

Magnetic Resonance Imaging (MRI)



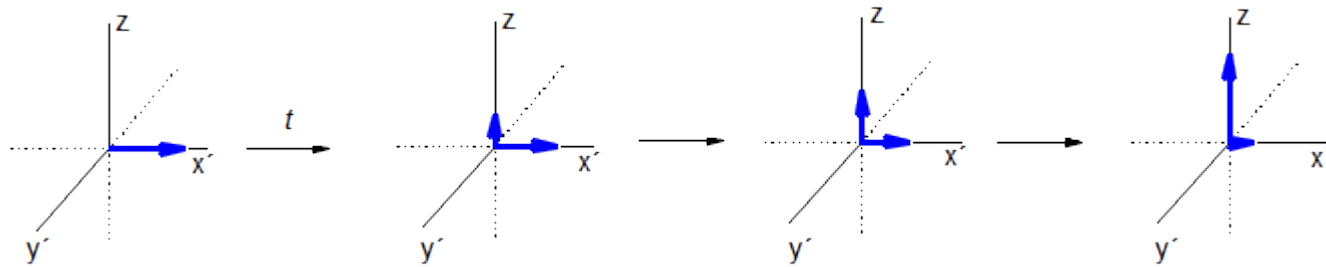
MR sagittal image of human head

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

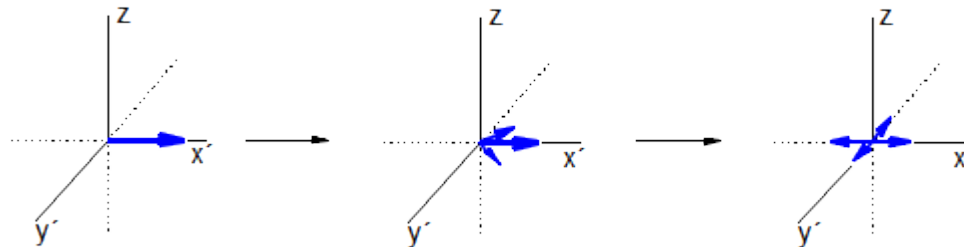
A MR-image represents a map of the intensity of the ^1H -NMR signal of water protons

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

T_1 Relaxation (Spin-Lattice Relaxation)



T_2 Relaxation (Spin-Spin Relaxation)



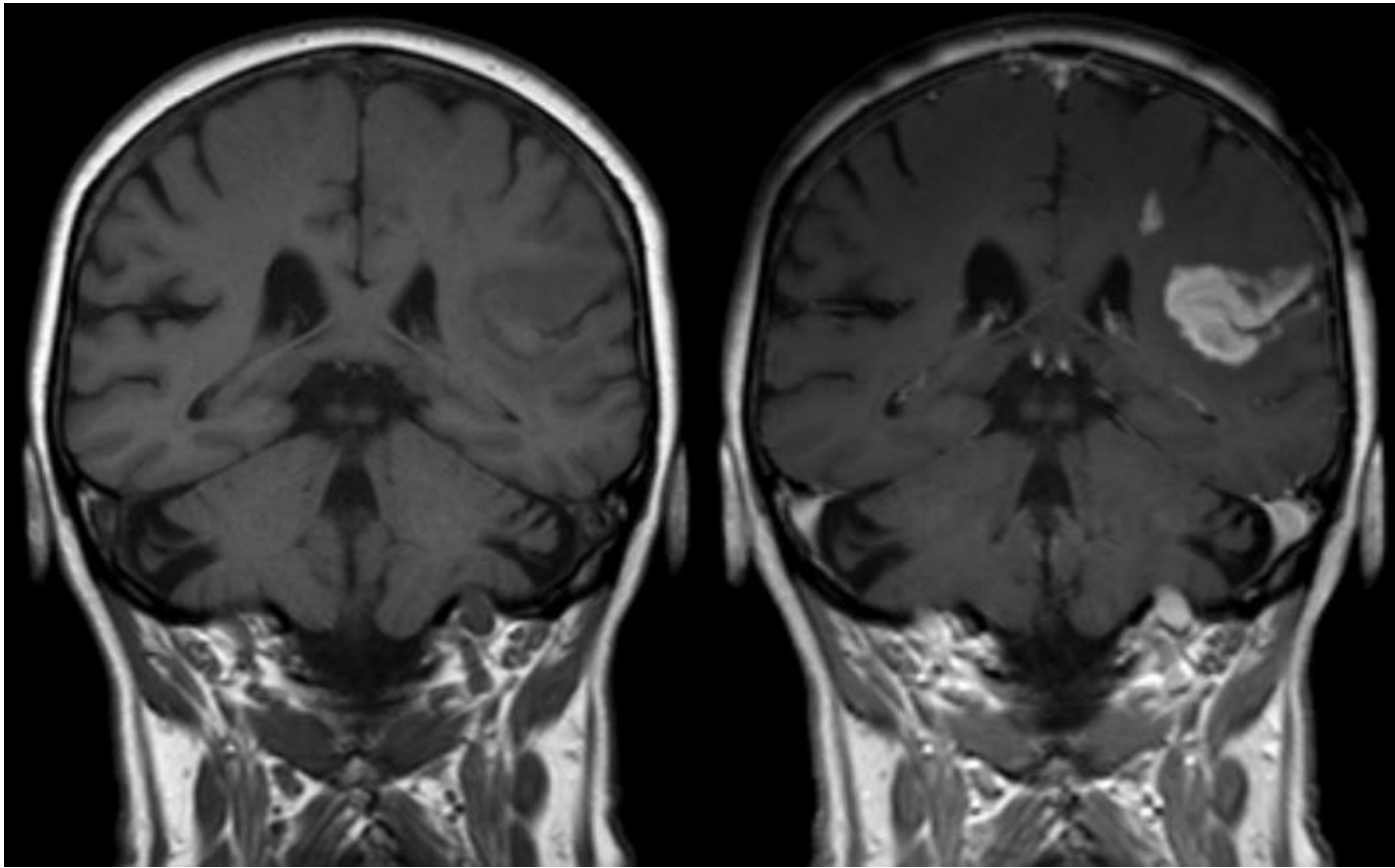
Contrast Agents (CA)

The purpose of a CA is to reduce T_1 (parallel to B_0) or T_2 (perpendicular to B_0) in order to obtain an hyper- or ipo-intense signal, respectively, in short times and with a better signal to noise ratio.

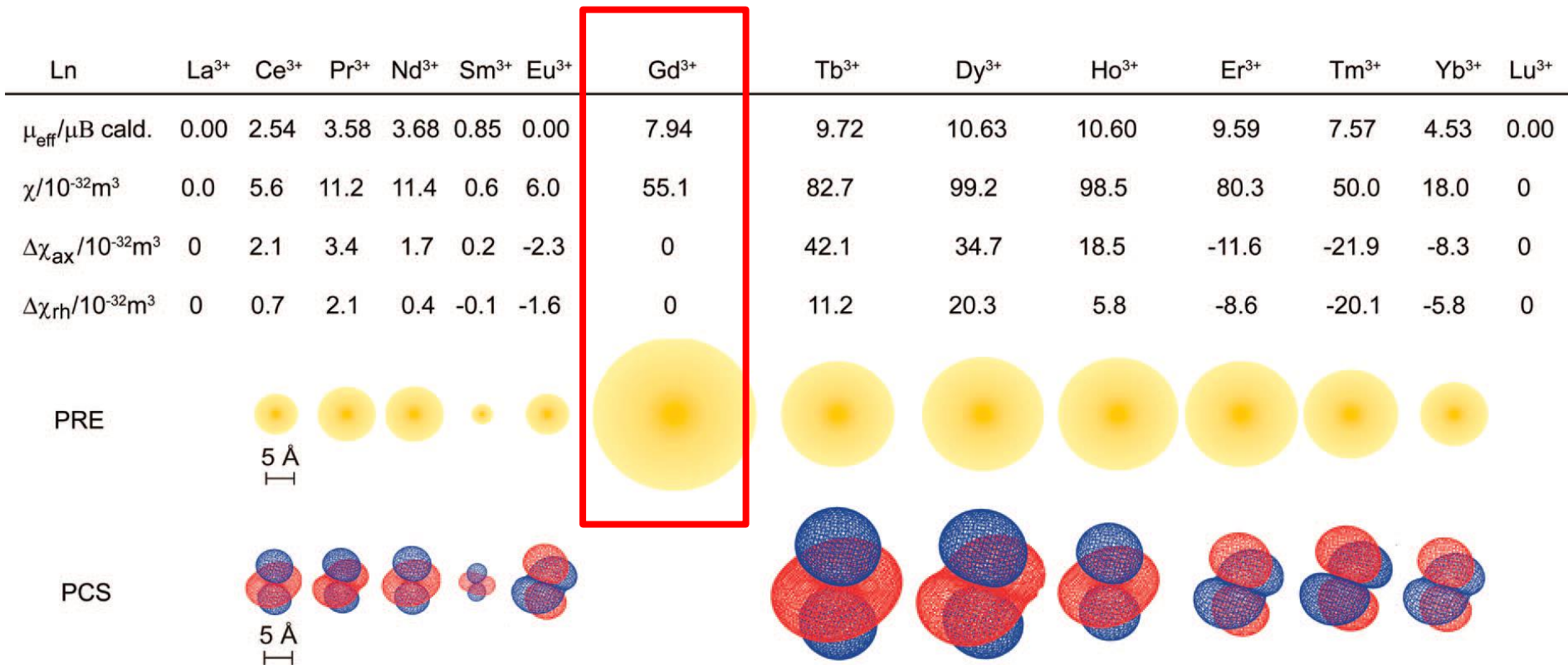
T_1 contrast agents (positive = hyper-intense signal):
paramagnetic metal complexes Mn(II), Gd(III)

T_2 contrast agents (negative = ipo-intense signal):
small super-paramagnetic iron oxide particles (SPIO) and ultra-small super-paramagnetic iron oxide (USPIO)

MRI CA's must have a catalytic (i.e. amplified) effect



Defect of the blood-brain barrier after stroke shown in MRI. T1-weighted images: left image = without; right image = with contrast medium administration



PRE = *Paramagnetic Relaxation Enhancement*

PCS = *Pseudo-Contact Shift*

il raggio della sfera gialla indica la distanza alla quale i segnali ^1H NMR subiscono un significativo accorciamento del tempo di rilassamento

>30 million MRI scans/year in USA
(>20 billion \$)

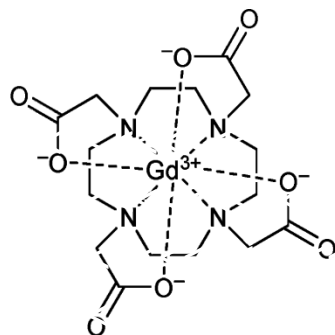
10 million MRI scans/year with Gd CA

9 commercially used Gd CA

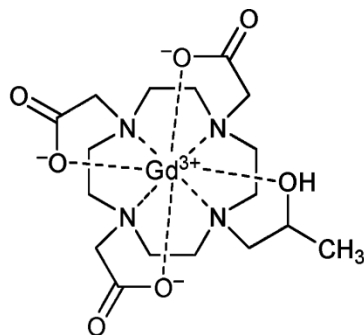
The technique has a low sensitivity: gram quantities of Gd compounds are used in each scan. This causes toxicity problems (nephrogenic systemic fibrosis)

The Gd(III) ion is quite toxic ($LD_{50} = 0.2 \text{ mmol} \cdot \text{kg}^{-1}$)

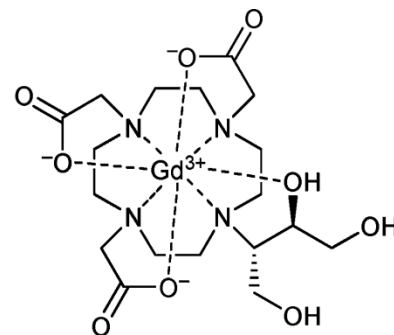
Some commercial T_1 contrast agents (extracellular fluid CAs)



