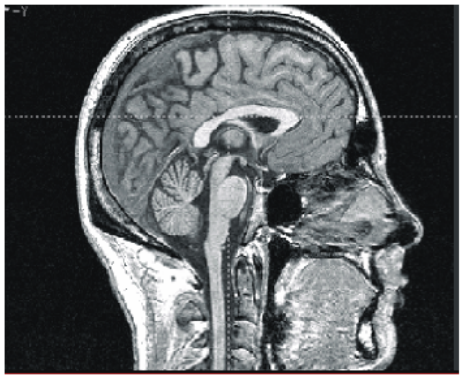
Magnetic Resonance Imaging (MRI)



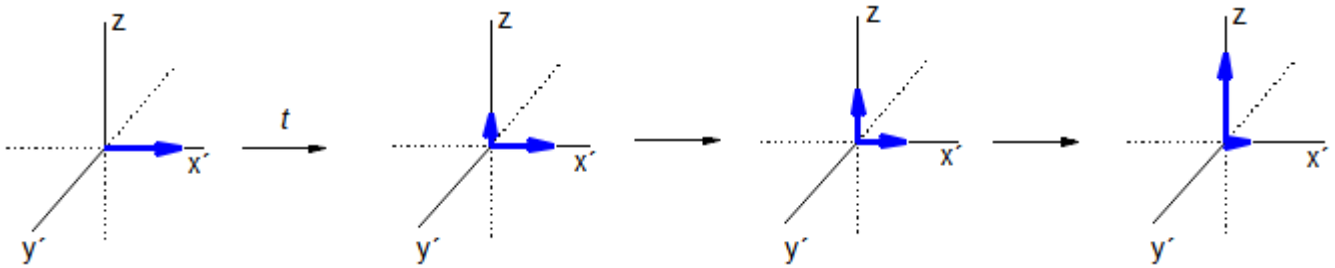
MR sagittal image of human head

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

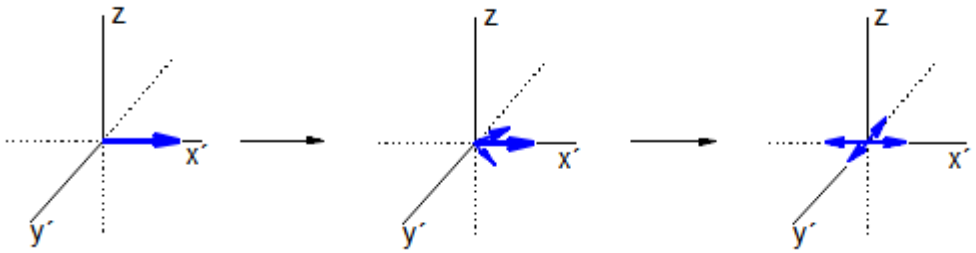
A MR-image represents a map of the intensity of the ^{1}H-NMR signal of water protons

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

T_1 Relaxation (Spin-Lattice Relaxation)



T_2 Relaxation (Spin-Spin Relaxation)



Contrast Agents (CA)

