

# REALTA' E POTENZIALITA' DEL NANOTECH IN LOMBARDIA



## ***Il ruolo delle nanotecnologie nel presente e futuro della diagnostica per immagini***

Milano, 14 Novembre 2011

**Alessandro Maiocchi – Bracco Imaging SpA**

Centro Ricerche Bracco



- What is Medical Imaging ?
- Contrast Agents and Medical Imaging
- Medical vs Molecular Imaging
- Microparticles Platforms for USI
- Nanoparticles platforms for MRI
- Conclusions

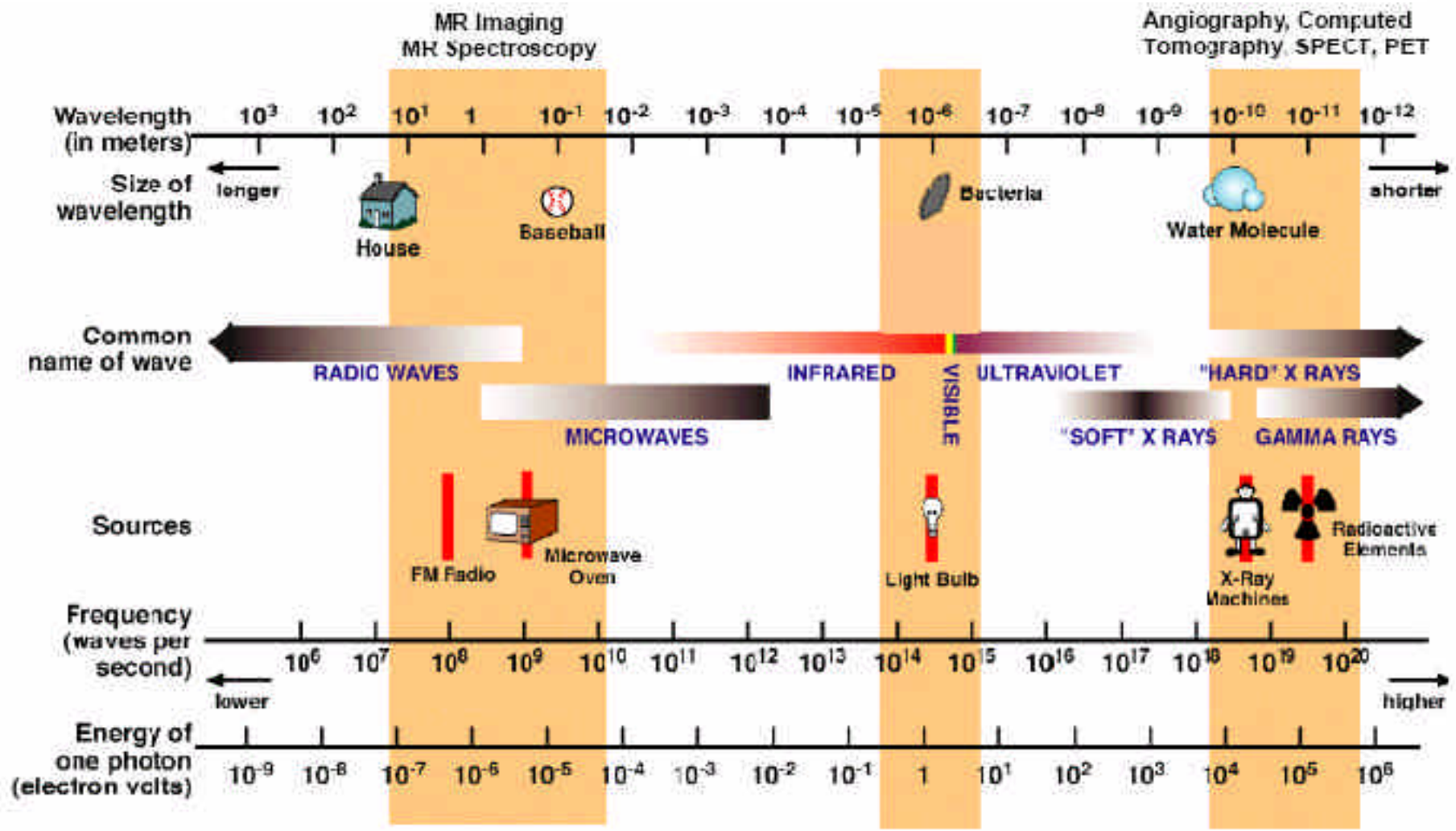
# What is medical Imaging ?

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*Medical imaging refers to the techniques and processes used to create images of the human body (or parts thereof) for clinical purposes (medical procedures seeking to reveal, diagnose or examine disease) or medical science (including the study of normal anatomy and function).*

# Electromagnetic Spectrum



*Ultrasound uses mechanical rather than electromagnetic energy to form an image*

Graber, Schmitz, SUNY Downstate Med Ctr

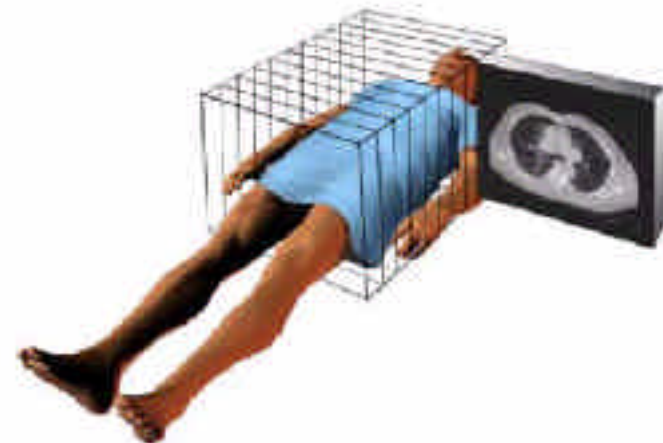


# Examples of Medical Images and Devices

- **Radiograph**: Intensity of diagnostic X-rays (10 – 150 keV) attenuated in body



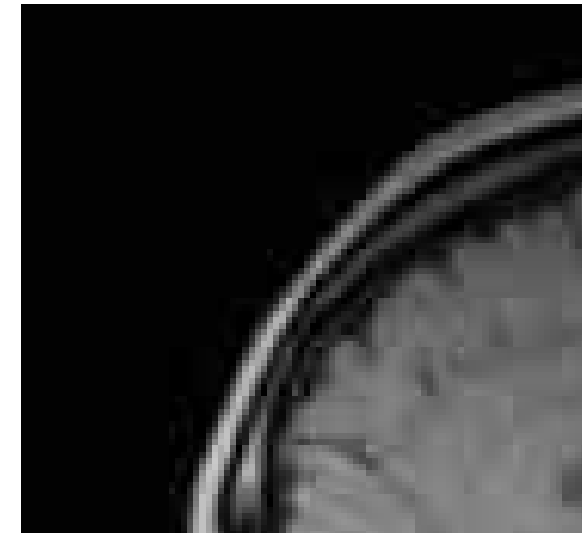
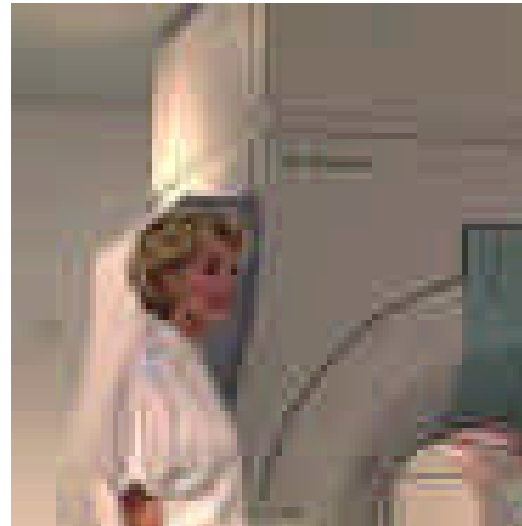
- **Computed Tomography**: Spatial distribution of X-Ray attenuation coefficients in body



# Examples of Medical Images and Devices



- **Magnetic Resonance Imaging**: Spatial distribution of proton density in body



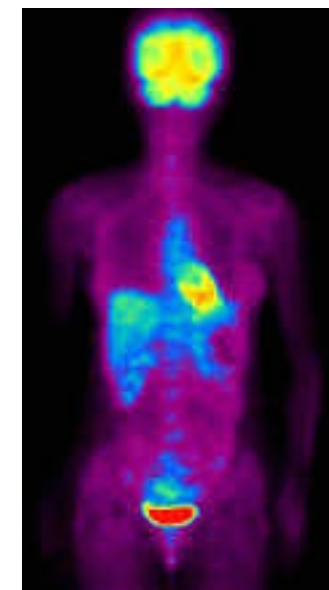
- **Ultrasound**: Intensity of ultrasonic (1-10 MHz) signal reflected in body



- **Nuclear Medicine**: Intensity of  $\gamma$ -rays from a radionuclide tracer distributed in body

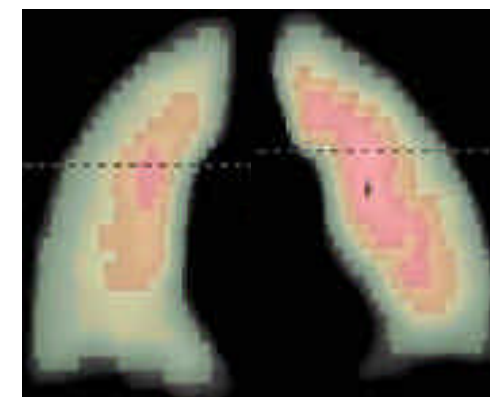
## Positron Emission Tomography PET

$\beta^+$  emitters ( $^{15}\text{O}$ ,  $^{13}\text{N}$ ,  $^{11}\text{C}$ ,  $^{18}\text{F}$ )



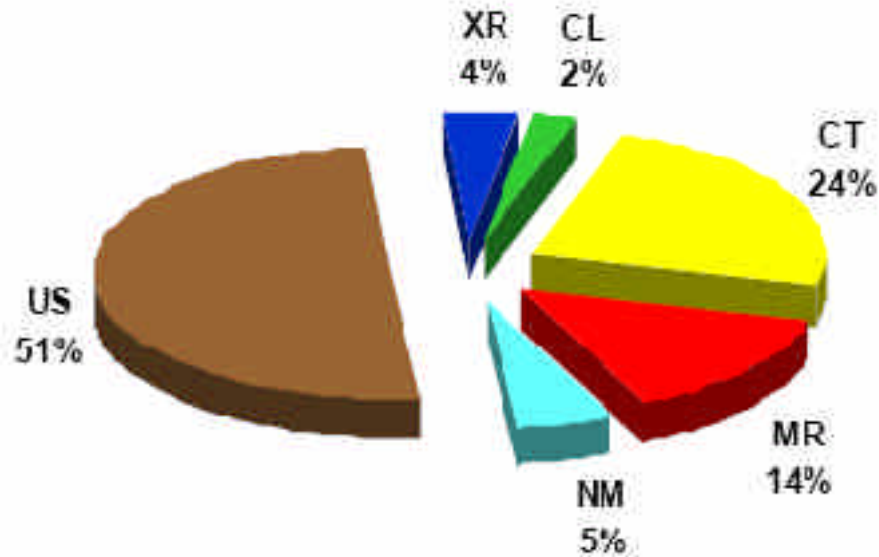
## Single Photon Emission Computed Tomography SPECT

$\gamma$  emitters ( $^{99\text{m}}\text{Tc}$ ,  $^{123}\text{I}$ ,  $^{111}\text{In}$ )

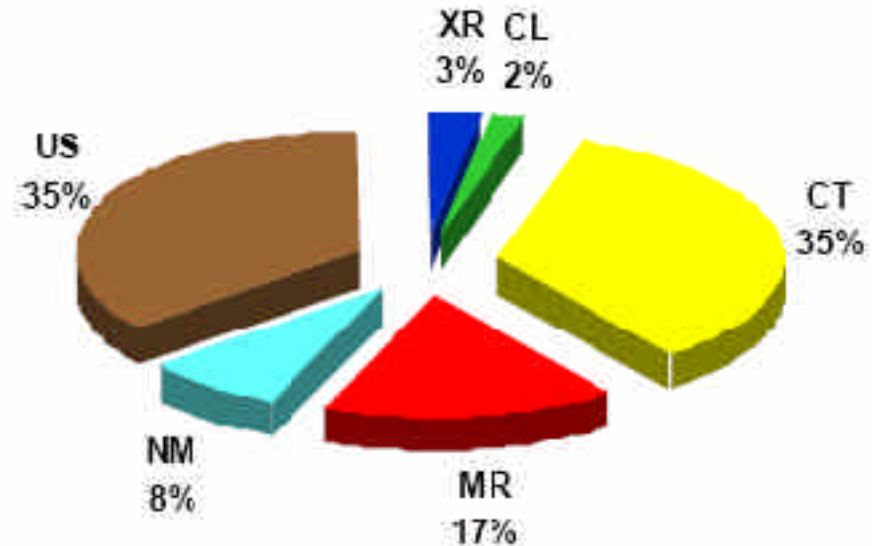


# Medical Imaging in the World

EUROPE: TOTAL PROCEDURES (2006)



USA: TOTAL PROCEDURES (2006)



\*XR ESCLUDE Barium & plain X-rays procedures.