Gd-DOTA
Dotarem®
(Guerbet)

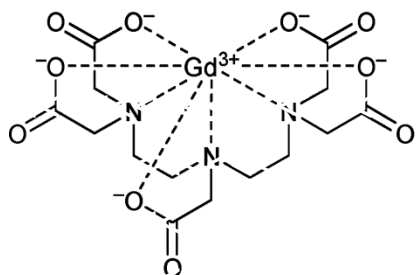


Gd-HP-DO3A
ProHance®
(Bracco)

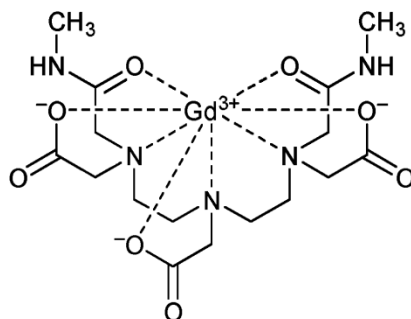


Gd-BT-DO3A
Gadovist®
(Schering)

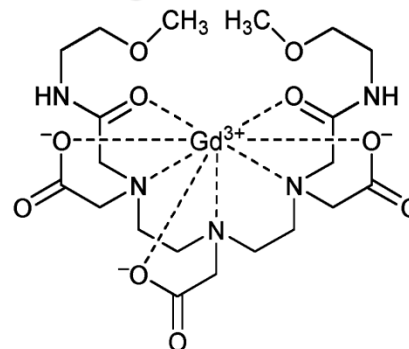
Typical dose =
0.1 – 0.3 mmoles/kg



Gd-DTPA
Magnevist®
(Schering)

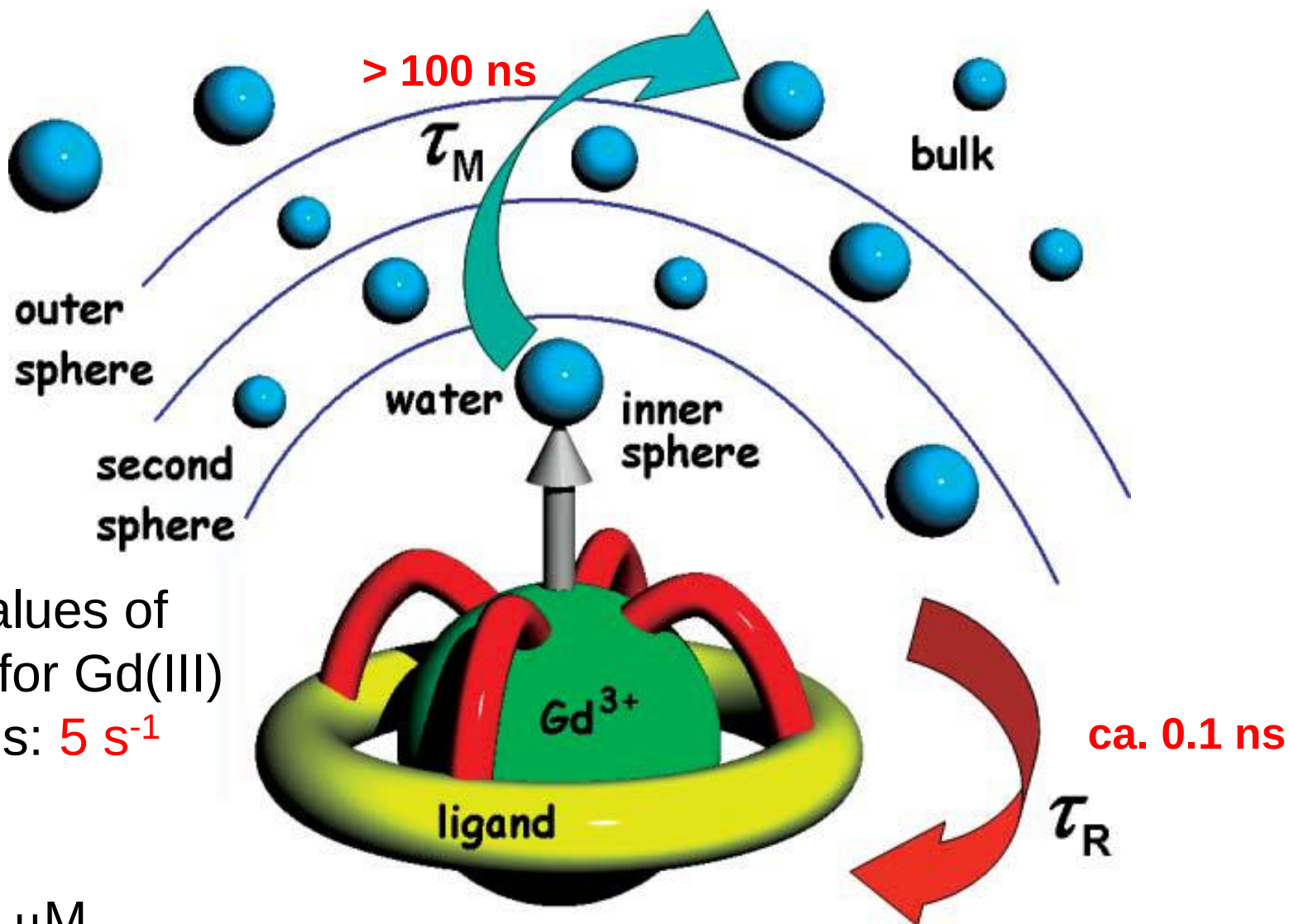


Gd-DTPA-BMA
Omniscan®
(Amersham)



Gd-DTPA-BMEA
OptiMARK®
(Mallinckrodt)

