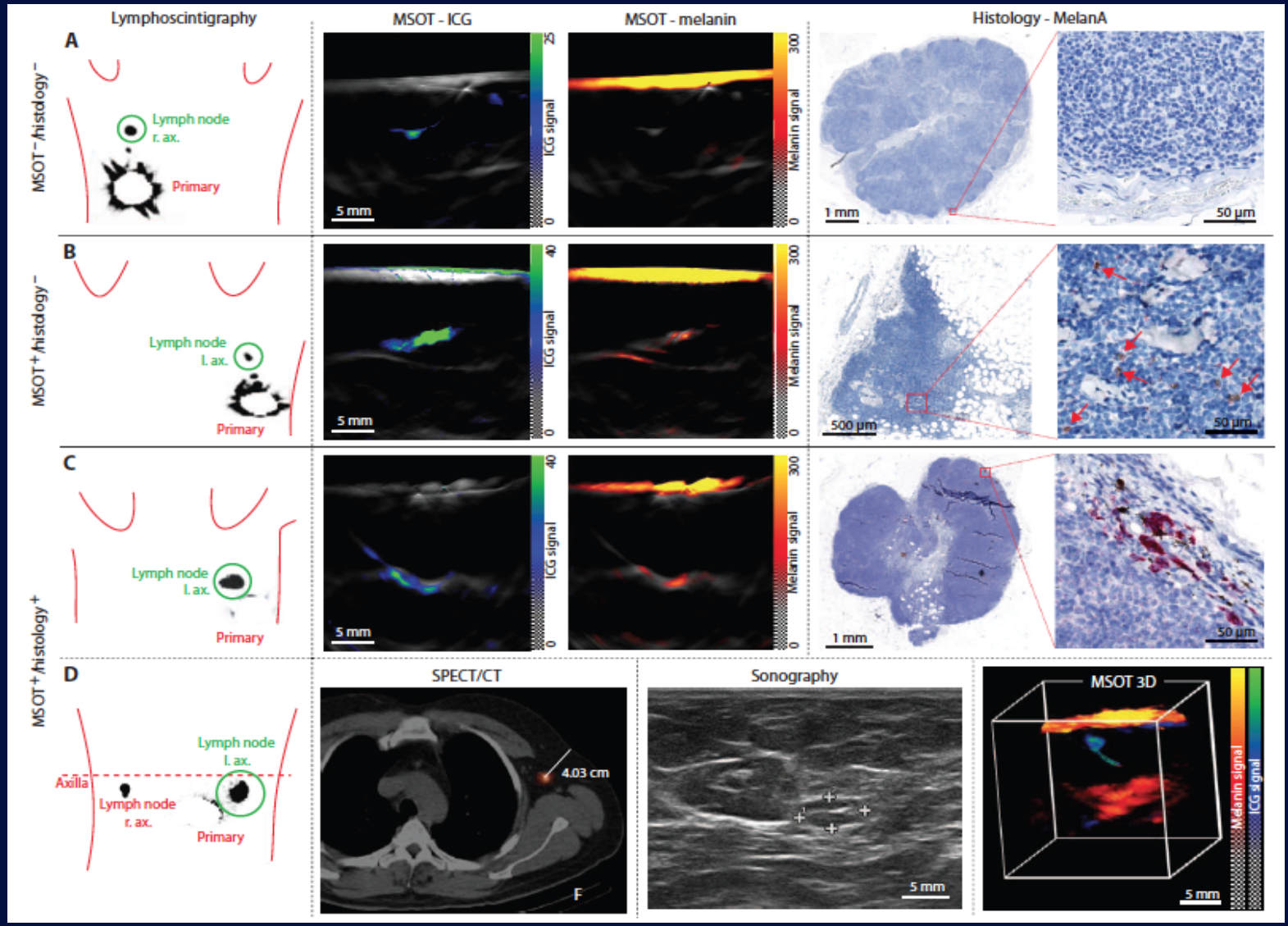


Fig. 3. In vivo detection of SLNs through ICG. (**A**) Schematic of an ICG injection for SLN detection and the generation and detection of photoacoustic signals. ICG indicates position of SLNs and in conjunction with a handheld 2D MSOT detector can indicate the location and metastatic status of the lymph node. (**B** to **D**) Representative preoperative images of inguinal, cervical, and axillary SLNs from the 2D detector, with ICG signal overlaid on a single-wavelength background image at 800 nm. Images are from three different patients. (**E**) Rendered view of an SLN imaged using the 3D MSOT detector, showing a network of lymph channels supplying the axillary lymph node of a different patient at ~10 mm. An animated version can be found in movie S3. (**F**) Pulse-echo ultrasound images of a lymph node overlaid with the 2D MSOT image. (**G**) Images of the inguinal SLN [same patient as in (B)] taken by a fluorescence camera before surgery and shortly after the excision.

Stoffels et al, Science Transl Med (2015)

Characterizing sentinel lymph nodes (ICG+melanin)



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Stoffels et al, Science Transl Med (2015)

Summary

- Ultrasound imaging is very extensively used in the clinic
- For anatomical, functional and molecular imaging purposes
- Microbubbles are routinely used as US contrast agents

- Optical imaging is highly versatile, but has certain limitations
- Optical imaging is very extensively used preclinically
- Several clinical applications of optical imaging are emerging

- Photoacoustic imaging combines optical and US imaging
- High contrast, high spatial resolution, quantitative
- Possibility to use endogenous contrast agents

thank you

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