AMR/Arlington Medical Resources, Inc., The Imaging Market Guide, 2006

Ultrasound, X-Ray CT and MRI are the most relevant Medical Imaging procedures in the health facilities.



# The use of Contrast Agents in Medical Imaging

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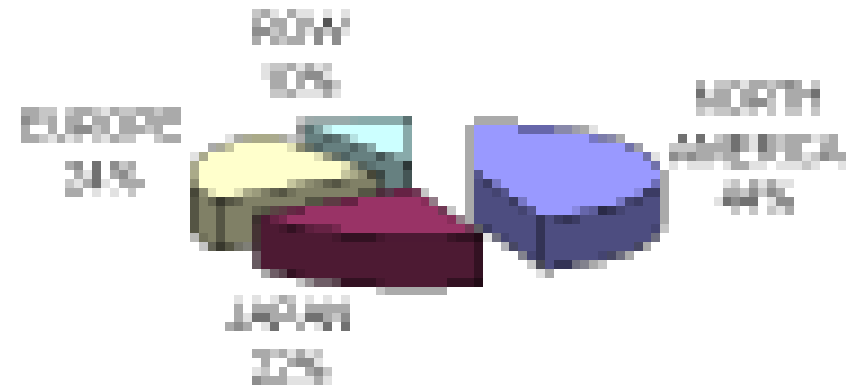
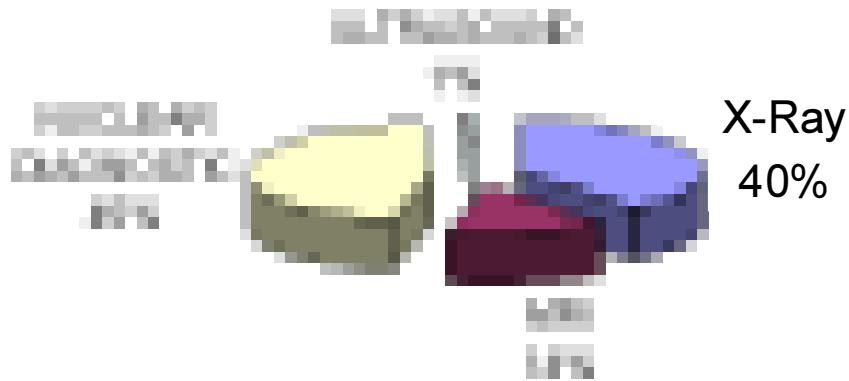
- Contrast agents are used in clinical protocols to enhance or create the necessary visual contrast in an image between the organ, vessel or tract in which they are present and the surrounding tissues in the body.
- Make it possible to visualise certain anatomical structures or physiological functions within the human body when the imaging techniques on their own cannot provide this information

# The Contrast Agents market



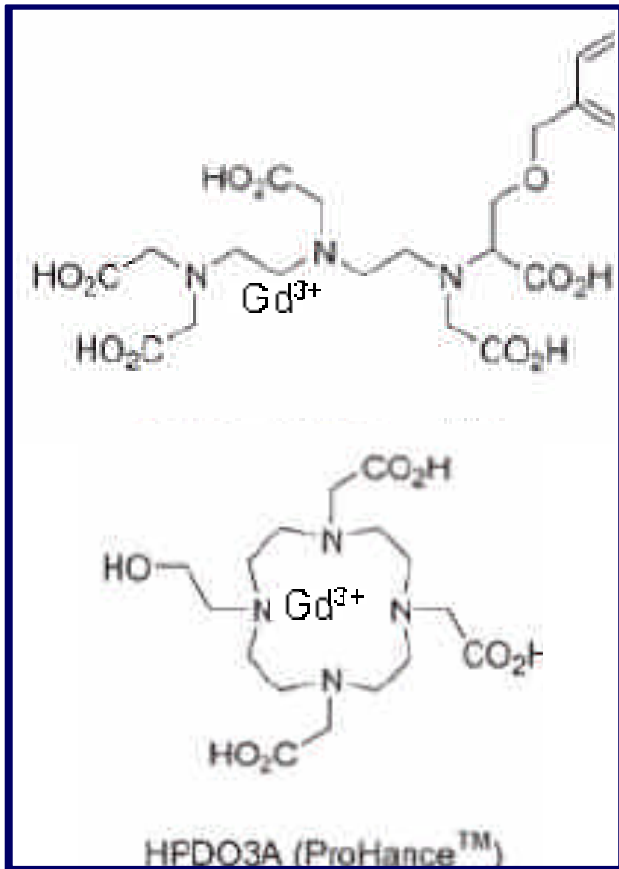
IMAGING AGENTS 2008 MARKET VALUE

IMAGING AGENTS 2008 MARKET VALUE

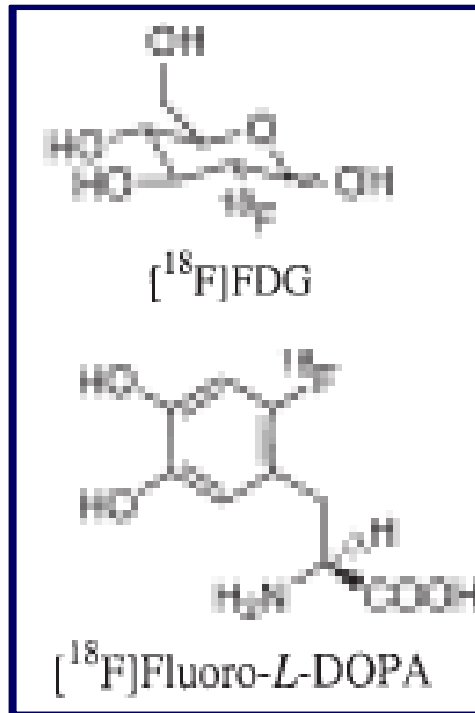


The imaging agent market is less than 1% (\$6 billion) of the whole pharmaceutical market in the world (\$850 billion)

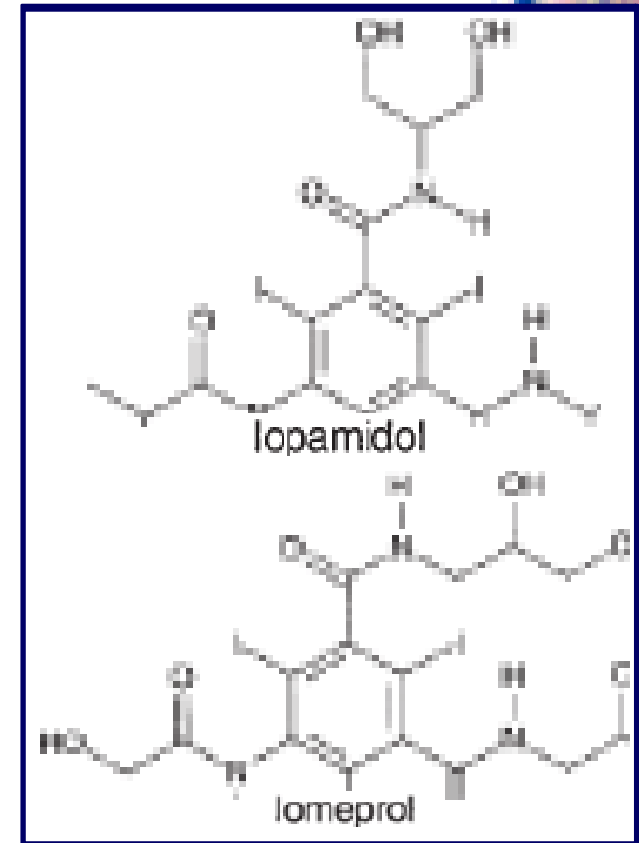
# Current Contrast Agents: some examples



MRI

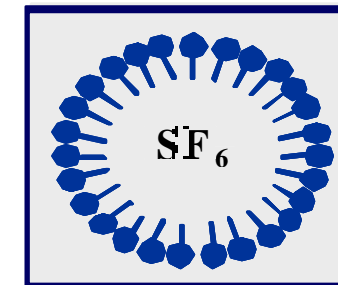
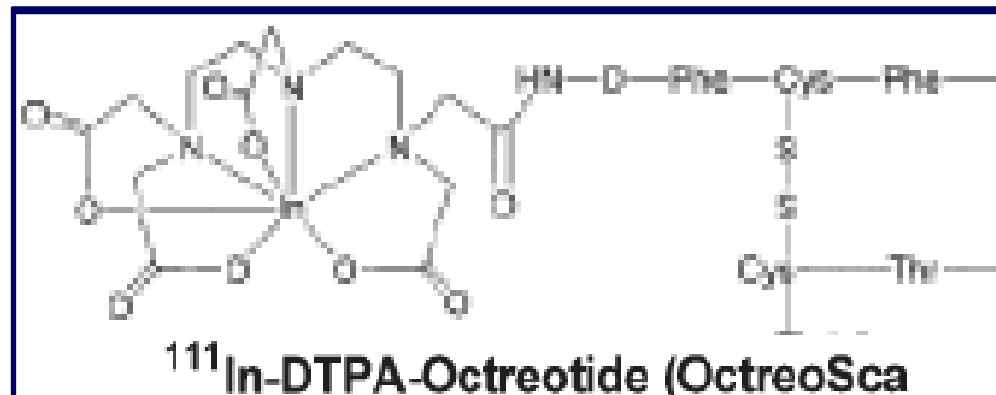