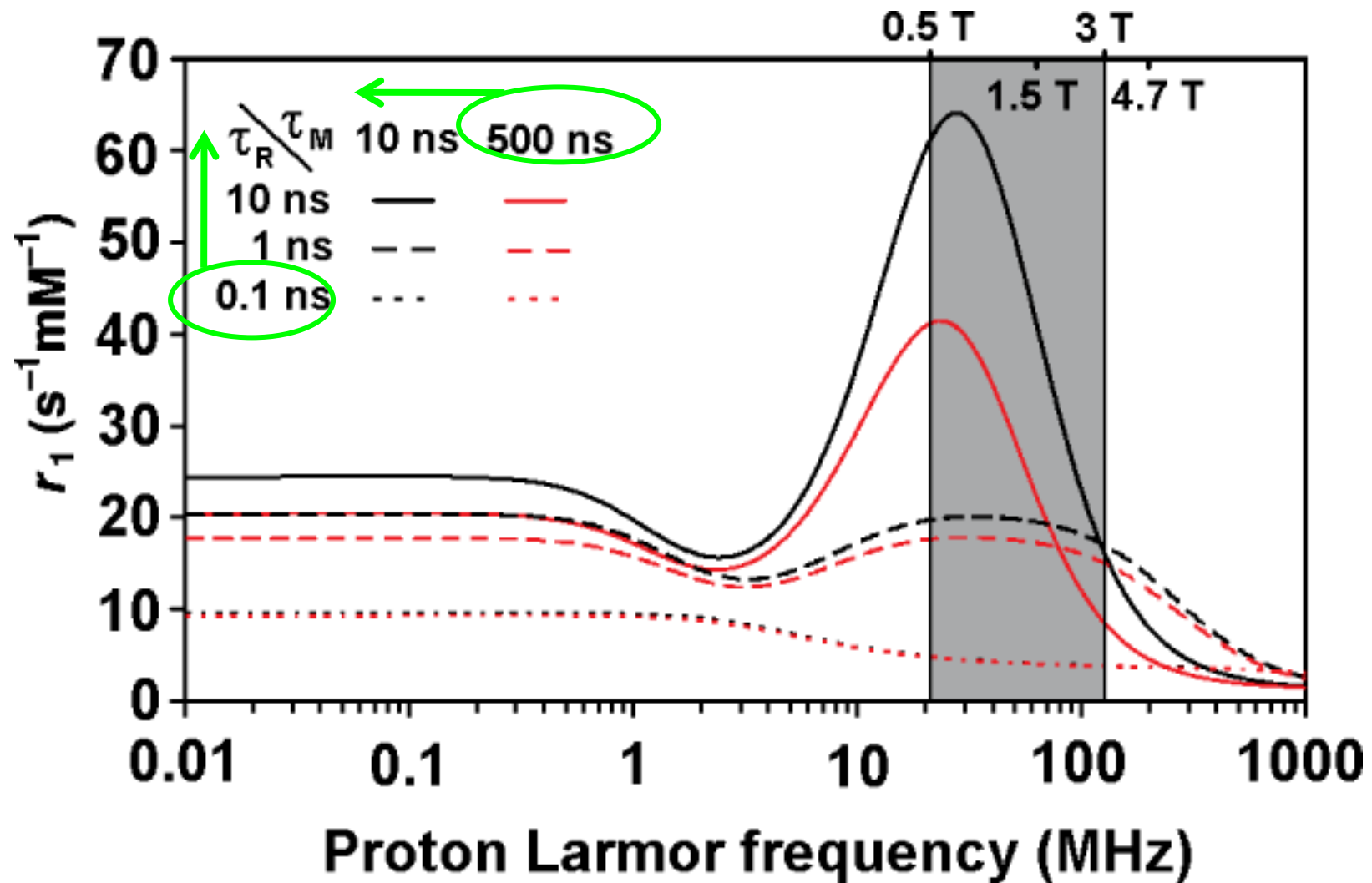
Parameters that affect Relaxivity

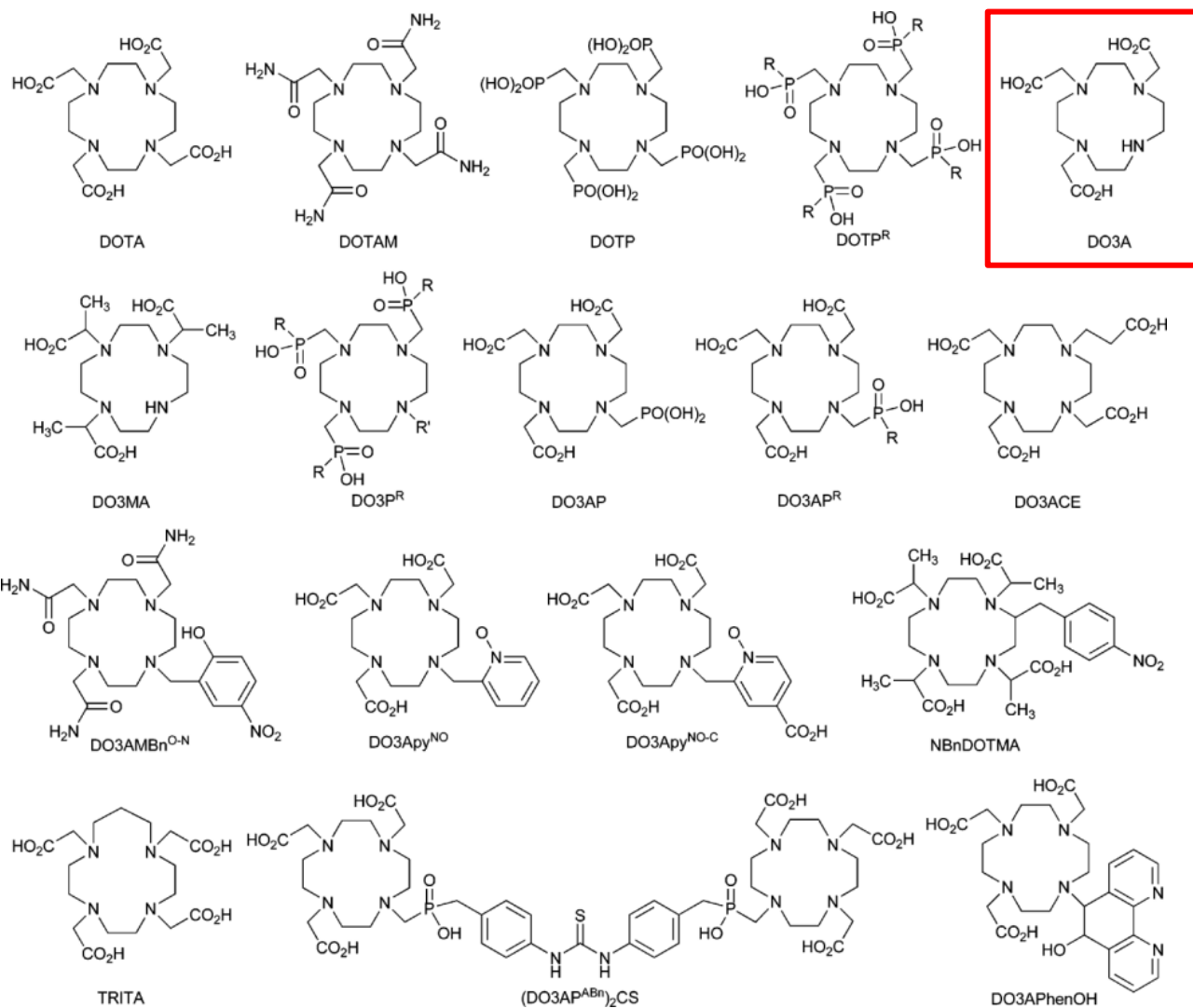


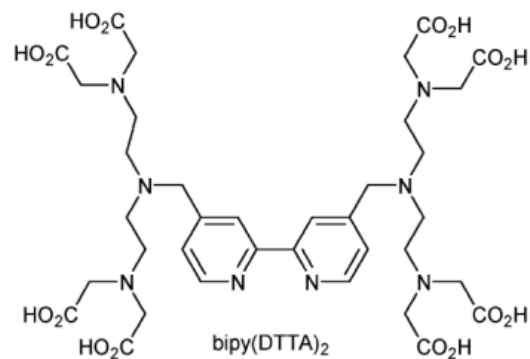
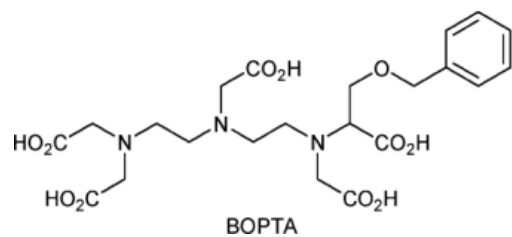
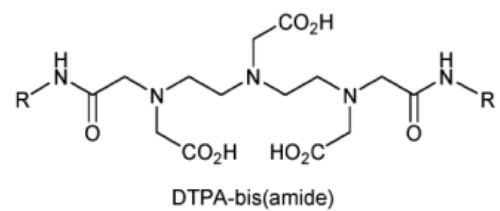
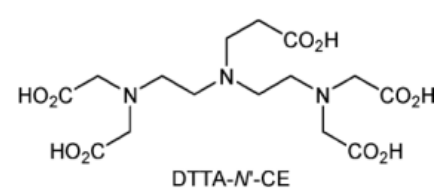
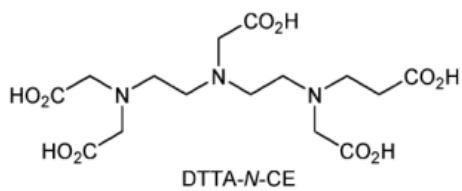
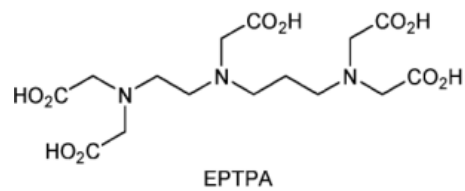
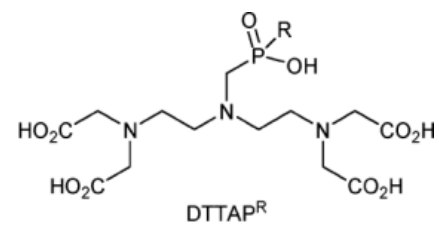
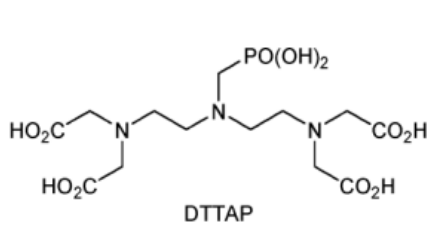
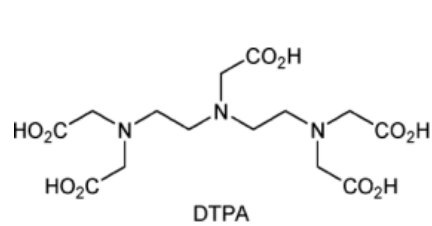
Typical values of
relaxivity for $\text{Gd}(\text{III})$
complexes: 5 s^{-1}
 mM^{-1}

$C > 125 \mu\text{M}$

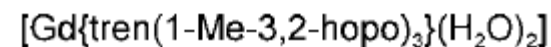
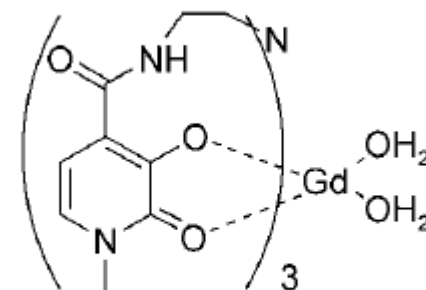
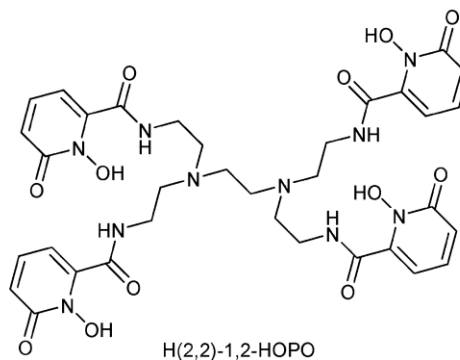
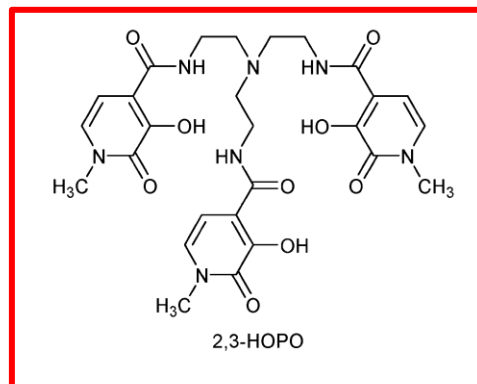
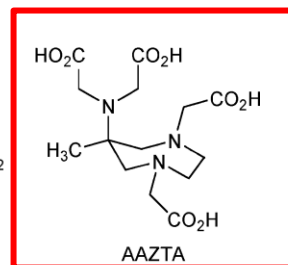
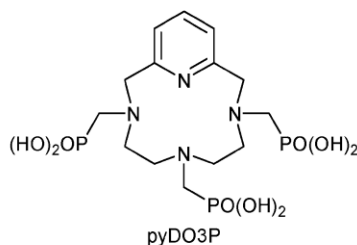
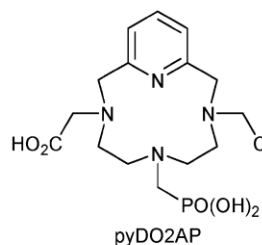
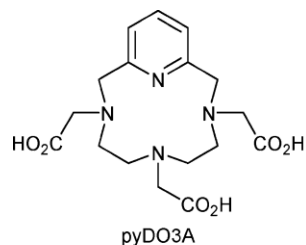
Teoria di Solomon-Bloembergen-Morgan (*SBM Theory*)



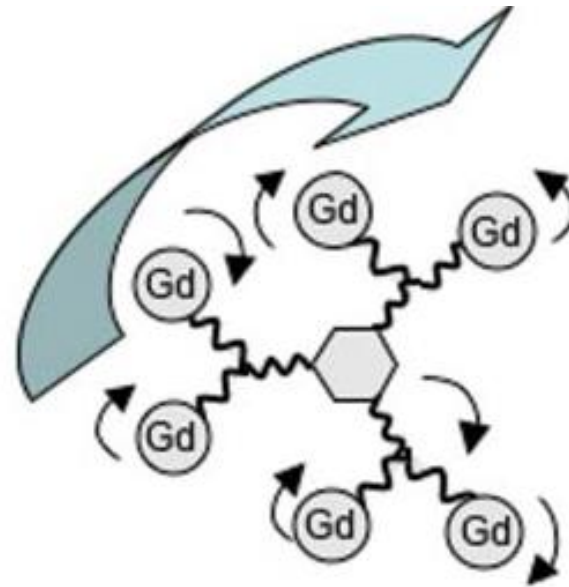
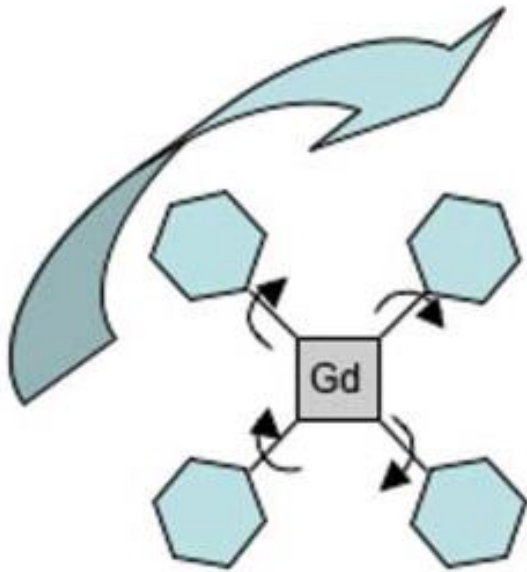




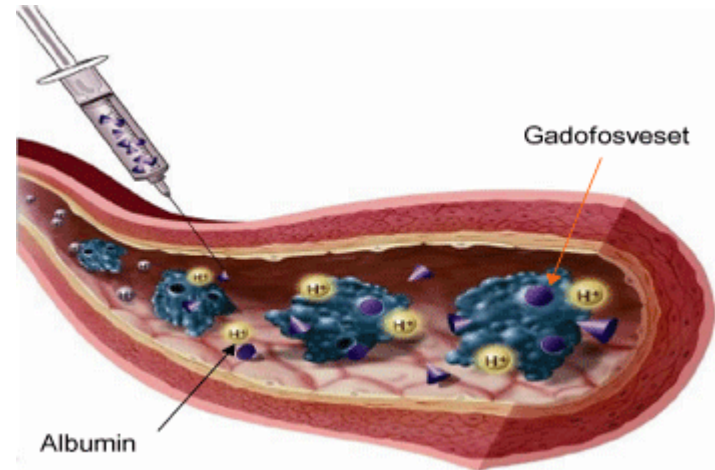
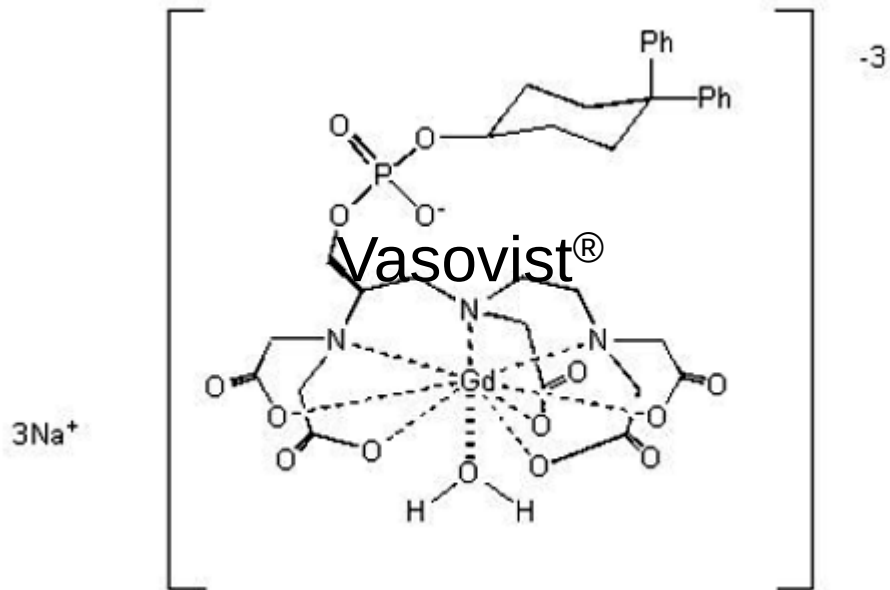
Nuovi leganti polidentati per CA di Gd(III)