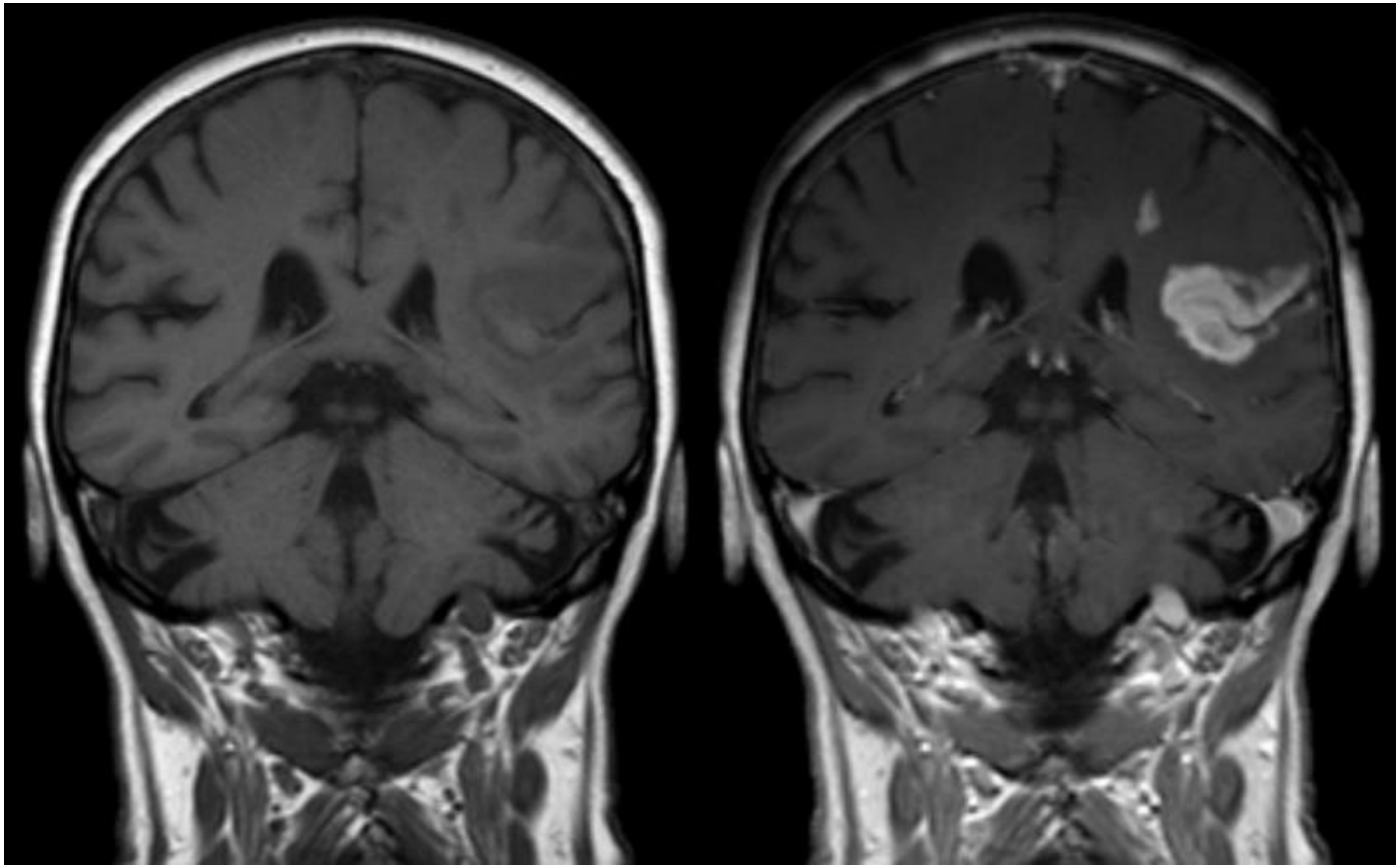
The purpose of a CA is to reduce T_1 (parallel to B_0) or T_2 (perpendicular to B_0) in order to obtain an hyper- or ipo-intense signal, respectively, in short times and with a better signal to noise ratio.

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

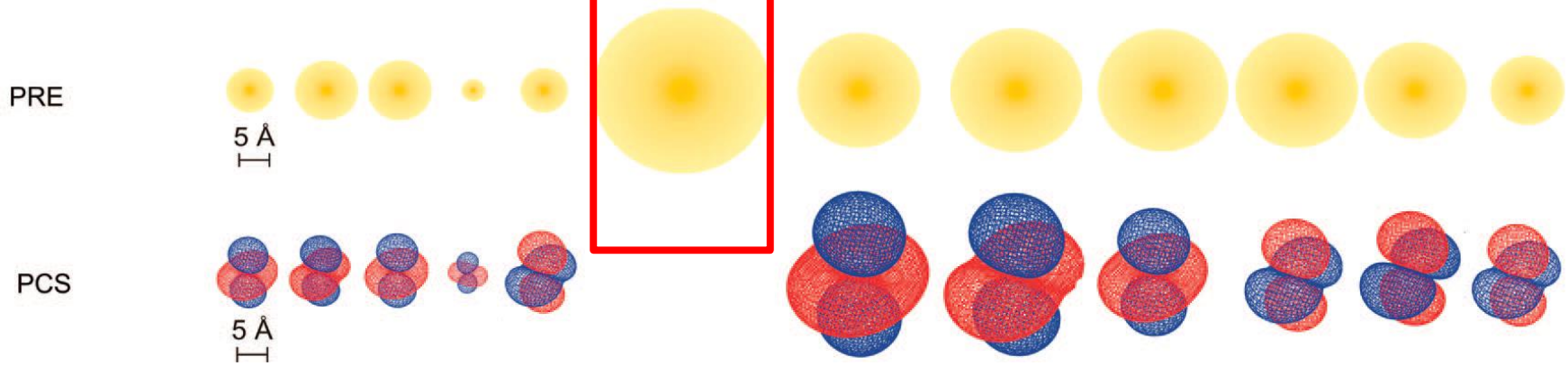
agenti extracellulari non-specifici, organo-specifici e del sangue