PET



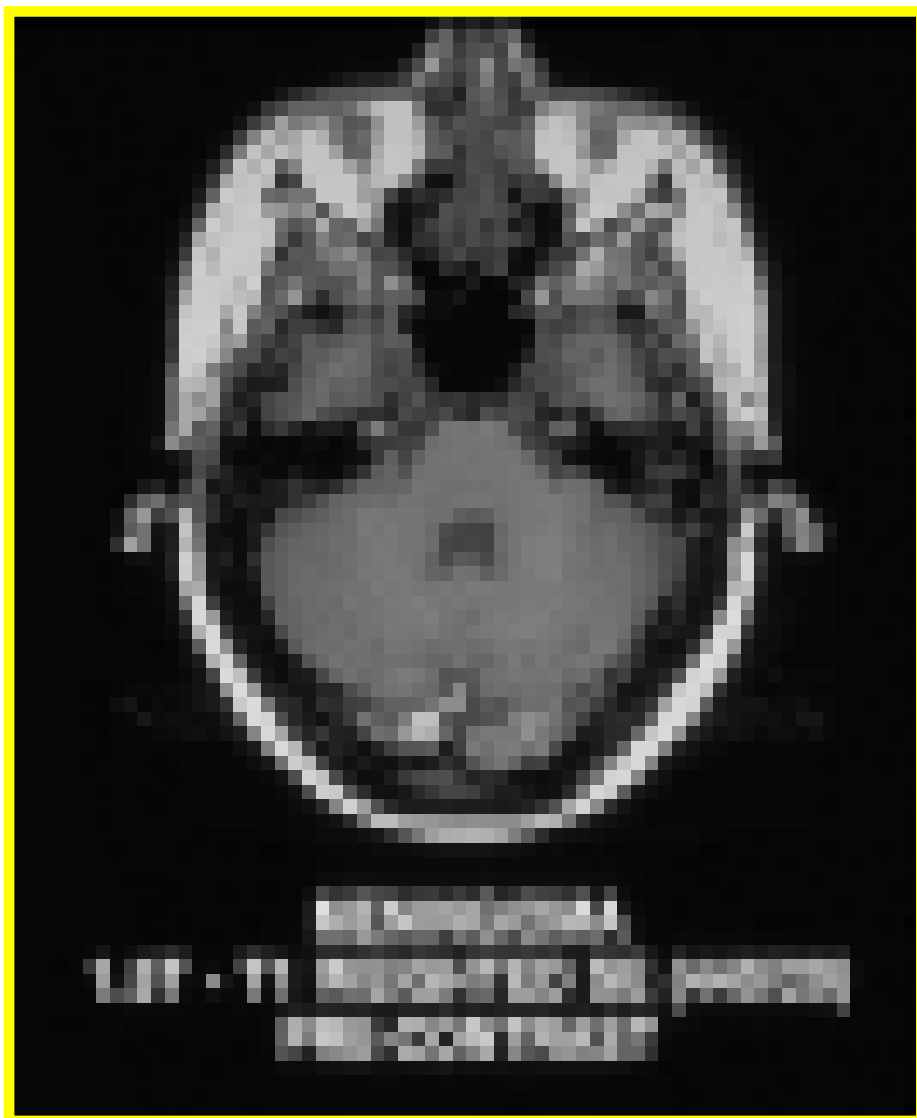
X-Ray

SPECT



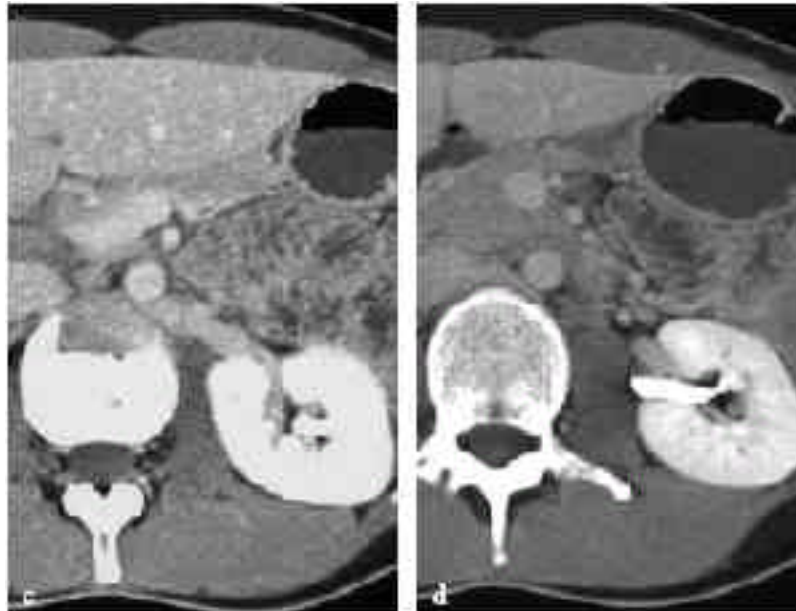
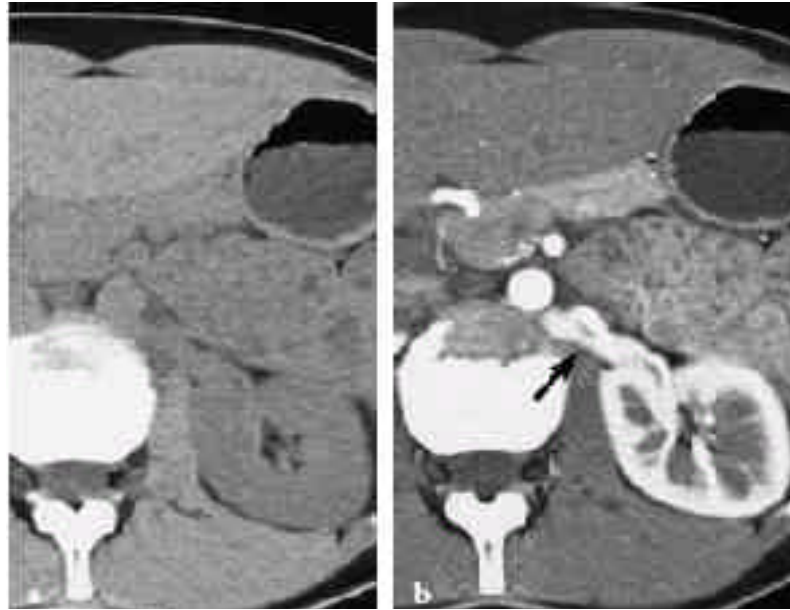
US

# Contrast Agents usage: some examples





# Contrast Agents usage: some examples



Angiogram

Main Areas: oncology, cardiovascular and neurology

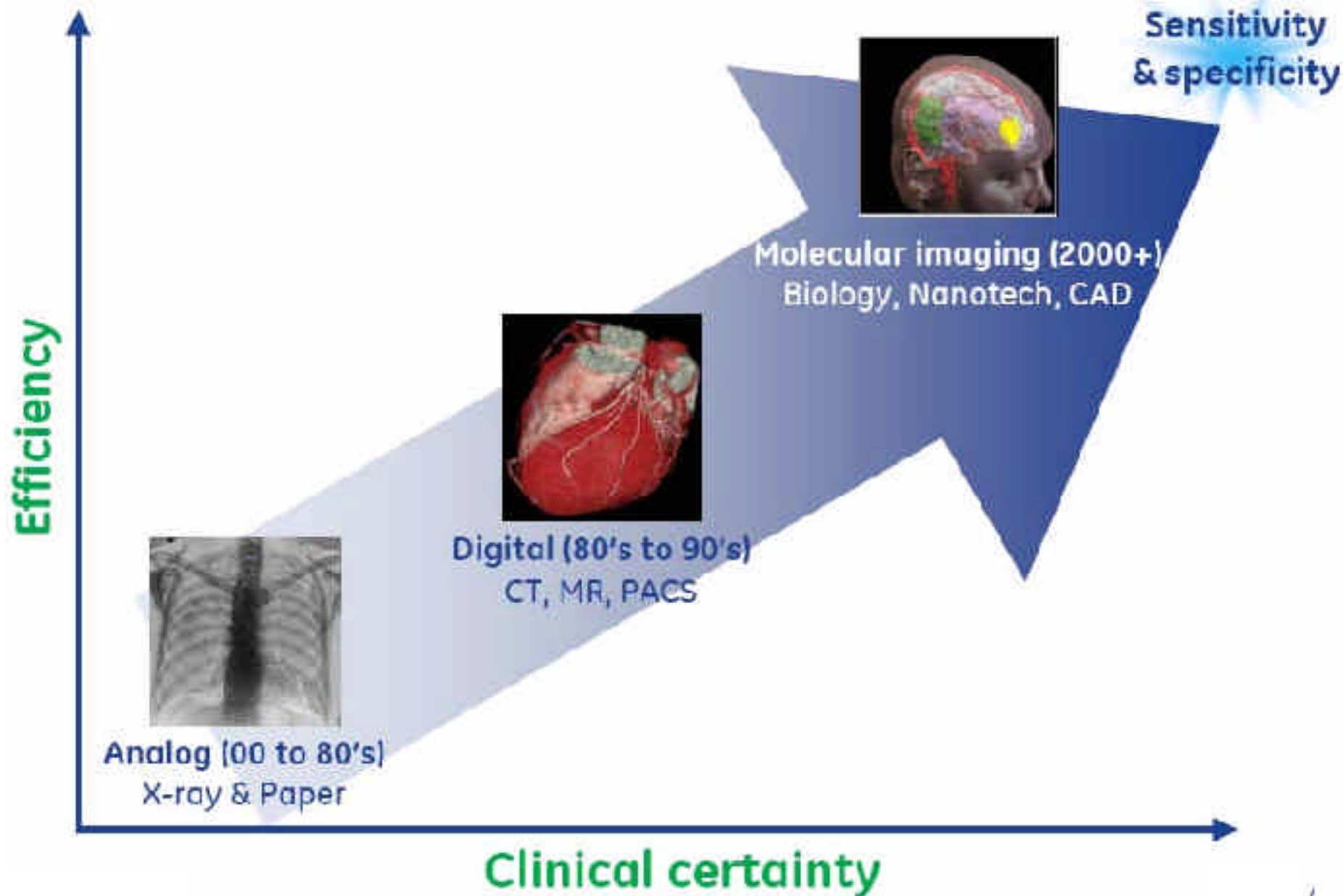
➤ Integrated solutions able to:

- ❑ Improve accuracy of diagnosis
- ❑ Guide the course of the treatment
- ❑ Understand the nature of the disease in order to predict the responders to a therapy (Molecular Medicine)
- ❑ Patients Follow up



Strong focus on improvement of  
Patient Management

# Medical Imaging and Molecular Imaging



# What is Molecular Imaging?

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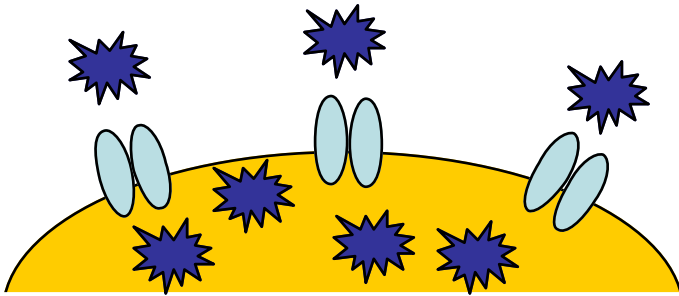
- ❑ Uses imaging technologies to assess biological activity in the body
- ❑ In vivo characterization of and measurement of biological process at cellular and molecular level
- ❑ Probe the molecular abnormalities at the basis of disease rather than imaging the end effects of the molecular alterations

*The practice of Medical Imaging in the era of Molecular Medicine*

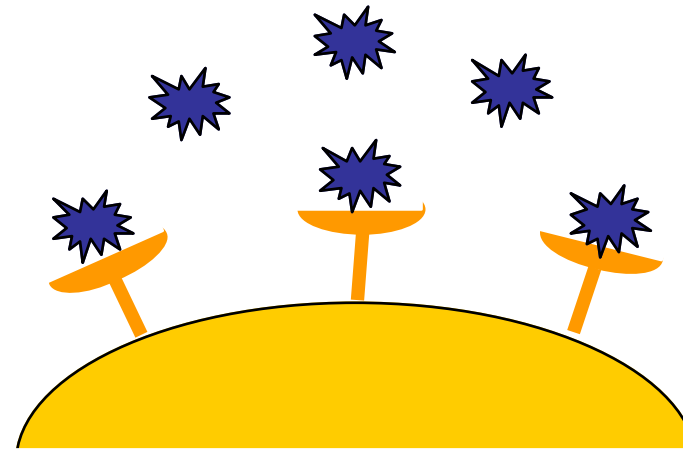




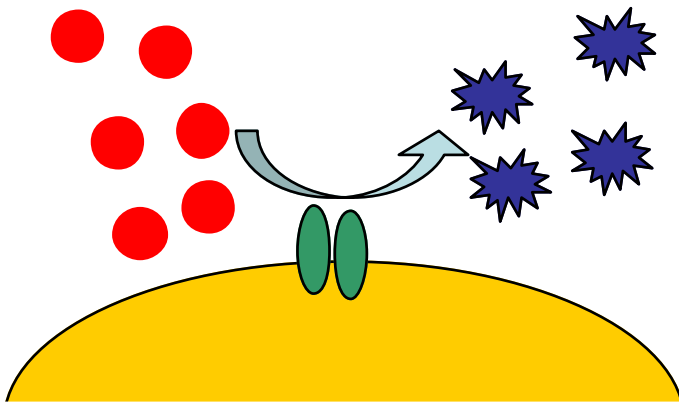
# Molecular imaging approaches



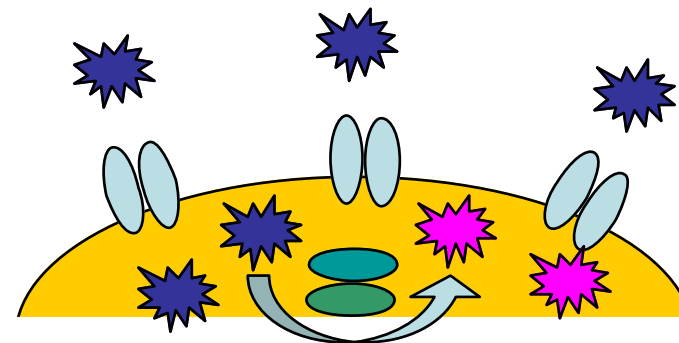
**Intracellular  
Accumulation**



**Molecular targeting**



**Enzymatic activity**



**Metabolic activity**

# Microtechnology and Ultrasound Imaging



<http://www.toshiba-europe.com/Medical/Materials/Visions:> *Magic Microbubbles*

**WebMDdaily** *Microbubbles: The Medicine of the Future?*

**BBC NEWS**: *Microbubbles to diagnose cancer*

**ScienceDaily**

*Microbubbles Can Image Blood Vessel Growth In Tumors*

**American Heart Association**  
*Learn and Live.*

*Imaging Tumor Angiogenesis With Contrast Ultrasound and Microbubbles*

**PHYSORG.COM**  
SCIENCE · PHYSICS · TECH · NANO · NEWS

*Nanoparticles and Lasers Create Cancer-Killing Microbubbles...*

**Radiology 2008**

**Science to Practice:** Can Contrast-enhanced US with Targeted Microbubbles Monitor the Response to Antiangiogenic Therapies?