Strategie per aumentare τ_M



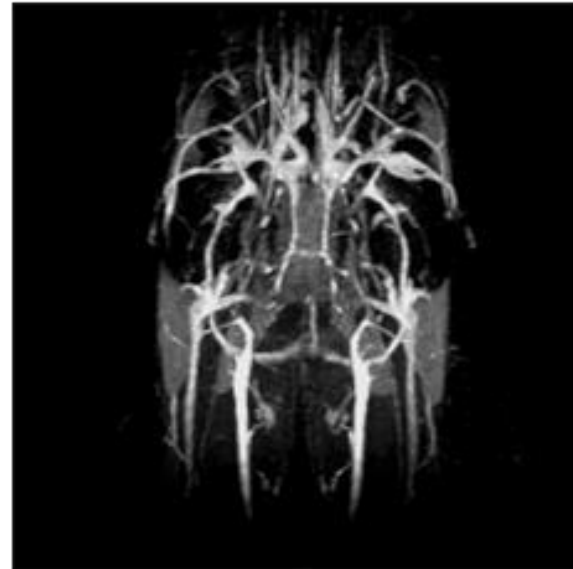
Blood pool contrast agents



Binding of the C.A. to serum albumin increases its tumbling time (τ_R)



**5 min after
0.1 mmol/kg i.v.
of extracellular CA**



**5 min after
0.015 mmol/kg i.v.
of angiographic ca**

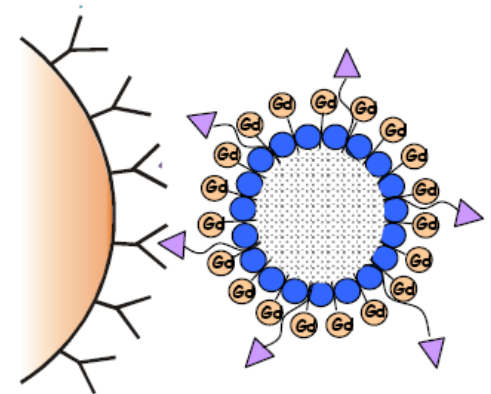
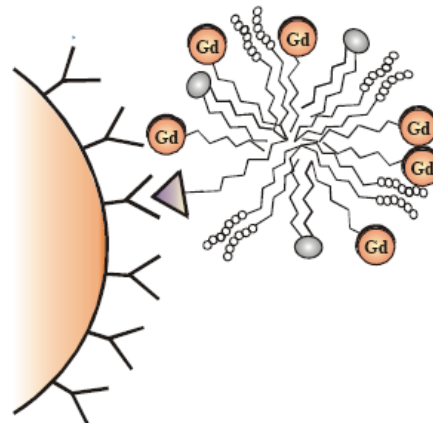
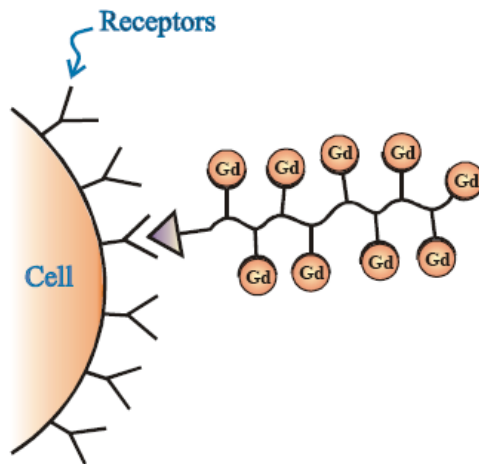
Towards molecular imaging with MRI

The very low concentration of the target requires the delivery of a high number, and possibly efficient, Gd(III) centres

$$C > 125 \mu\text{M}$$

Several strategies
can be adopted

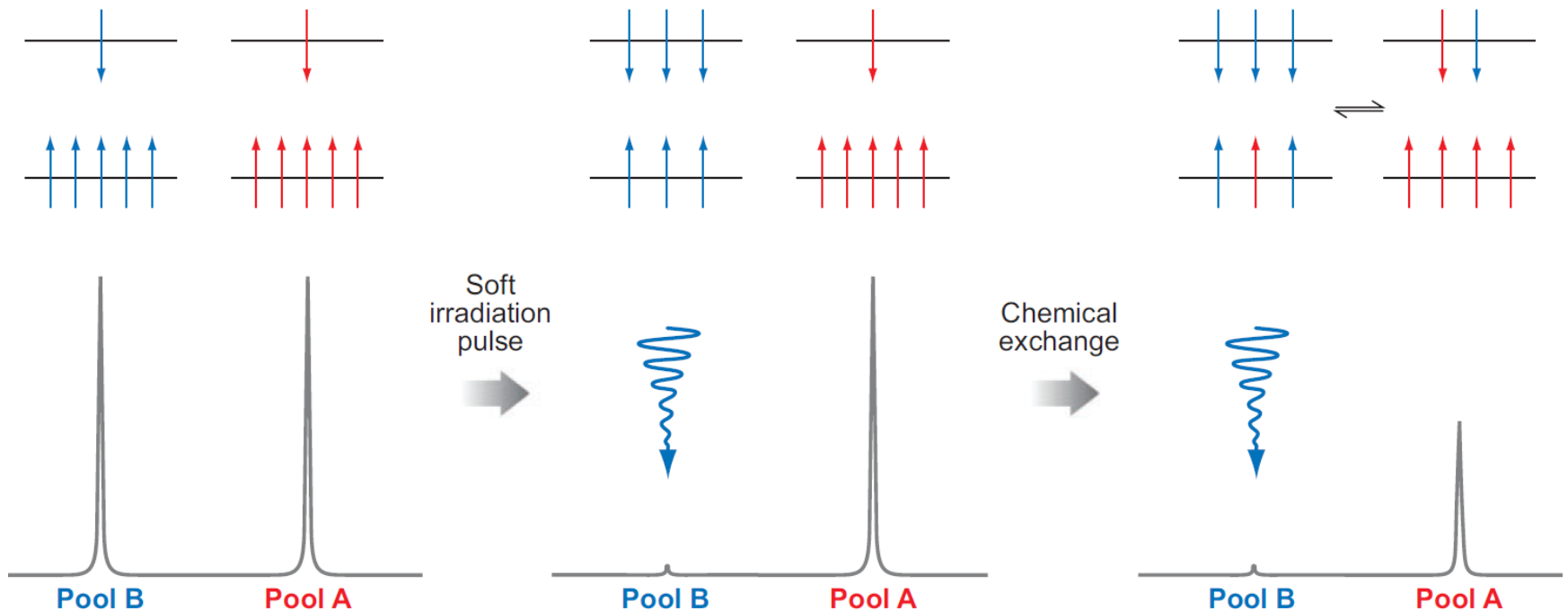
- Gd-chelates covalently or non-covalently linked to biocompatible polymer (proteins, polysaccharides, etc...)
- Self-assembling of complexes (e.g. micelles)
- Use of Gd-loaded nanoparticles (e.g. liposomes,...)



CEST Contrast Agents

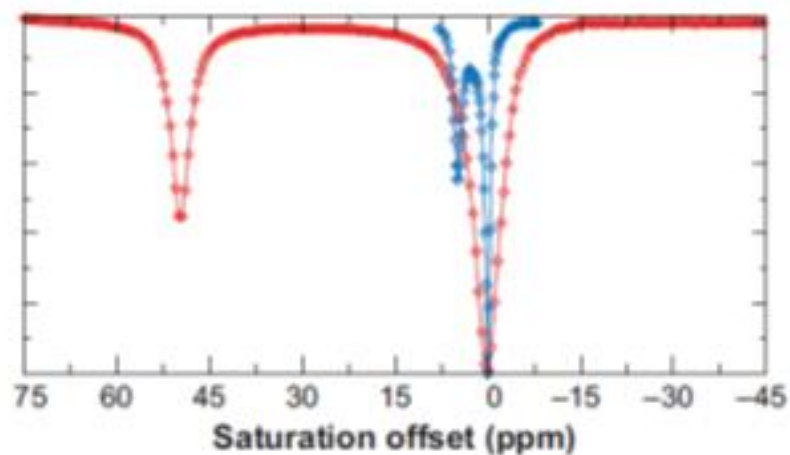
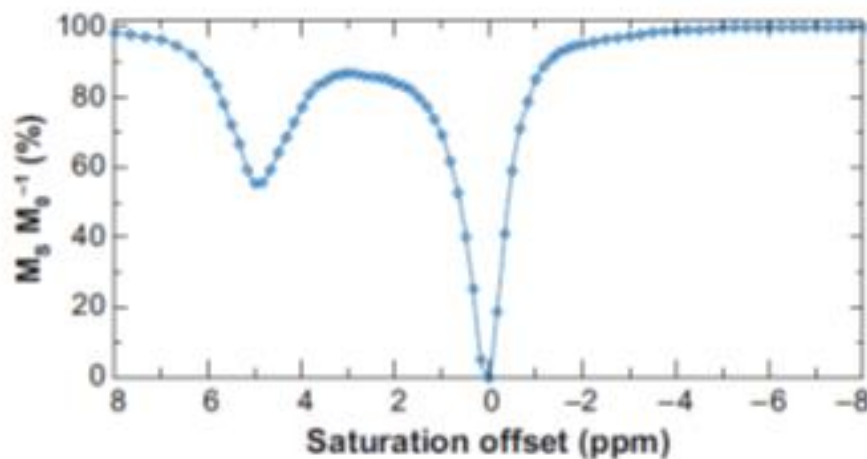
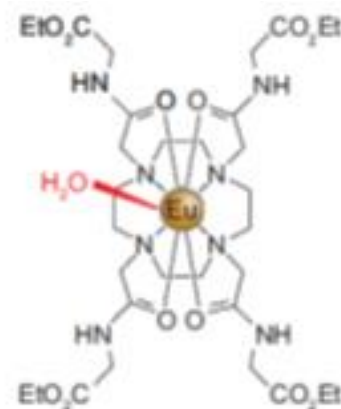
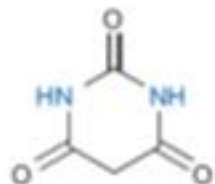
Chemical Exchange Saturation Transfer