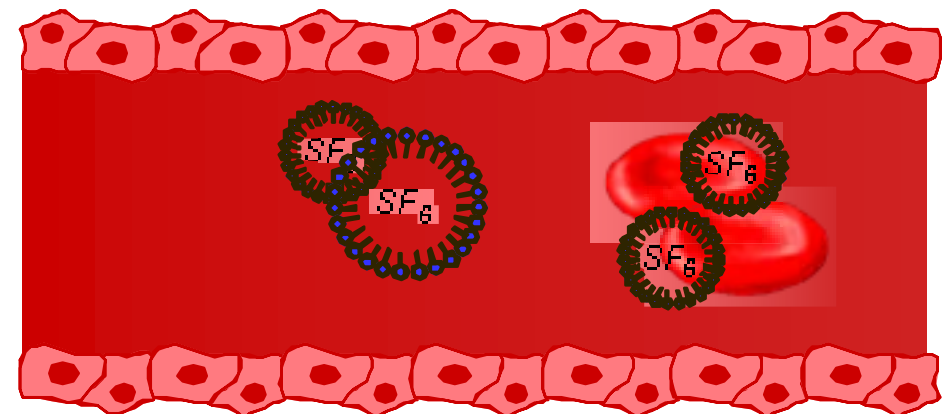
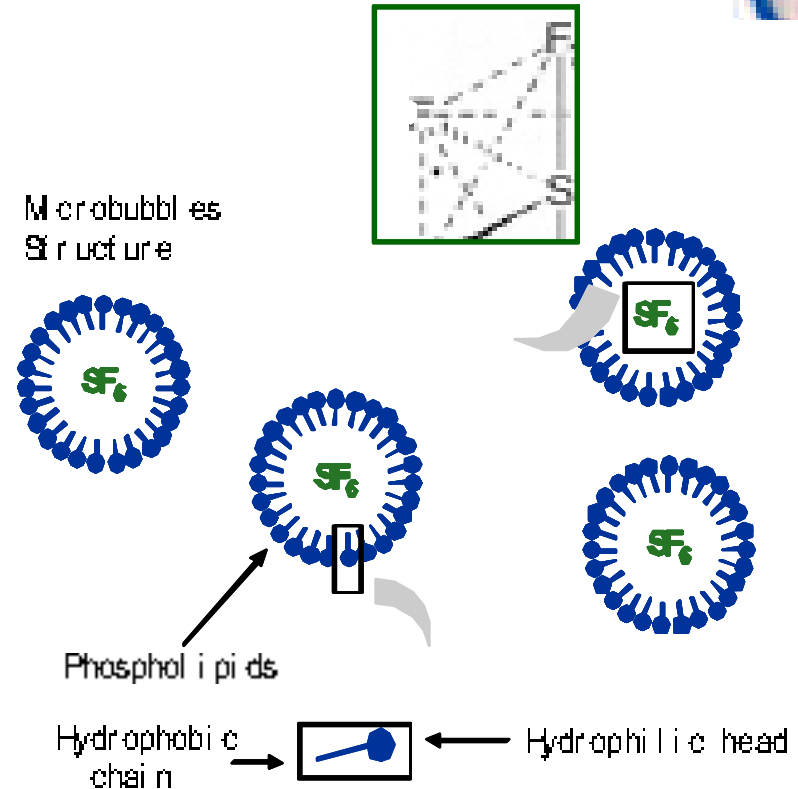
**CNN's live-show on Microbubbles and Ultrasound Contrast Agent**



# Microtechnology and Ultrasound Imaging

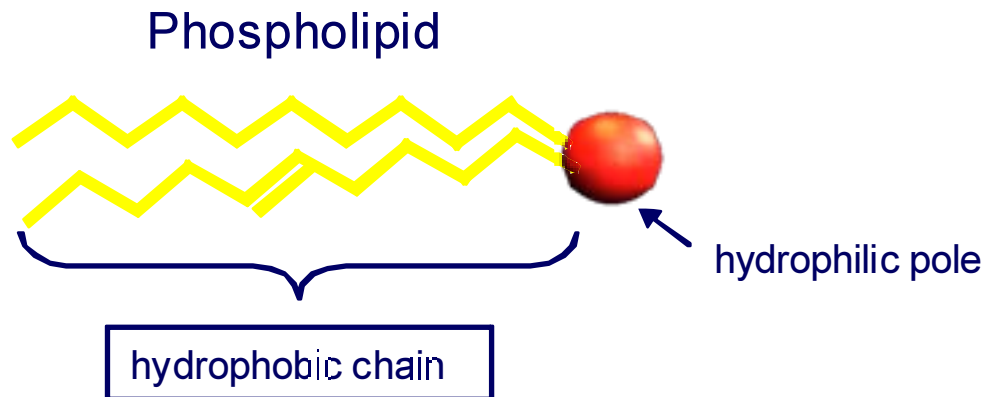
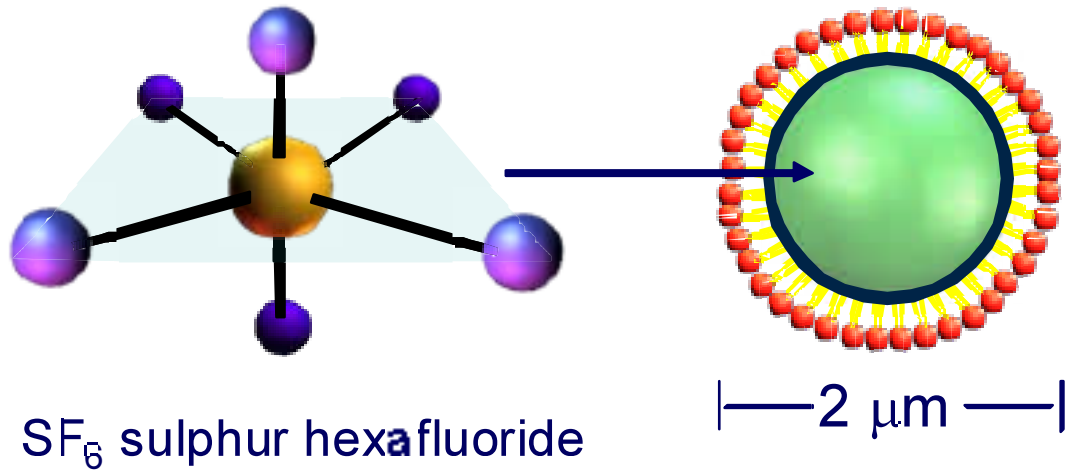


Contrast in ultrasound arises from different compressibilities of tissues. As compressibility in gases is orders of magnitude higher than that of fluids (tissues), gas-filled microbubbles are sensitive ultrasound contrast agents.





## Ultrasound Imaging: Gas-microbubbles

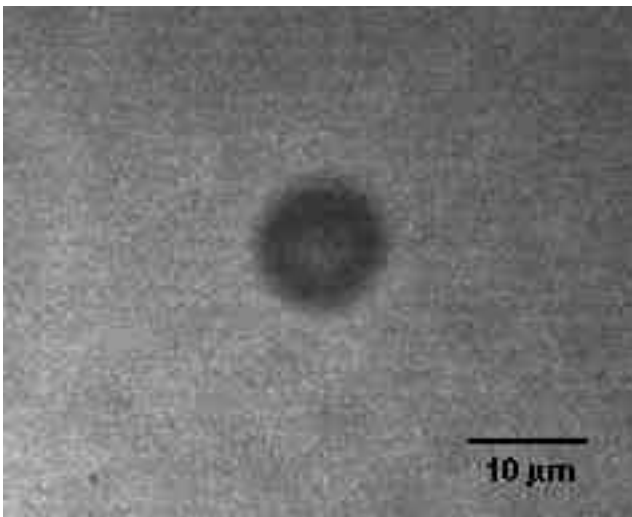


### SonoVue™ kit



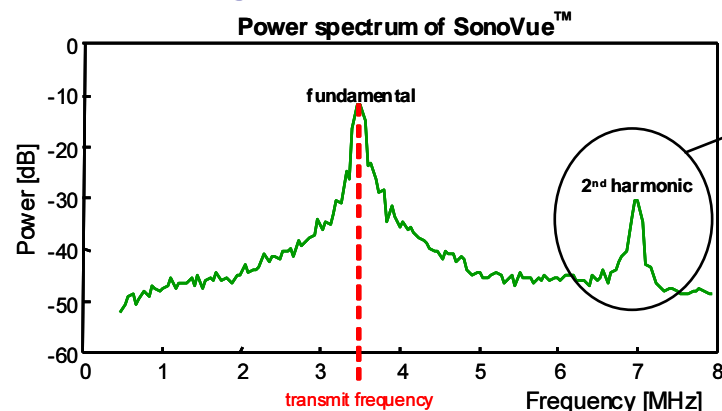


# Acoustic properties of soft-shell agents

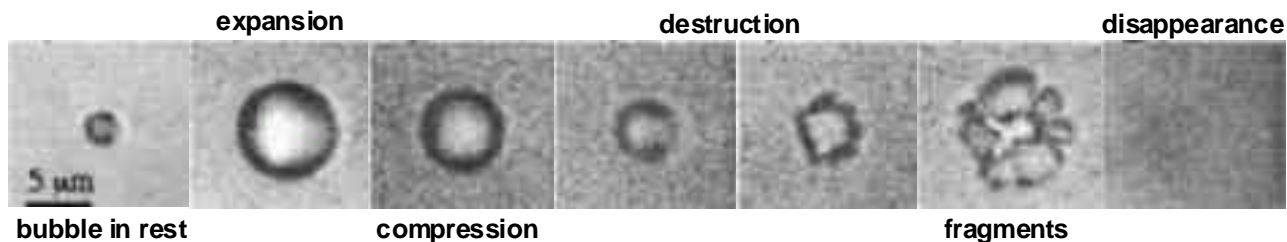


- Bubble oscillates linearly at extremely low acoustic pressures.
- Bubble oscillates **nonlinearly** (higher harmonics) at slightly higher acoustic pressures.

=> basis for contrast agent specific detection techniques!



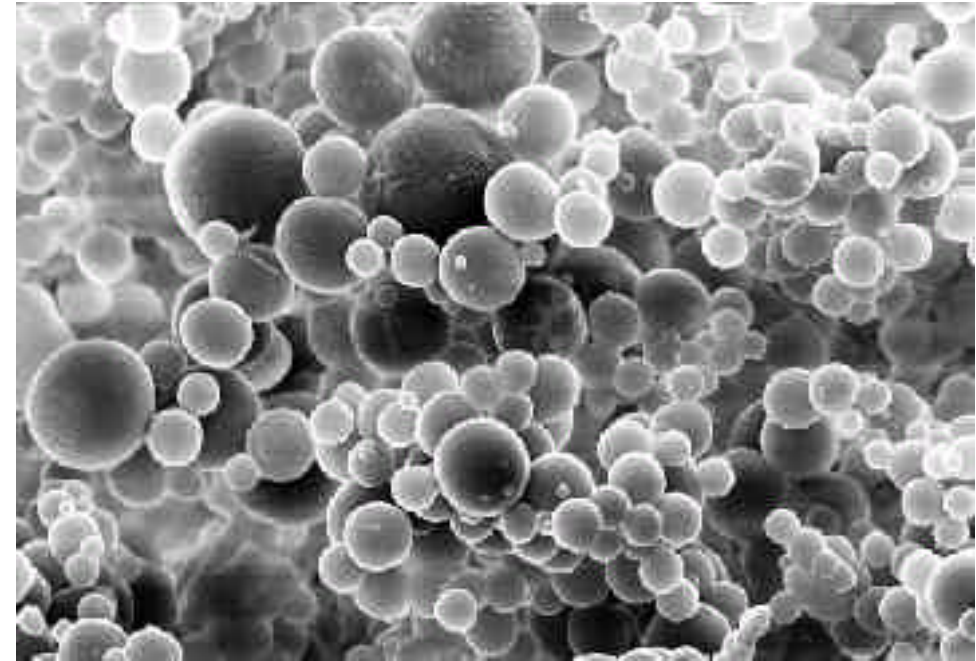
At high acoustic pressure, contrast agent microbubbles can be destroyed.



High-speed camera recording (K. Ferrara - UC Davis).

Bubble destruction may be used for local perfusion quantification, by monitoring replenishment.

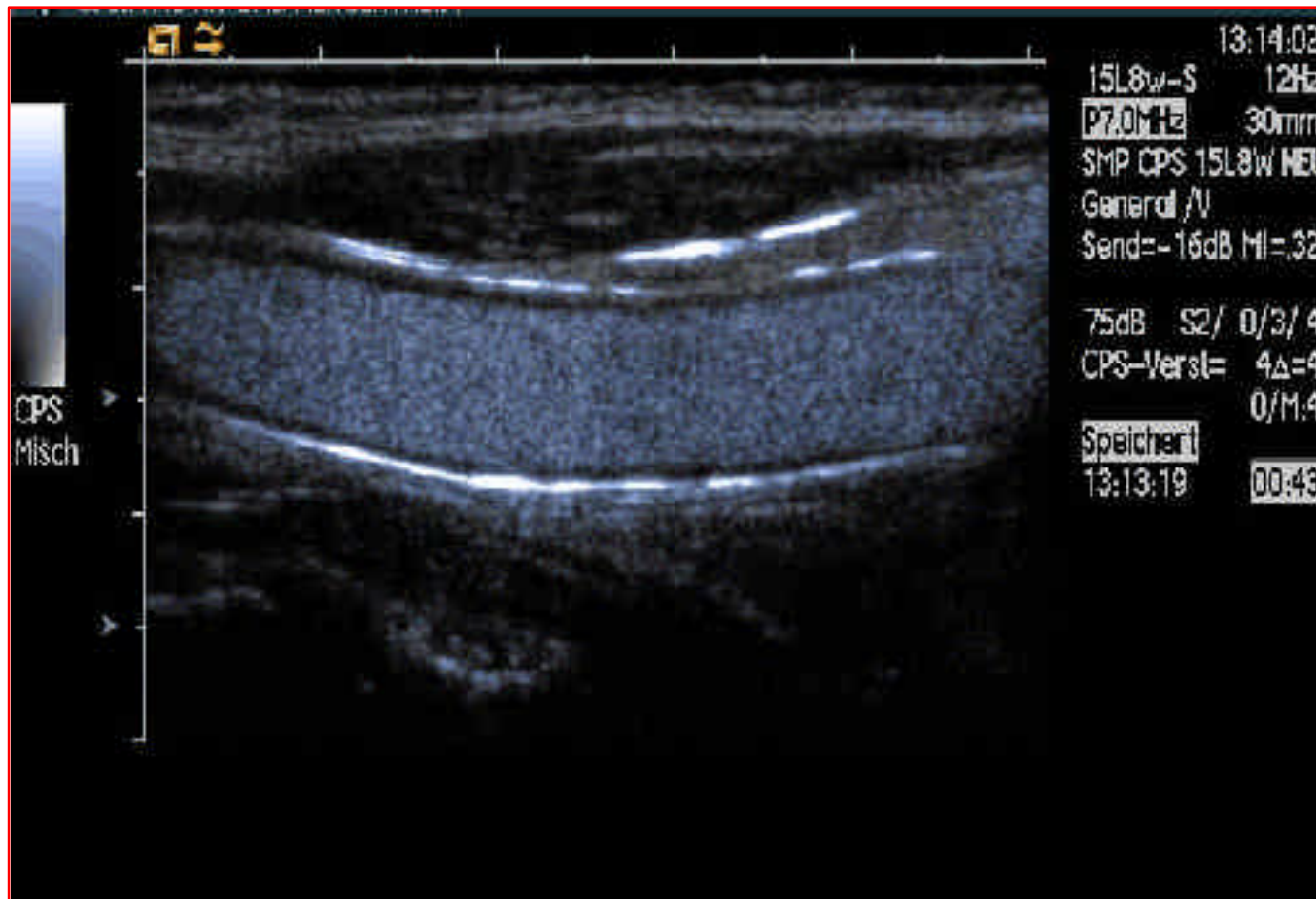
$$T = \frac{r_0^2 \cdot \rho}{2D \cdot C_b}$$