composti mobili con protoni in scambio lento con l'acqua di *bulk*

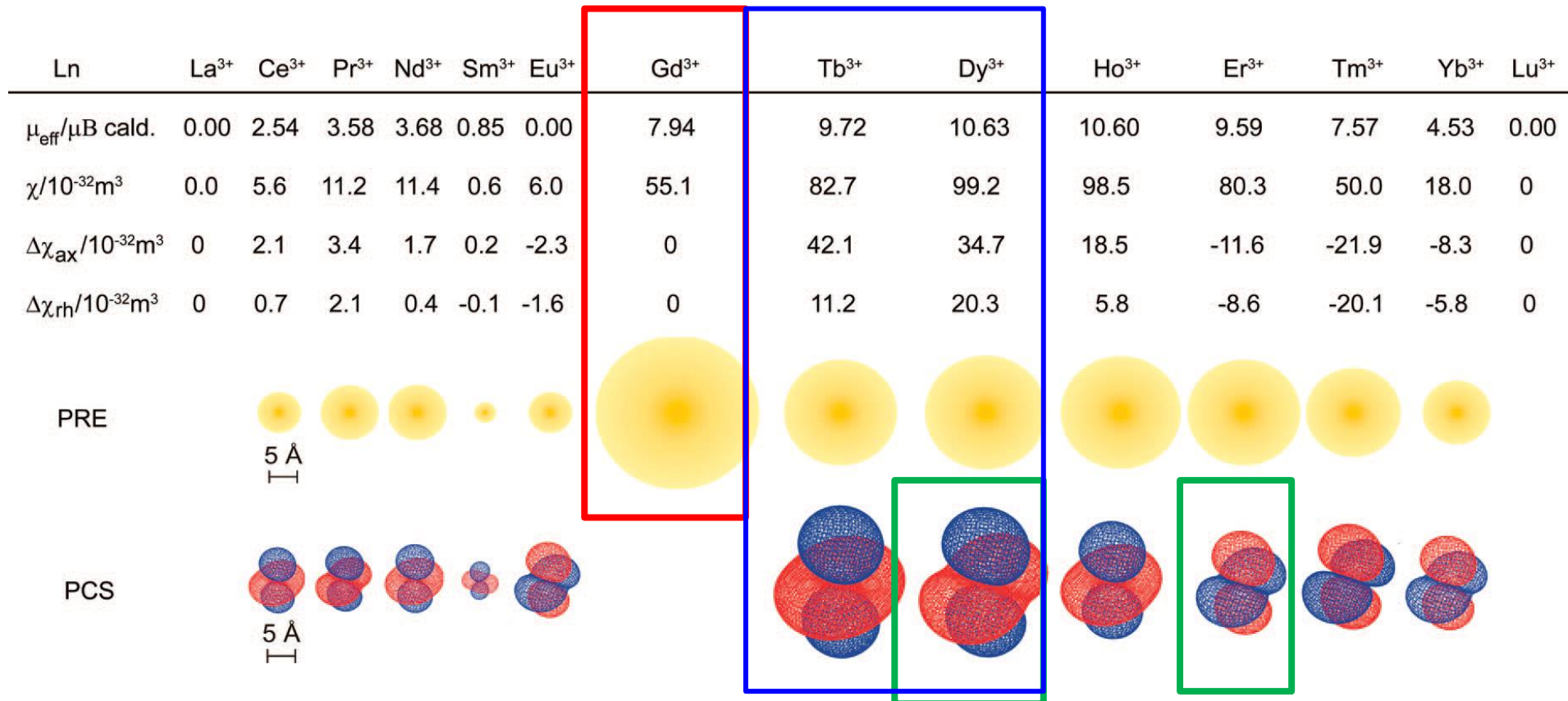


$$k_{\text{CEST}} < \Delta\omega$$

CEST and PARACEST agents: saturation offset



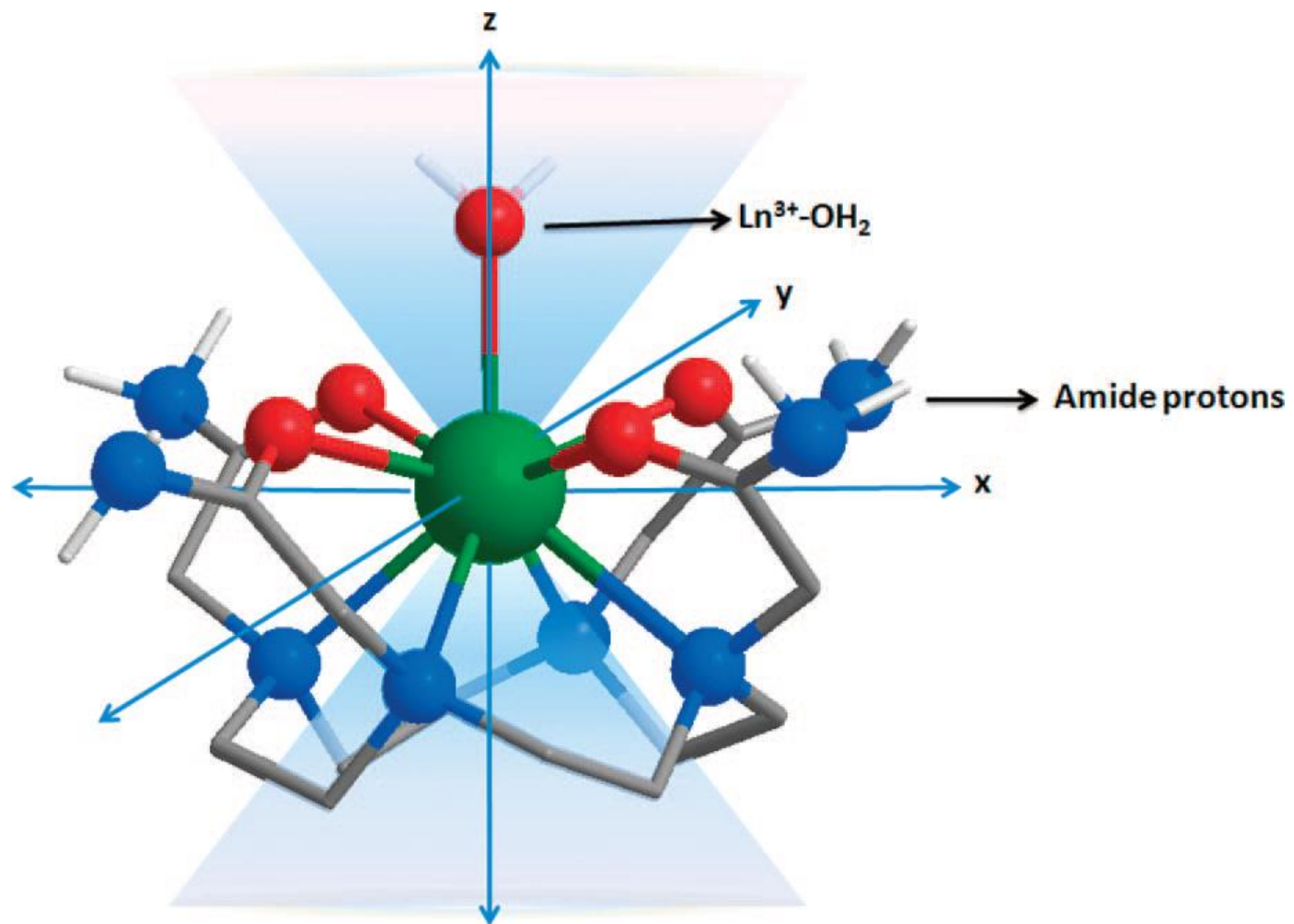
isotroppo

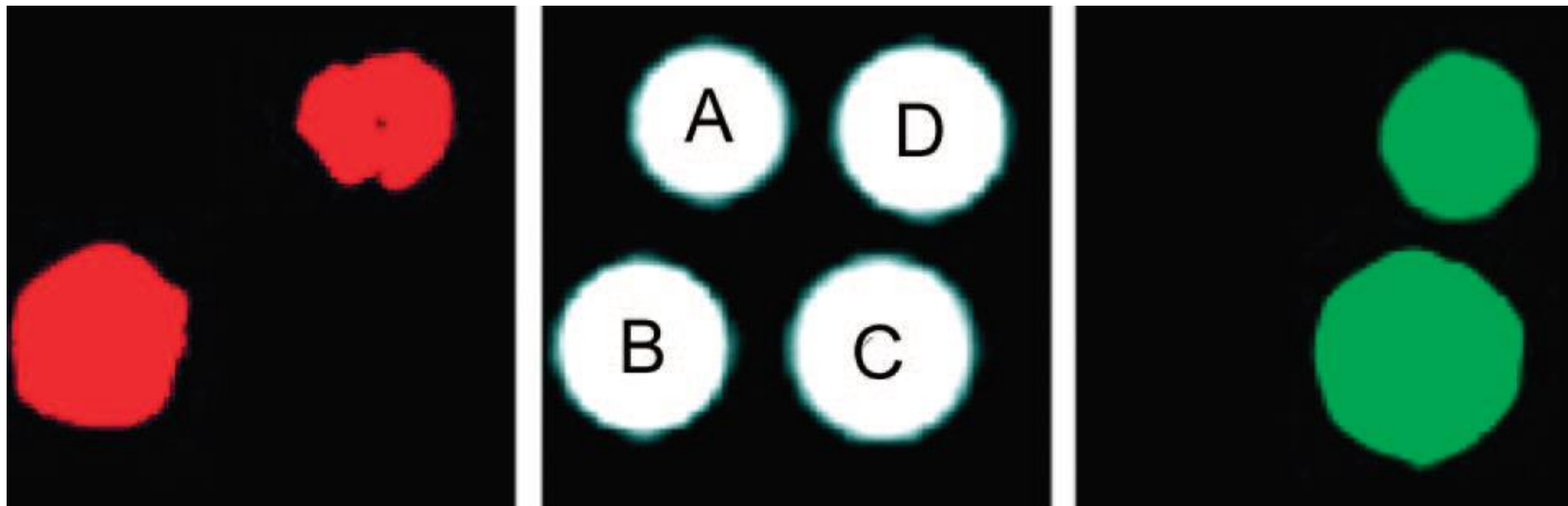


PRE = *Paramagnetic Relaxation Enhancement*

PCS = *Pseudo-Contact Shift*

determina la variazione di chemical shift indotta da ciascuno ione sui nuclei vicini e le iso-superfici rappresentano la grandezza e il segno del chemical shift



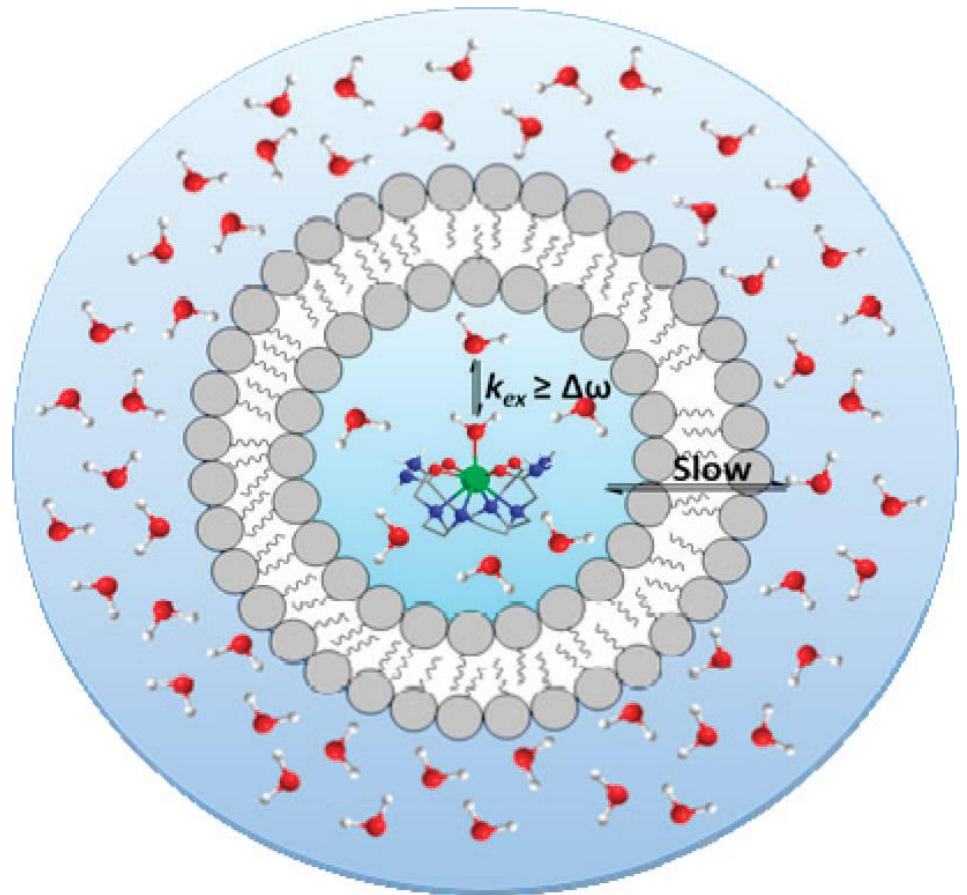
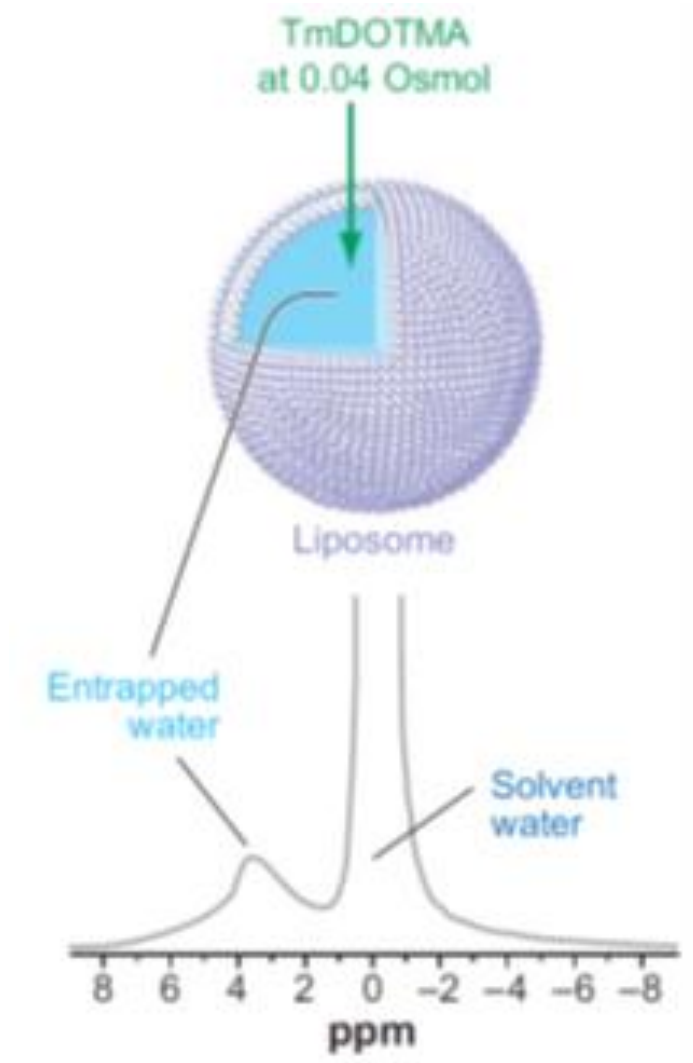