- Bubble radius **r**
- Gas density  **$\rho$**
- Diffusion coeff. **D**
- Conc. gas in blood  **$C_b$**

# Atherosclerotic plaques (CEUS )

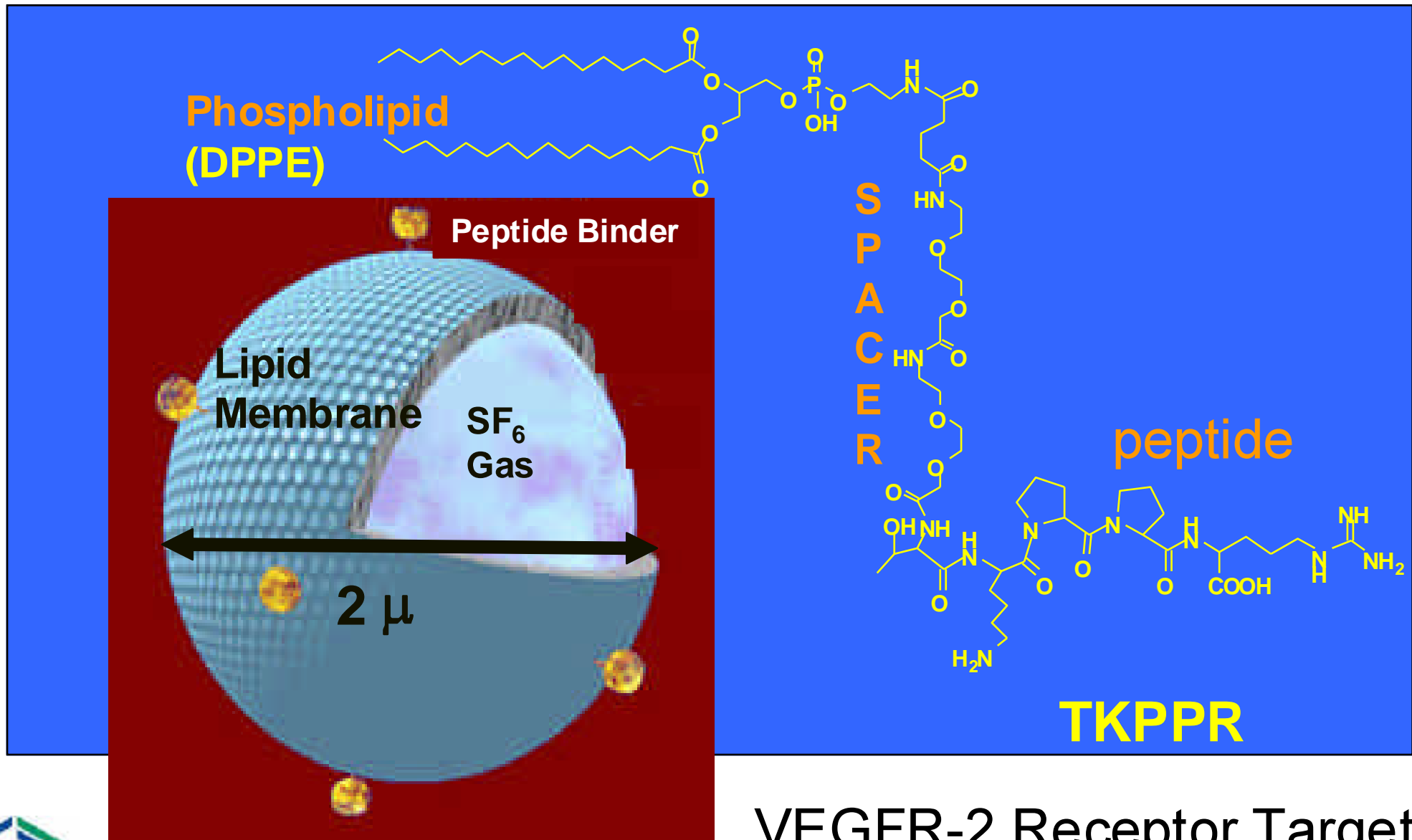
## Detection of vulnerable plaques of carotid



Prof. Dietrich, Bad Mergentheim, D

Presence de microcirculation inside the plaques might indicate the instability of the plaques

# New microparticles platforms for Ultrasound



VEGFR-2 Receptor Targeting



# New microparticles platforms for Ultrasound

Signal obtained in two different tumor models with KDR-targeted Echo III bubbles

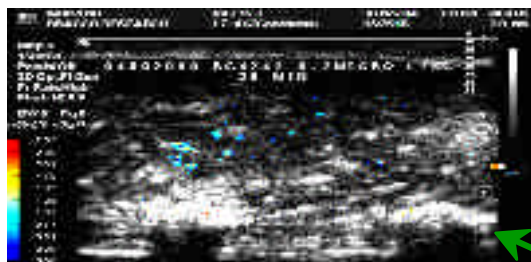
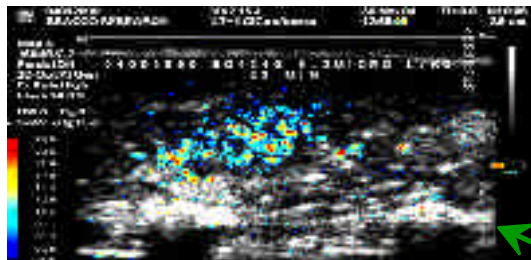
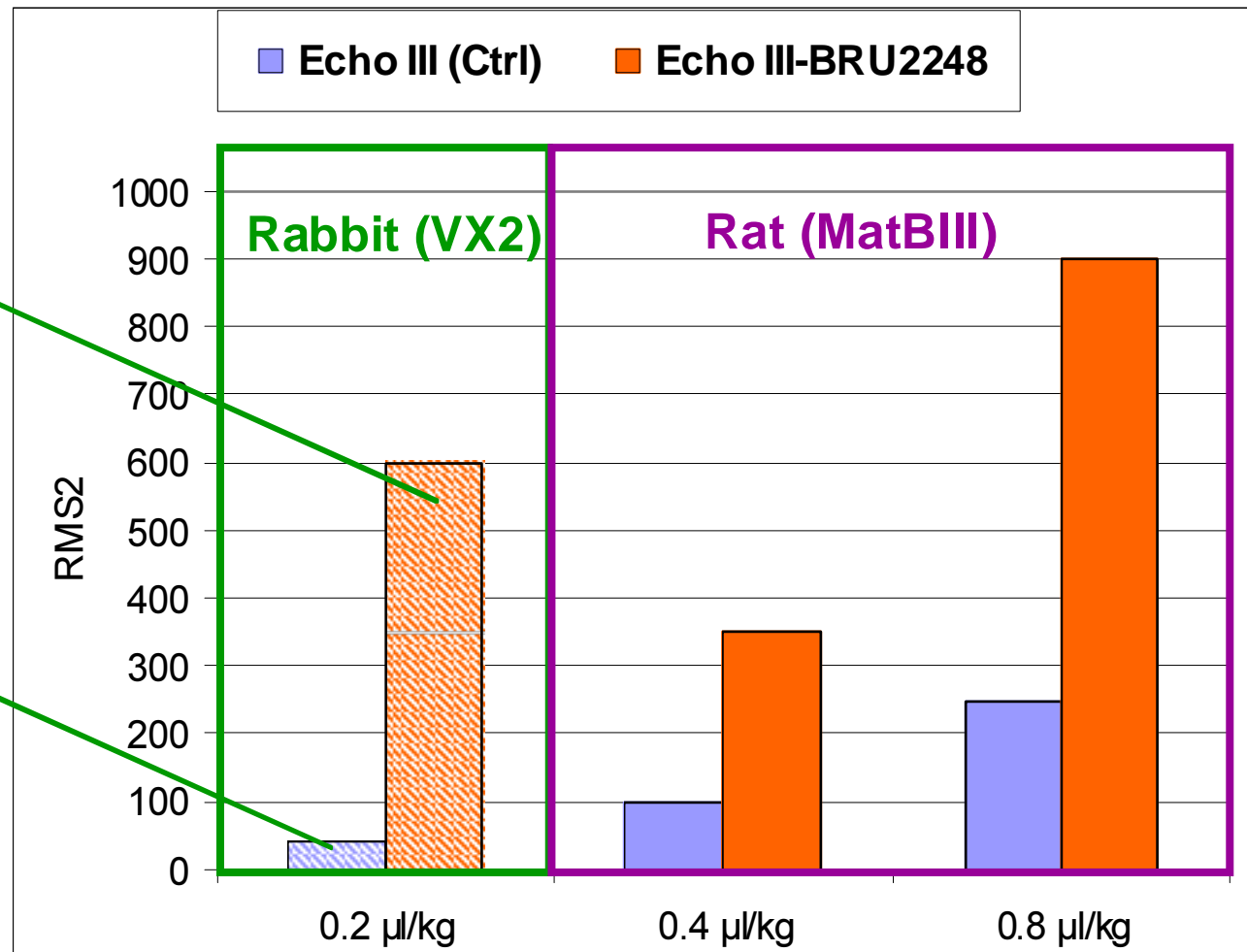


Image obtained 25 min post-injection

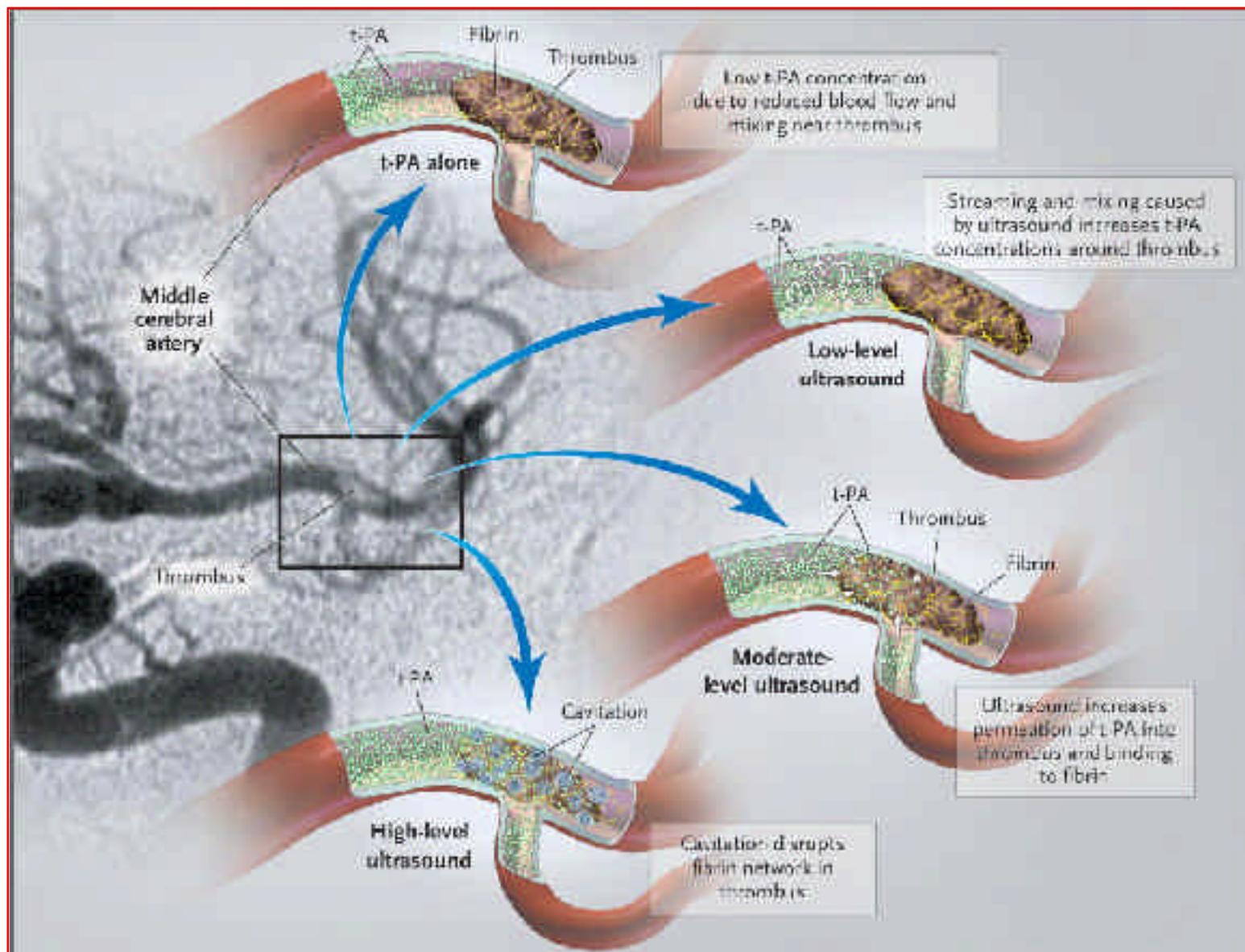


# New microparticles platforms for Ultrasound

## Ultrasound guided thrombolysis



Tissue plasminogen activator it is a serine protease that catalyzes the conversion of plasminogen to plasmin, the major enzyme responsible for clot breakdown