$B = [\text{Tb-DOTAMGly}]^-$

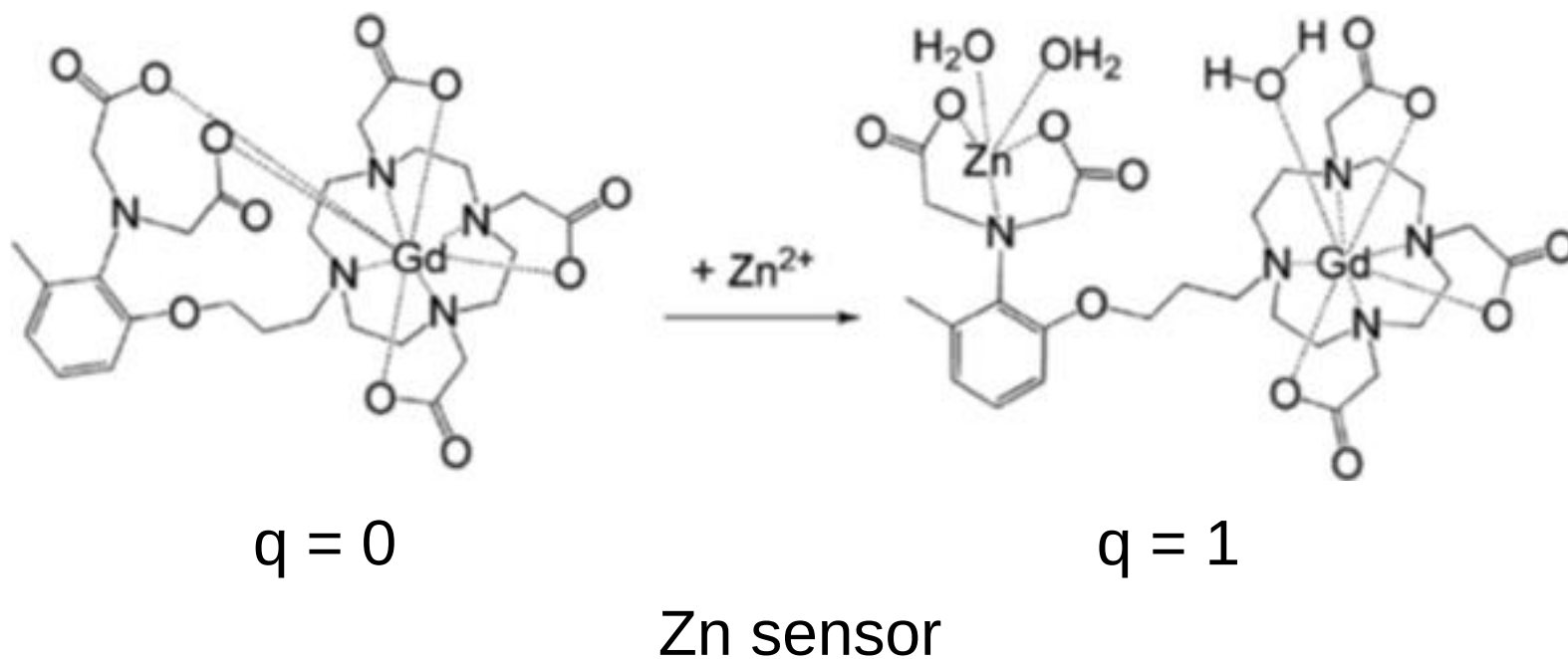
$C = [\text{Eu-DOTAMGly}]^-$

$D = [\text{Tb-DOTAMGly}]^- + [\text{Eu-DOTAMGly}]^-$

LipoCEST



Responsive (*smart*) CA



T₂ contrast agents

super-paramagnetic iron oxide particles (SPIO)

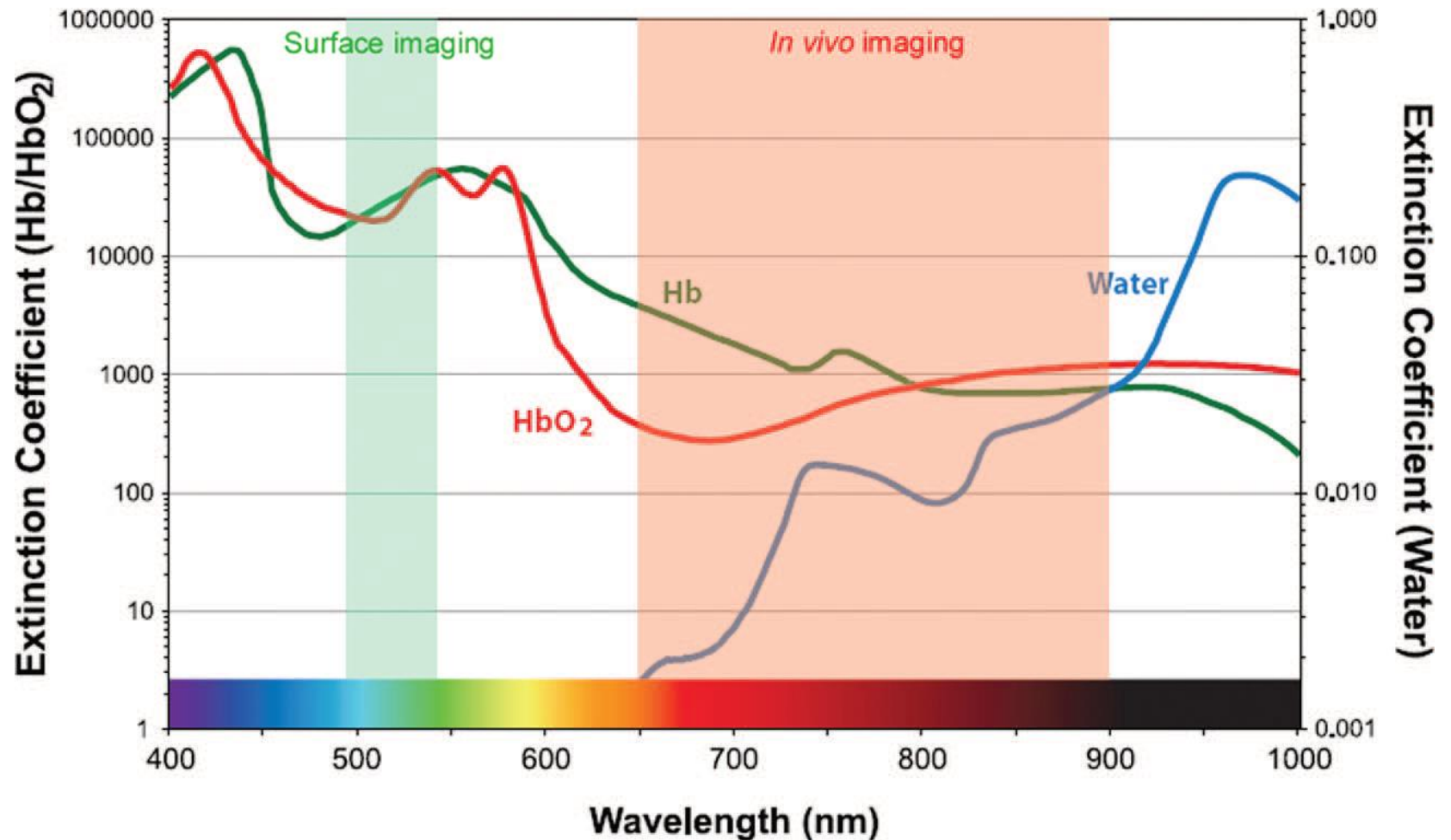
d = 60 – 250 nm

Pre-Clinical Agent	Commercial Name	MR Target	Status
AMI-25	Ferumoxide, Feridex, Endoderm	Liver	Approved
OMP	Abdoscan	Bowel	Approved
AMI-121	Gastromark, Ferumoxsil, Lumirem	Bowel	Approved
SHU555A	Resovist	Liver	Approved (EU, Japan, Australia), Phase III (USA)
AMI-227	Combidex, Sinerem, Ferumoxtran	Lymph Node Metastases	Phase III
CODE 7228	Feraheme, Ferumoxytol	Vasculature	Phase II

Imaging ottico

- Sensibilità paragonabile a quella di SPECT e PET
- Possibilità di agenti *switchable (responsive)*
- Possibilità di *time-resolved detection*
- No quantificazione

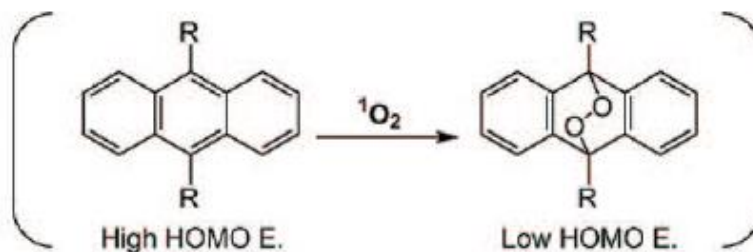
- Window
- Stokes shift
- Brightness
- Stability



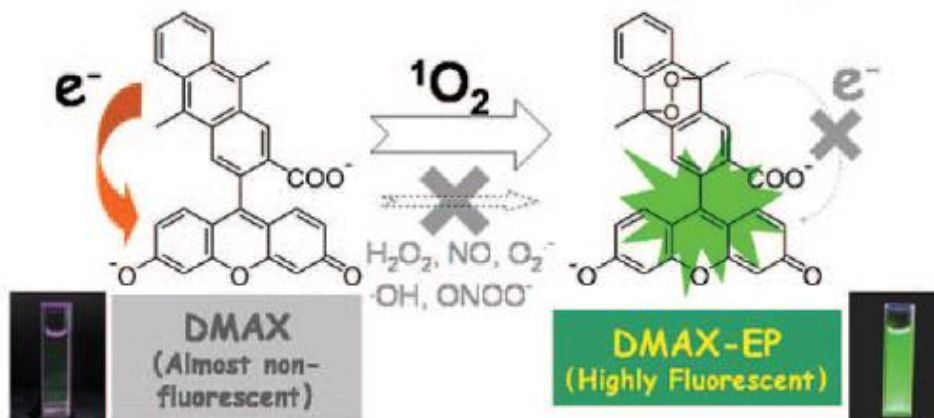
Esempio di switchable fluorescent probe sensore di $^1\text{O}_2$

(a) Singlet Oxygen Probes

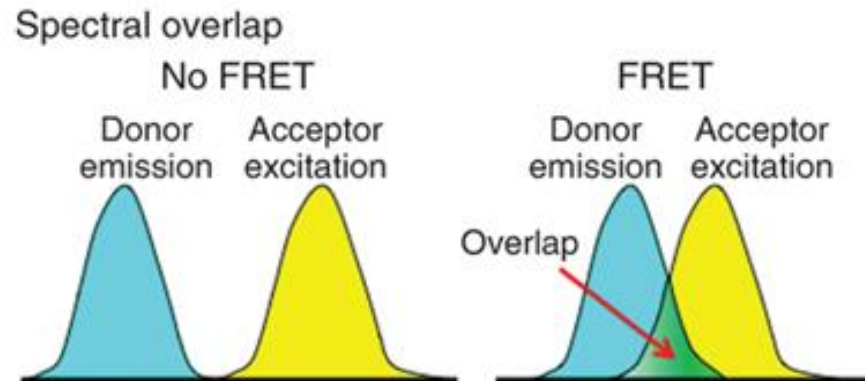
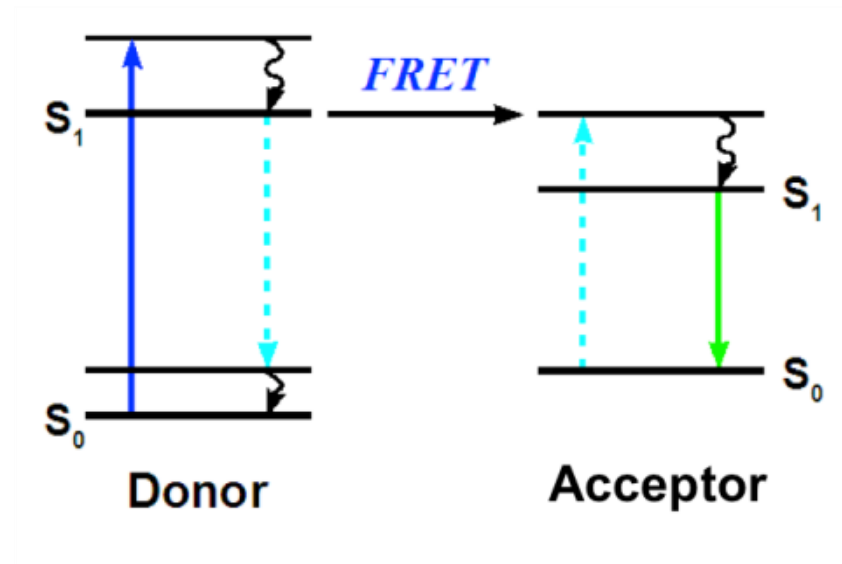
Key reaction: Endoperoxide formation



Reaction scheme for detection of singlet oxygen



FRET fluorescence – resonance energy transfer



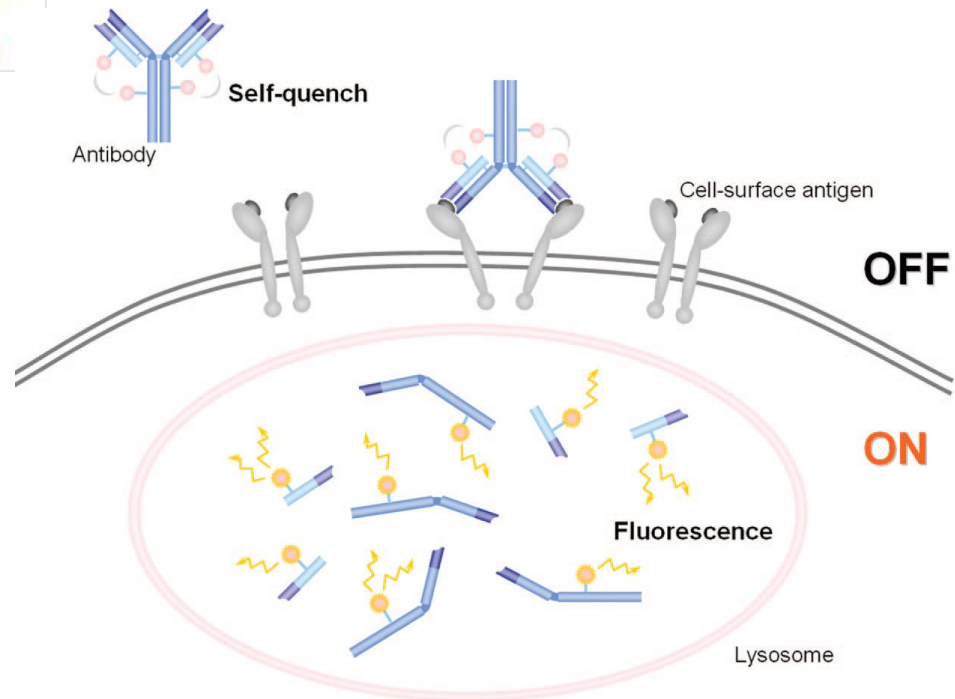
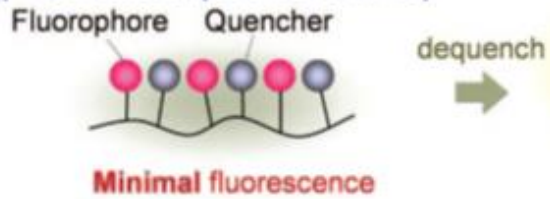
a) Self-quench (Homo-FRET)



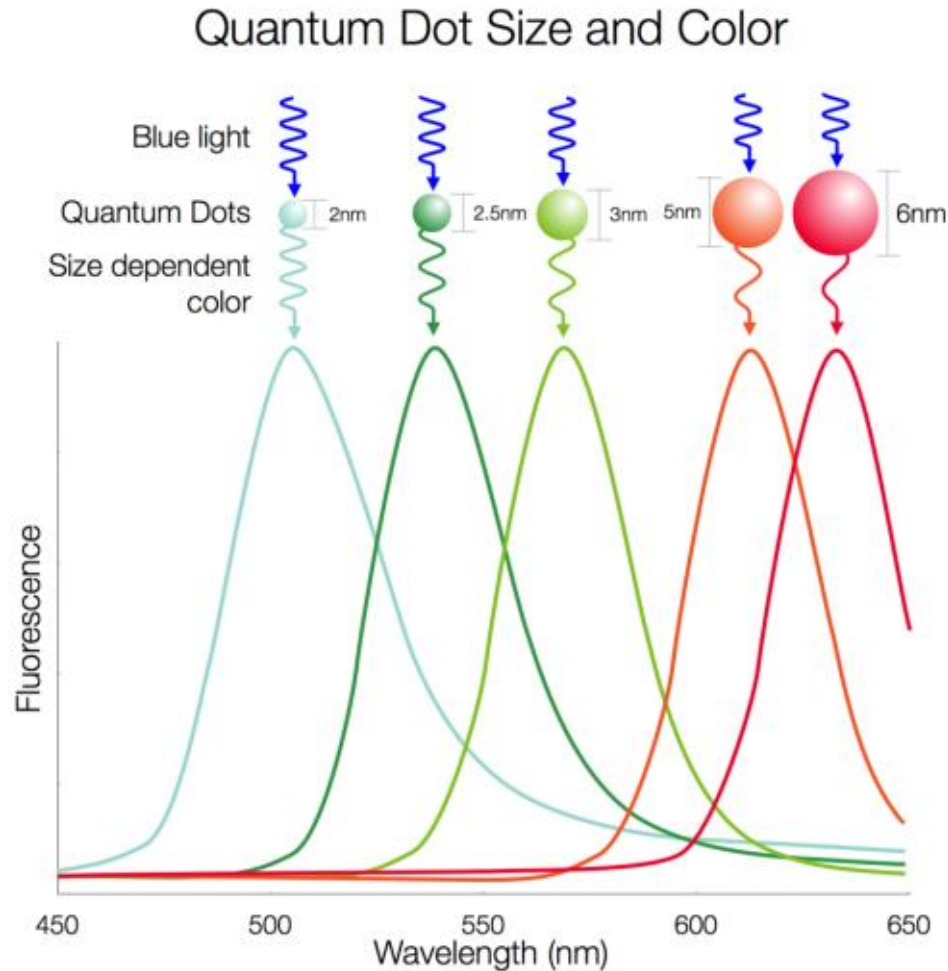
b) Fluorophore protein interaction



c) Quencher (Hetero-FRET)



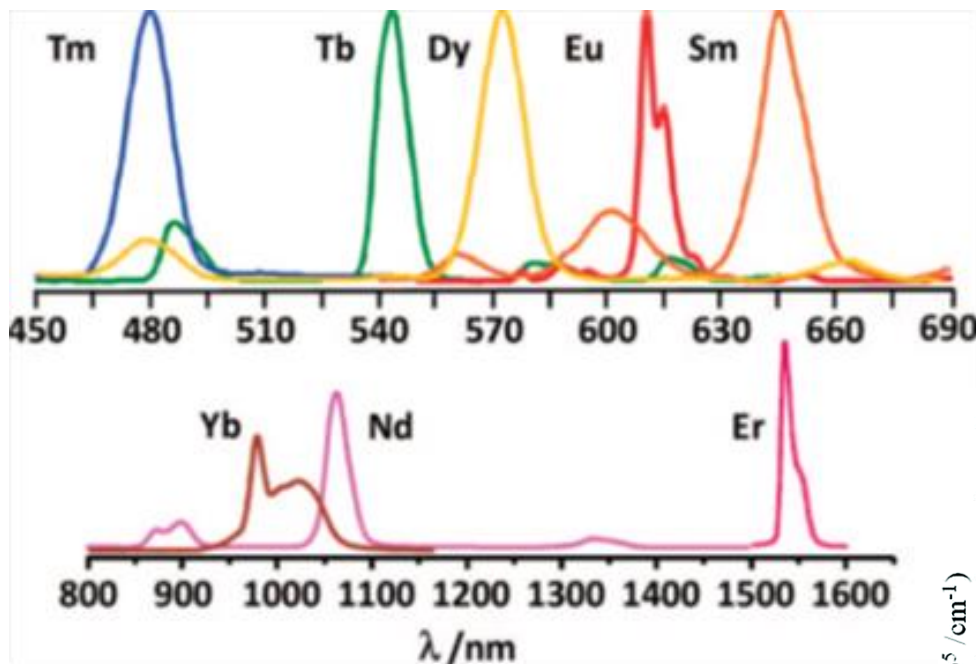
quantum dots (QD) nano-cristalli di semiconduttori (e.g. CdSe)