MR sagittal image of human head

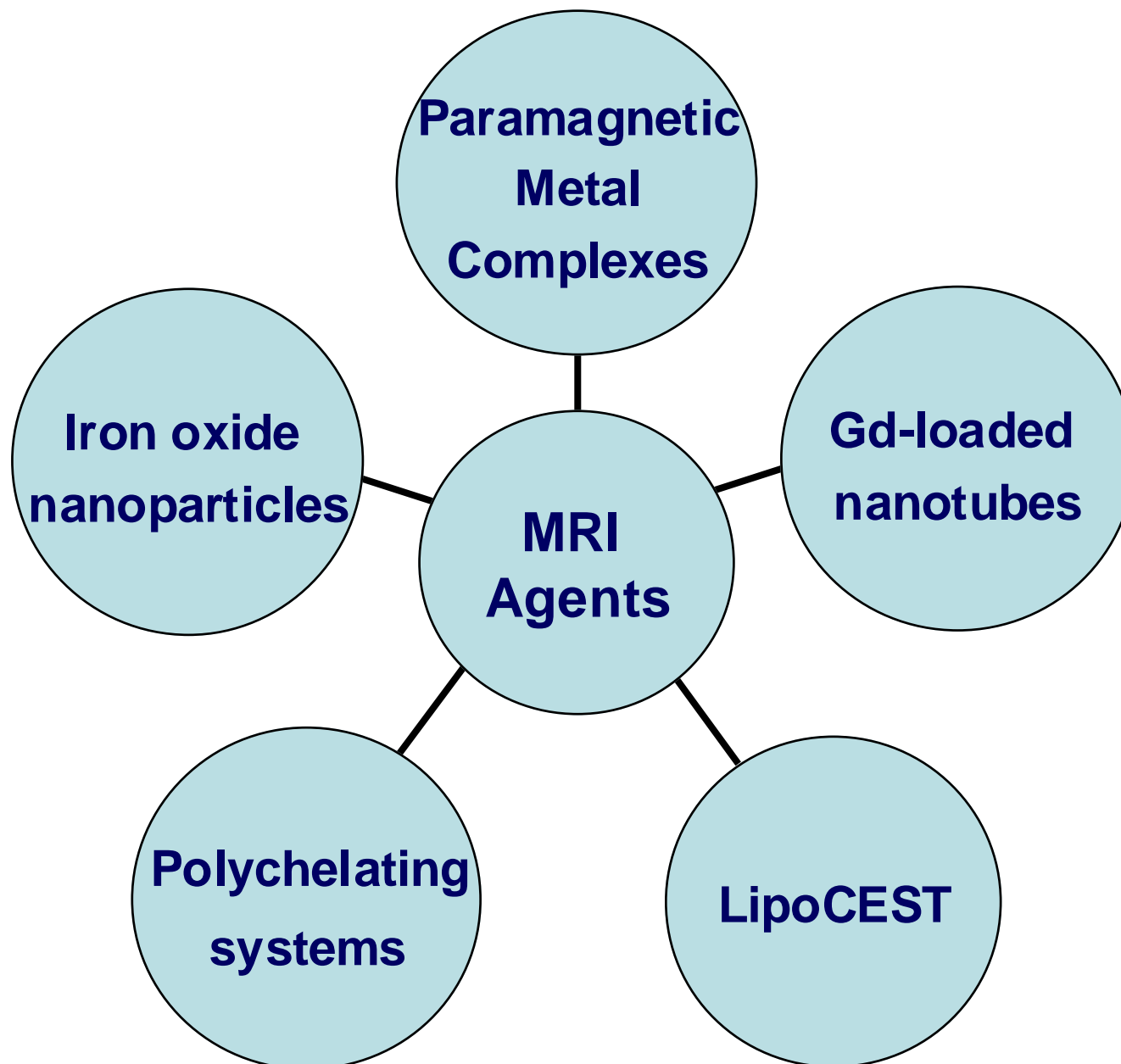
- Non-invasive and safe technique
- Great spatial resolution (mm scale)
- Outstanding diagnostic capability

A MR-image represents a map of the intensity of the  $^1\text{H}$ -NMR signal of water protons

The contrast is mainly generated by difference in the relaxation times ( $T_1$  and  $T_2$ ) of water protons

# Alternative platforms for MRI CA Design

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# Superparamagnetic Particles for MRI

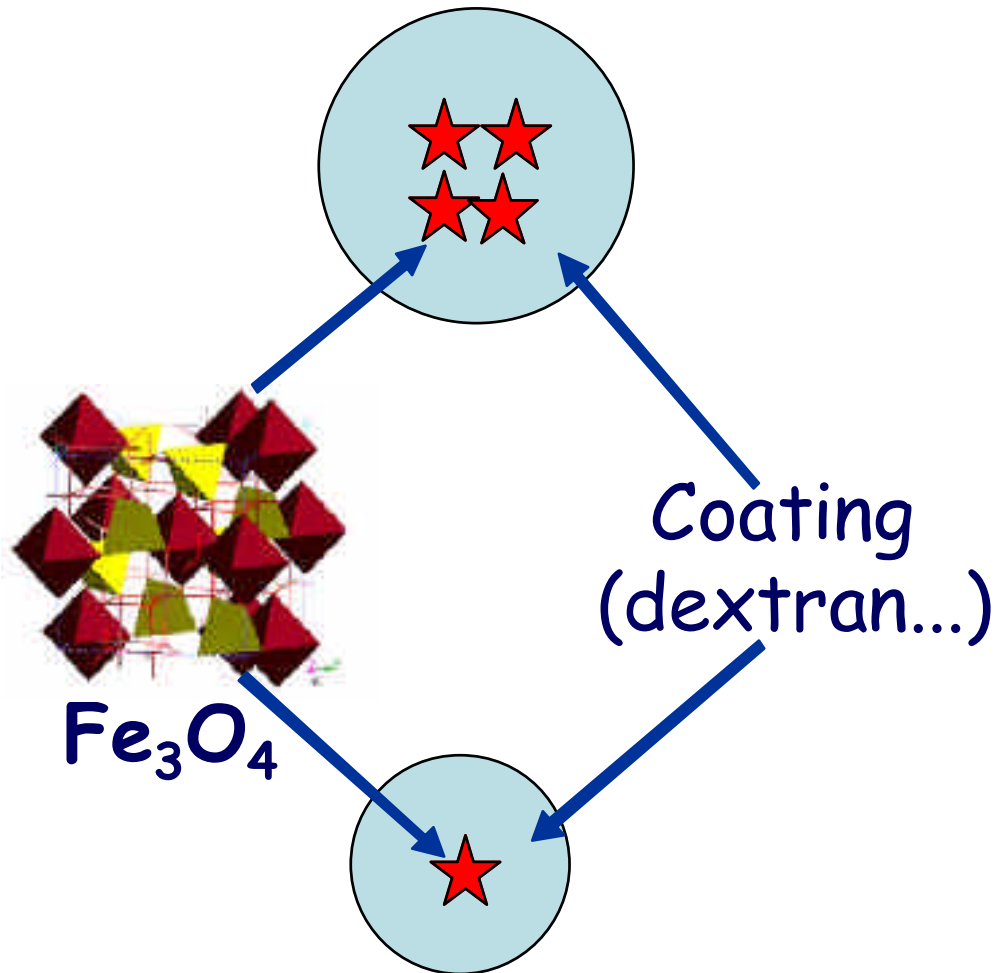
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Normally, coupling forces in ferromagnetic materials cause the magnetic moments of neighboring atoms to align, resulting in very large internal magnetic field.

When the thermal energy is sufficient to overcome the coupling forces the atomic magnetic moments can fluctuate randomly and the material exhibits paramagnetic behavior.

Superparamagnetism occurs when the material is composed of very small crystallites (1-10 nm).



## SPIO

Endorem®

Internal diameter = 4.3-4.8 nm

Particle diameter = 200 nm

(Superparamagnetic Iron Oxides)

## USPIO

Sinerem®

Internal diameter = 4.3-4.9 nm

Particle diameter = 50 nm

(Ultrasmall Superparamagnetic Iron Oxides)



# Iron Oxides particles for MRI

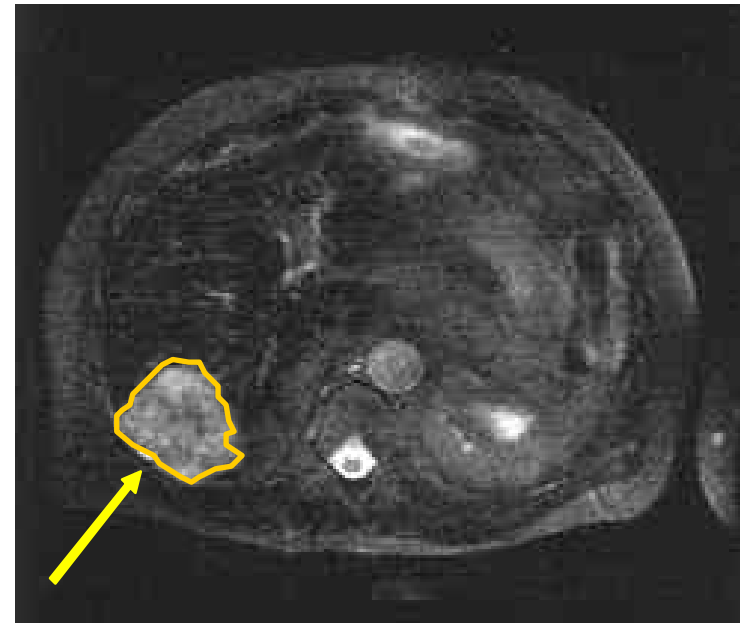


Reference	Chemical composition	Particle size (nm)	Surface coating	Application	Year
1	Fe <sub>3</sub> O <sub>4</sub>	10-15	None	Contrast agent	1980
2	Fe <sub>3</sub> O <sub>4</sub>	10-15	PAA	Contrast agent	1990
3	Fe <sub>3</sub> O <sub>4</sub>	10-15	PAA, PEG	Contrast agent	1995
4	Fe <sub>3</sub> O <sub>4</sub>	10-15	PAA, PEG, BSA	Contrast agent	2000
5	Fe <sub>3</sub> O <sub>4</sub>	10-15	PAA, PEG, BSA, Chitosan	Contrast agent	2005
6	Fe <sub>3</sub> O <sub>4</sub>	10-15	PAA, PEG, BSA, Chitosan, Hyaluronic acid	Contrast agent	2010
7	Fe <sub>3</sub> O <sub>4</sub>	10-15	PAA, PEG, BSA, Chitosan, Hyaluronic acid, Folic acid	Contrast agent	2012
8	Fe <sub>3</sub> O <sub>4</sub>	10-15	PAA, PEG, BSA, Chitosan, Hyaluronic acid, Folic acid, Aptamer	Contrast agent	2015
9	Fe <sub>3</sub> O <sub>4</sub>	10-15	PAA, PEG, BSA, Chitosan, Hyaluronic acid, Folic acid, Aptamer, Gold nanoparticles	Contrast agent	2018
10	Fe <sub>3</sub> O <sub>4</sub>	10-15	PAA, PEG, BSA, Chitosan, Hyaluronic acid, Folic acid, Aptamer, Gold nanoparticles, Quantum dots	Contrast agent	2020

# Iron Oxides particles for MRI: some examples



**MRI image of liver metastasis before the administration of contrast agent**



**Following infusion of Endorem®, (Guerbert, UK), there is signal dropout in the normal liver, with increased definition of the metastasis**

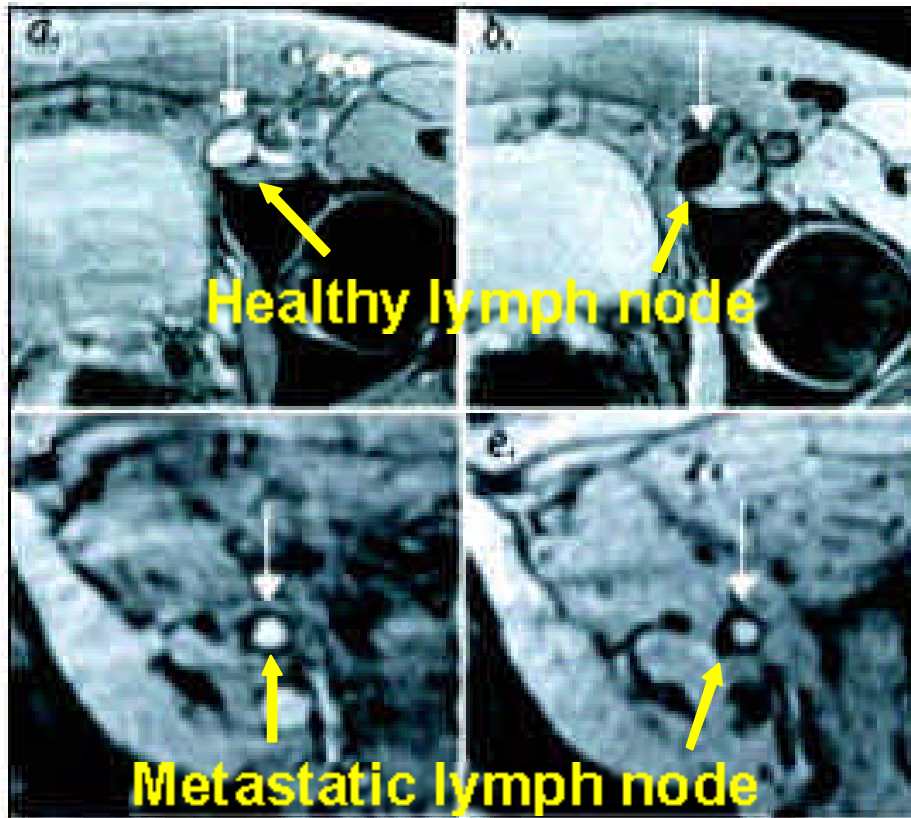
# Iron Oxides particles for MRI: some examples



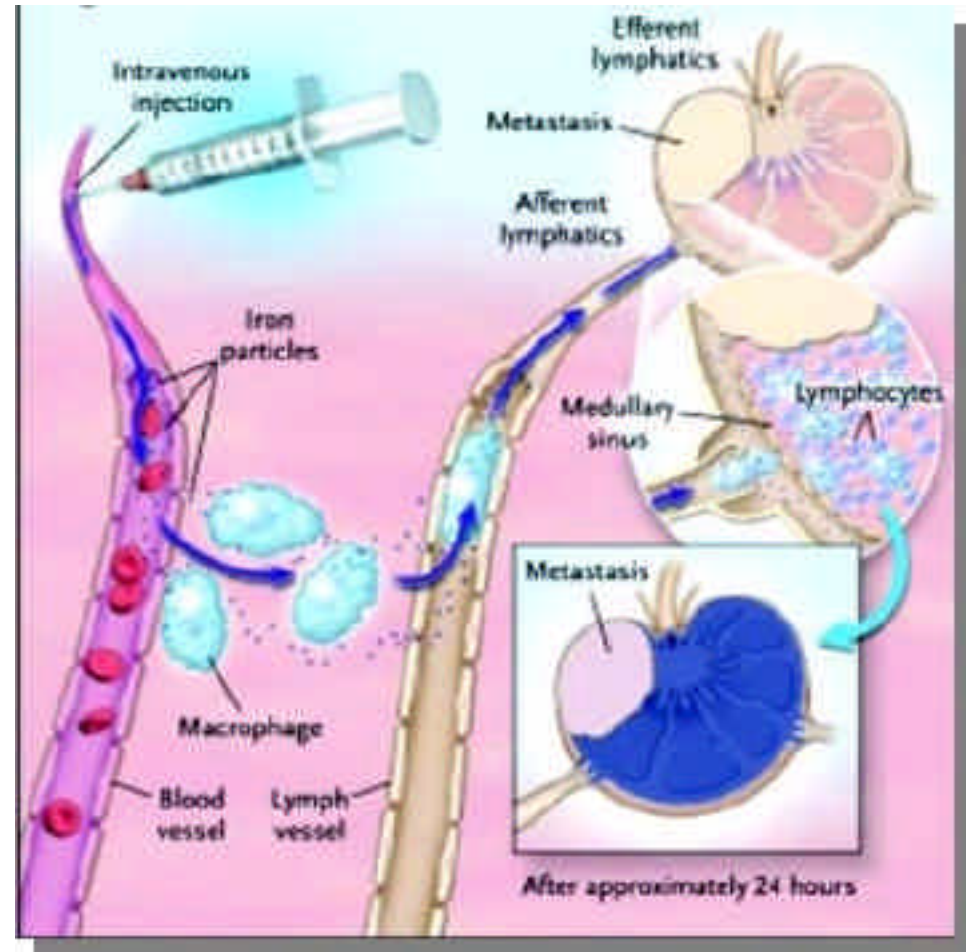
## Detection of lymph node metastases

Pre-contrast

Post-contrast



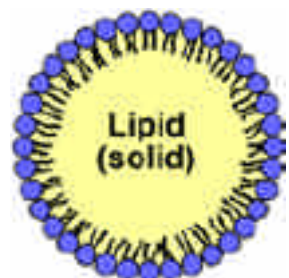
## Detection mechanism



# Self-assembled nanoparticles for MRI



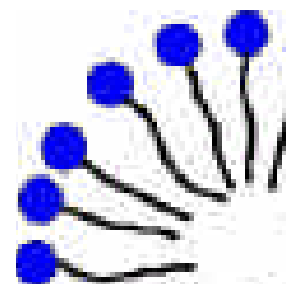
## Other nanostructured platforms under current evaluation



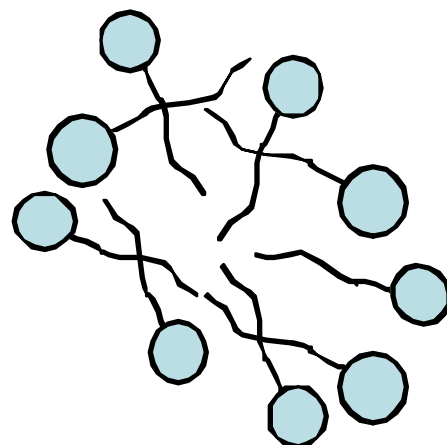
SLN



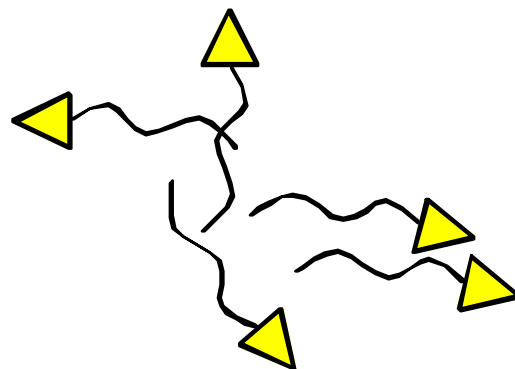
Liposome



Micelles



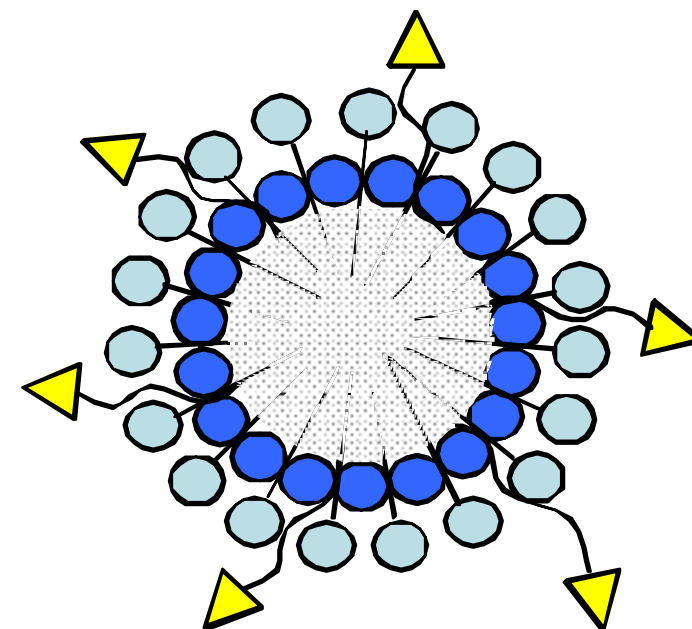
Amphiphilic  
Gd-complex



Target ligand

+

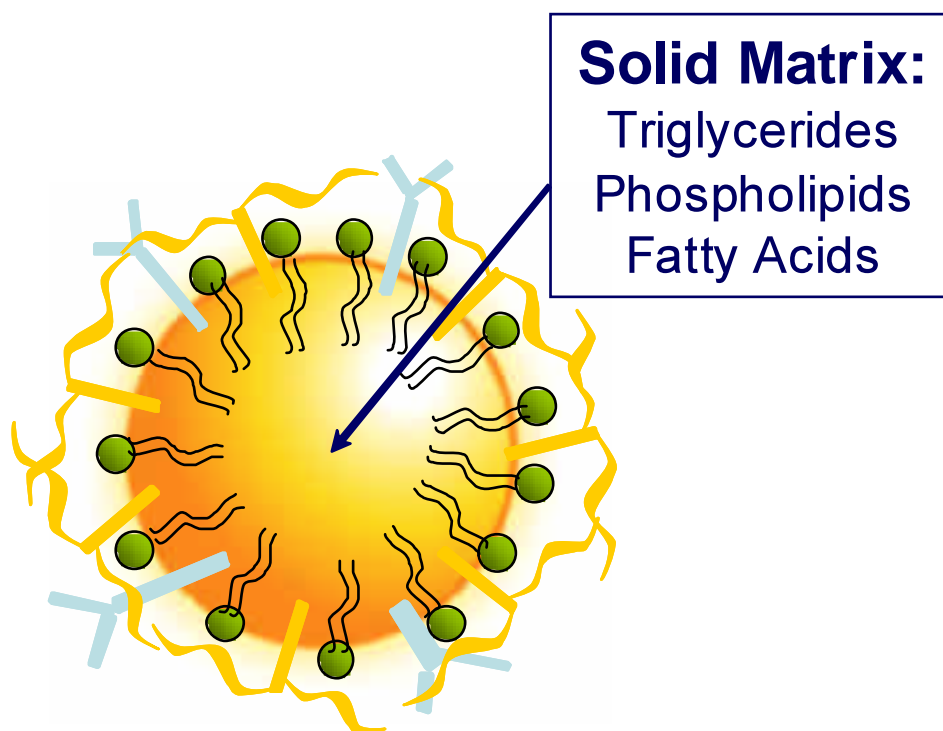
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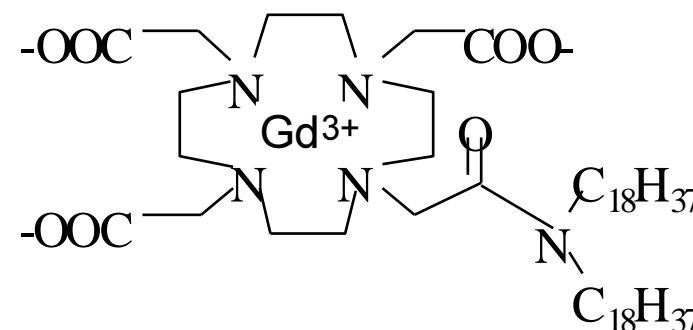
Nanostructured  
Gd-containing  
carrier

# Self-assembled nanoparticles: paramagnetic SLN

New MRI contrast agents platforms can be designed using Solid Lipid Nanoparticles