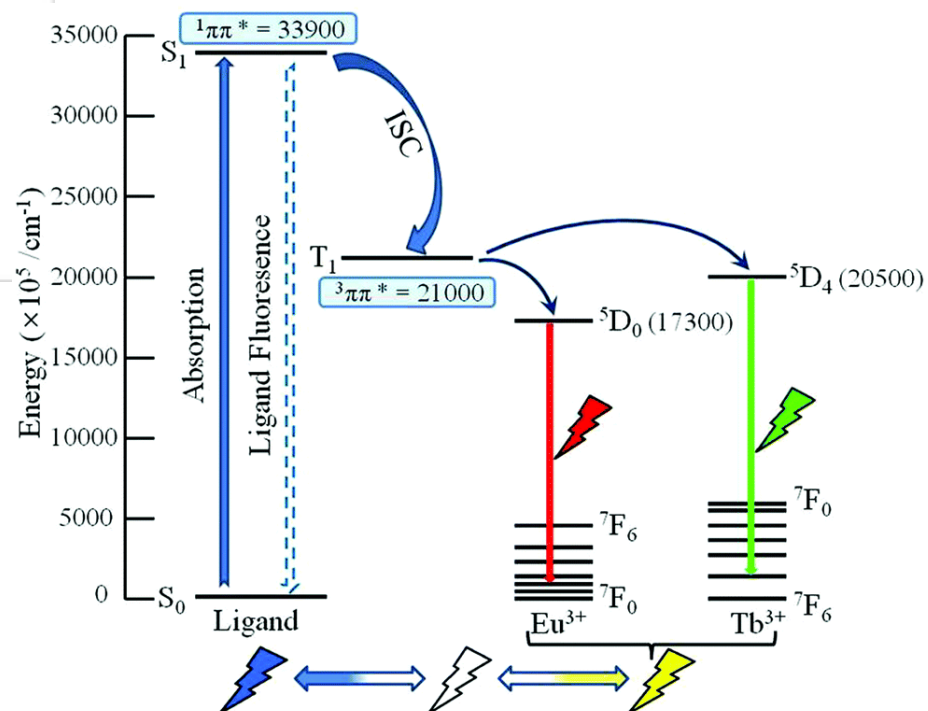
Ø 2 – 10 nm

Banda di emissione stretta, molto intensa e modulabile con le dimensioni del QD

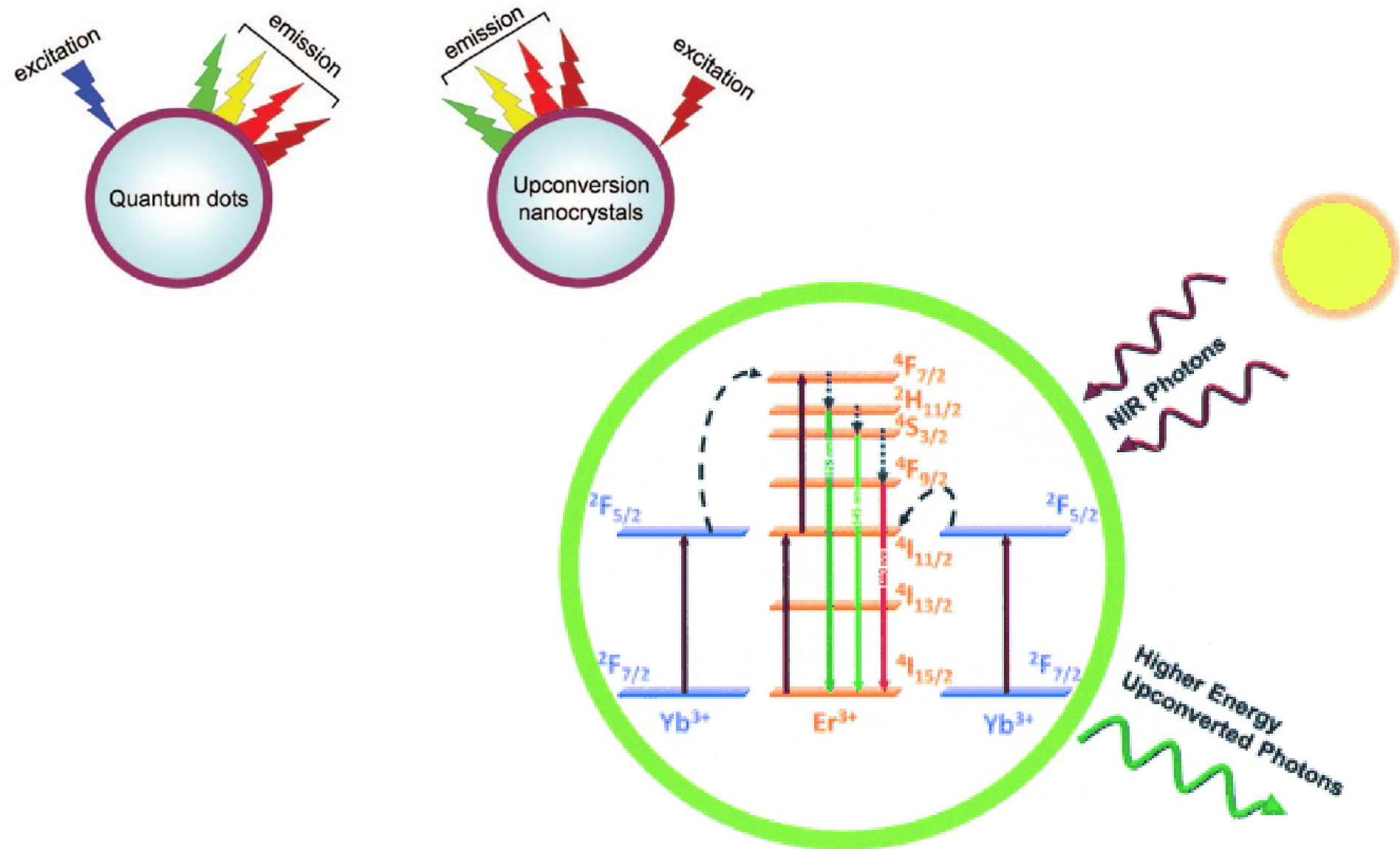
Complessi dei lantanidi



Effetto antenna dei leganti

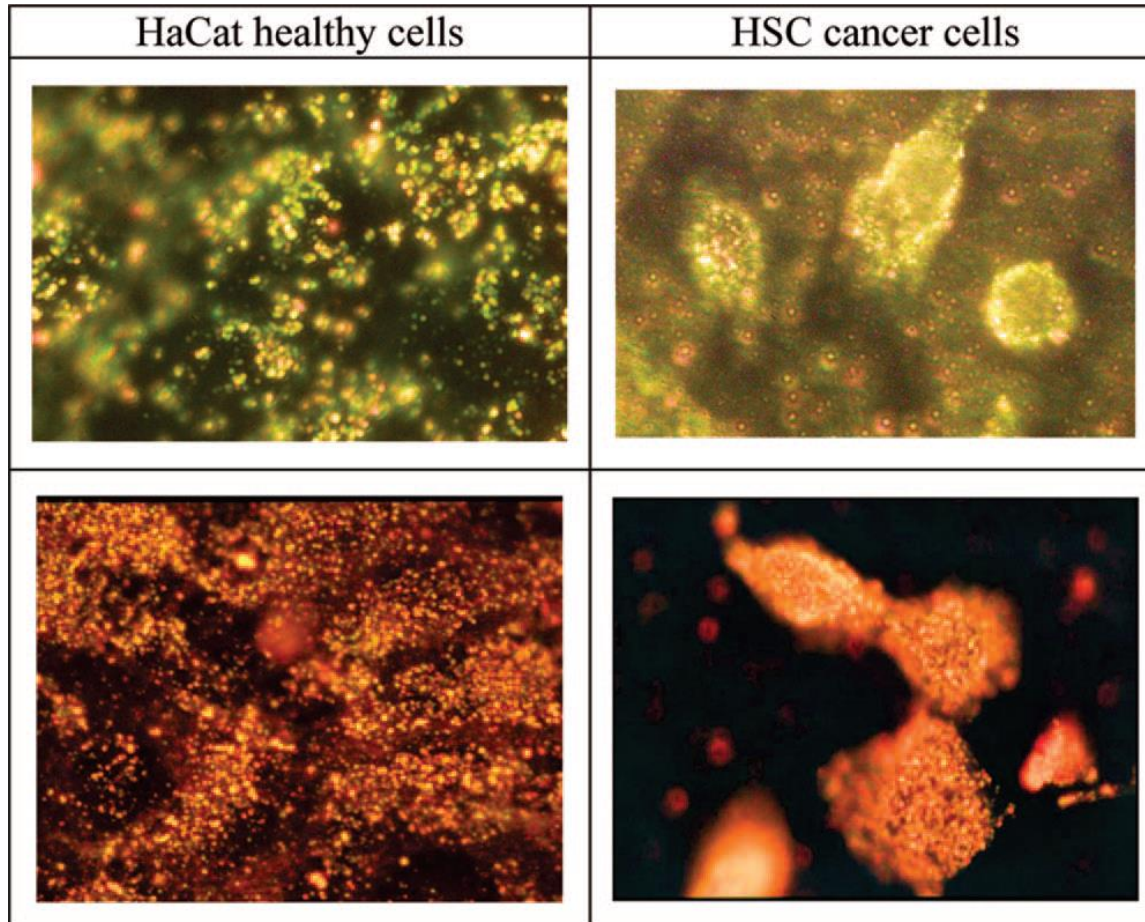


Upconverting QDs e LnNPs



Dark-field fluorescence imaging con AuNP

scattered
light



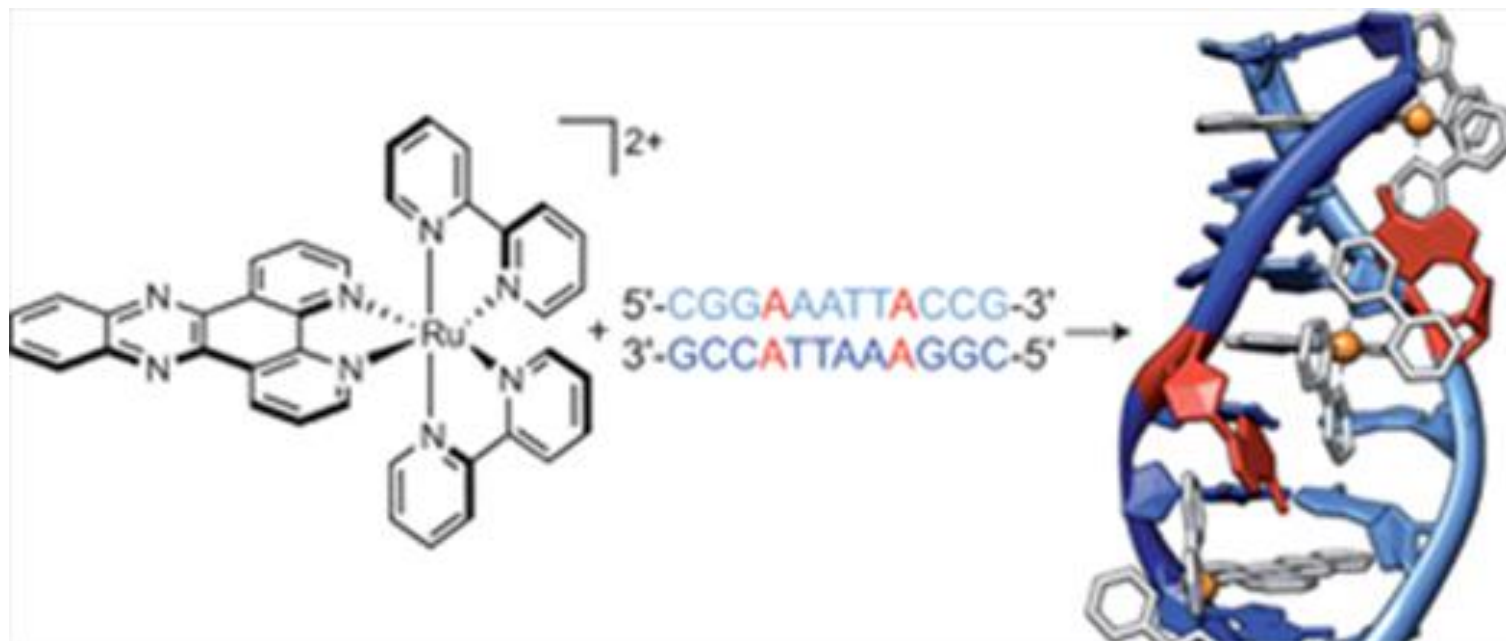
Au nanospheres

Au nanorods

AuNP coniugate a anticorpi anti-EGFR

EGFR = epidermal growth factor receptor, marcatore tumorale

Complessi polipiridilici di Ru(II) come *DNA light switch*



Sviluppi futuri

Multimodal imaging agents and theranostics