 **Imaging probe**



Stealth Agent



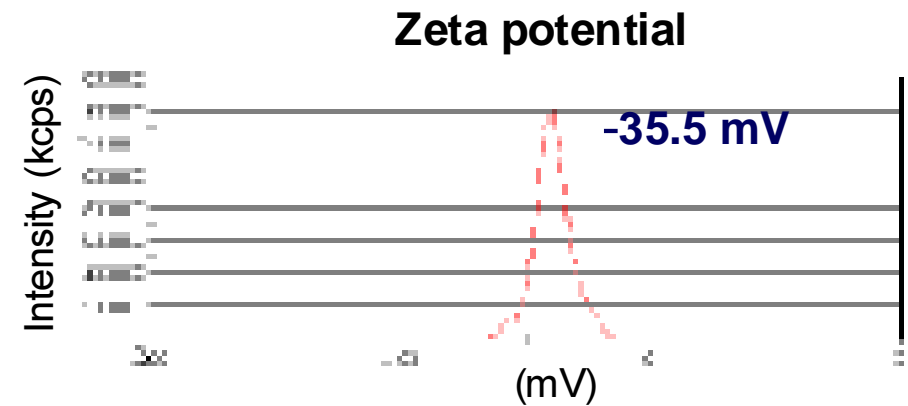
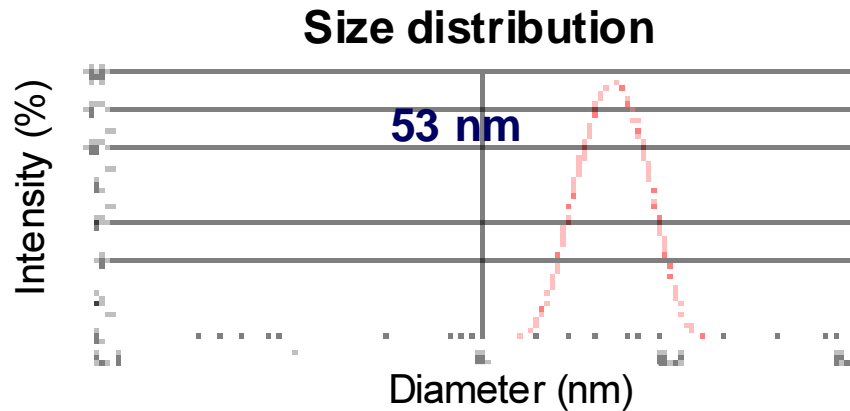
i.e. DSPE-PEG(2000)

Targeting Ligand



i.e. RGD

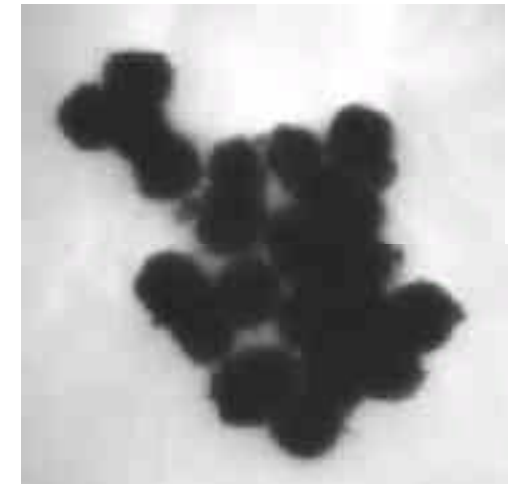
# Self-assembled nanoparticles: paramagnetic SLN



$$\frac{1}{T_1} = \frac{1}{T_{1d}} + r_1 \times [C]_p$$

20 MHz  
25°C, water

$1/T_{1d}$ (Empty SLN)	0.386 s <sup>-1</sup>
$r_1$ (SLN – Gd(III) )	23.41 mM <sup>-1</sup> s <sup>-1</sup>



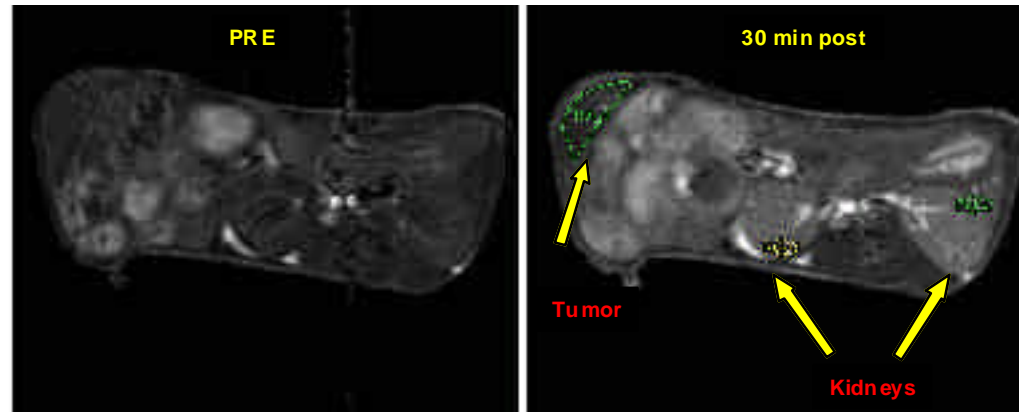




## - IGROV-1

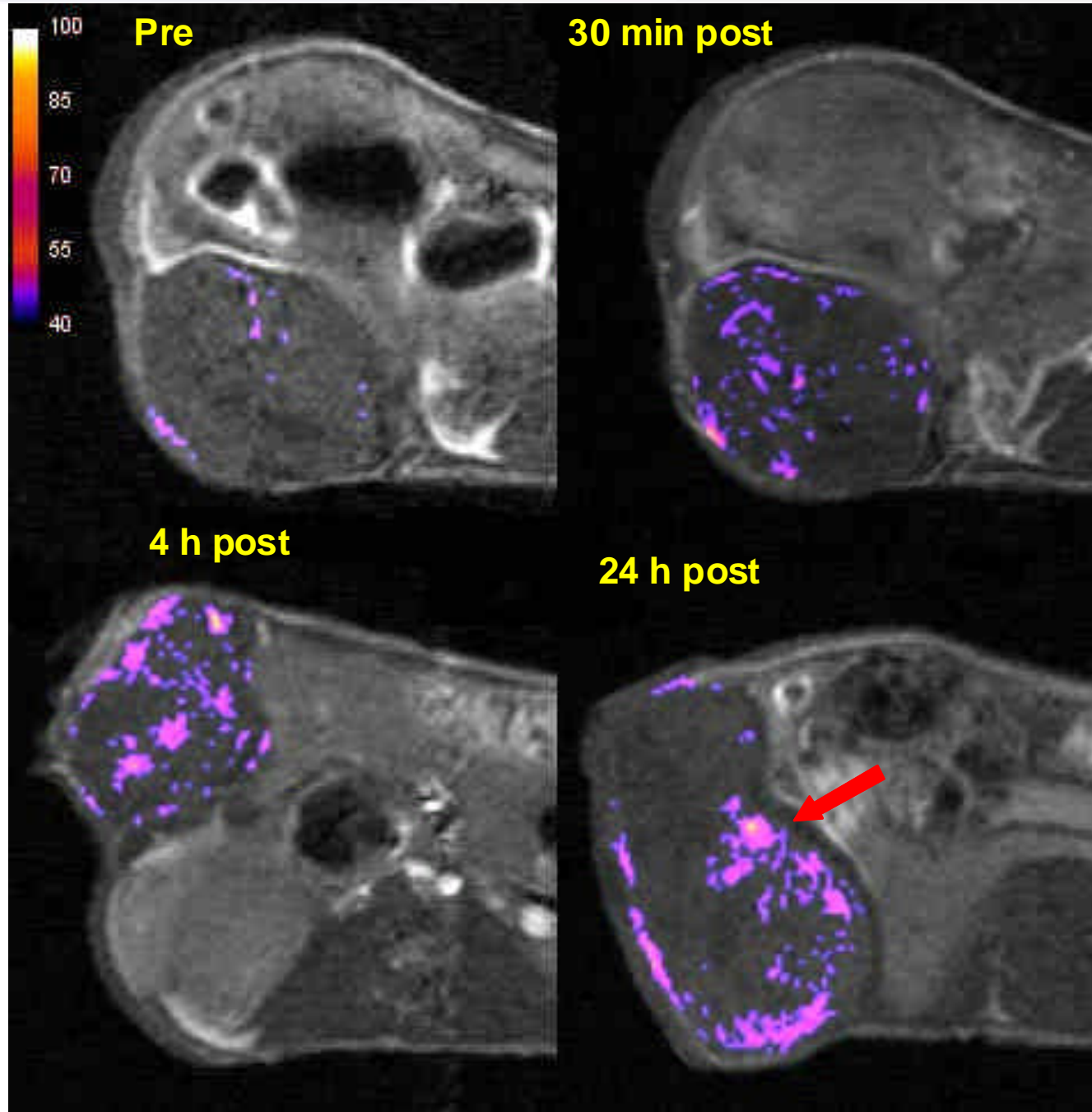
Ovarian carcinoma bearing Balb/C nu/nu mouse;  
10 million cells subcutaneously injected in the  
flank

3 weeks after:



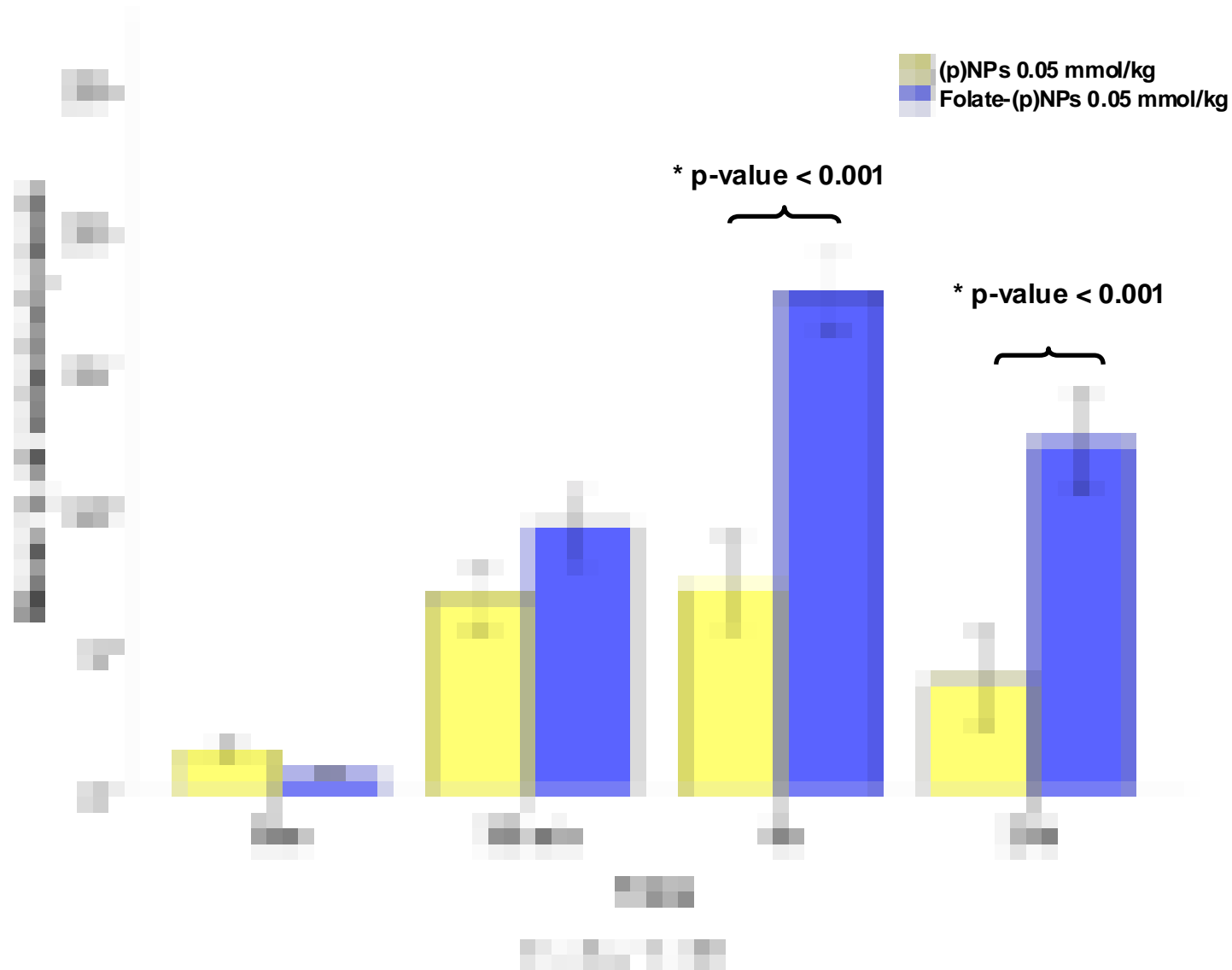
*MSME: TR / TE = 160 / 8.4 ms, FOV = 3.5 cm, NEX = 6*  
*spatial resolution in plane = 198  $\mu$ m*

# Tumor targeting: example of Folate-(p)SLNs results



Mouse a02:  
time course  
snapshots after  
Folate-loaded (p)NPs  
injection

# Tumor targeting: complete study results



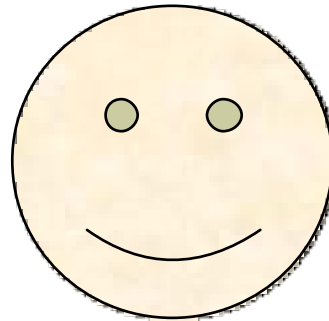
## Sensitivity

Equipments & post-processing

Amplification of signals

Higher signals from single probes

High extravasation in tissues



## Specificity

Pathology & Molecules

High affinity molecular vectors

Low RES uptake

## Safety

Biocompatible materials

Self-assembled systems

Extracellular agents

Short blood life-time

# Thank you for your attention



Rembrandt – Lezione di anatomia del professor Nicola Tulp - 1632