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

Il tempo di rilassamento del momento di spin elettronico del Gd(III) è molto più lungo che per gli altri ioni lantanidici (stato di spin totalmente simmetrico)

Ln	La^{3+}	Ce^{3+}	Pr^{3+}	Nd^{3+}	Sm^{3+}	Eu^{3+}	Gd^{3+}	Tb^{3+}	Dy^{3+}	Ho^{3+}	Er^{3+}	Tm^{3+}	Yb^{3+}	Lu^{3+}
$\mu_{eff}/\mu B$ cald.	0.00	2.54	3.58	3.68	0.85	0.00	7.94	9.72	10.63	10.60	9.59	7.57	4.53	0.00
$\chi/10^{-32}m^3$	0.0	5.6	11.2	11.4	0.6	6.0	55.1	82.7	99.2	98.5	80.3	50.0	18.0	0
$\Delta\chi_{ax}/10^{-32}m^3$	0	2.1	3.4	1.7	0.2	-2.3	0	42.1	34.7	18.5	-11.6	-21.9	-8.3	0
$\Delta\chi_{rh}/10^{-32}m^3$	0	0.7	2.1	0.4	-0.1	-1.6	0	11.2	20.3	5.8	-8.6	-20.1	-5.8	0



PCS = *Pseudo-Contact Shift*

PRE = *Paramagnetic Relaxation Enhancement*

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

~40% MRI scans use a Gd CA

~40 million MRI scans/year use a Gd CA worldwide

i.e. ~50 tons of Gd

9 commercially used Gd CA

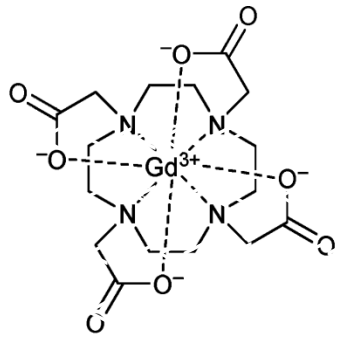
Market > 1 billion $/year

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

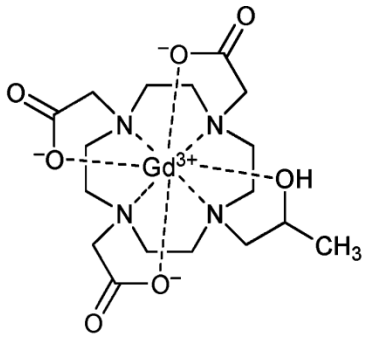
The Gd(III) ion is quite toxic (LD_{50} = 0.2 mmol·kg^{-1})

Some commercial T_1 contrast agents

(extracellular fluid CAs)

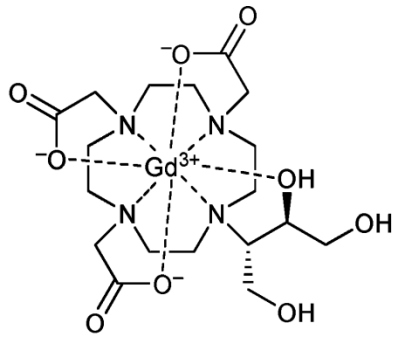


Gd-DOTA
Dotarem®
(Guerbet)

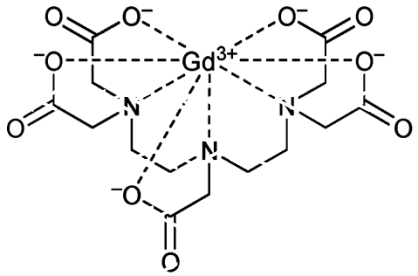


Gd-HP-DO3A
ProHance®
(Bracco)

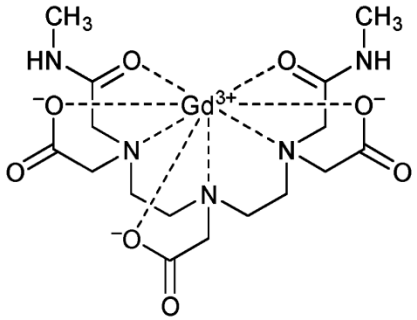
Typical dose =
0.1 – 0.3 mmoles/kg



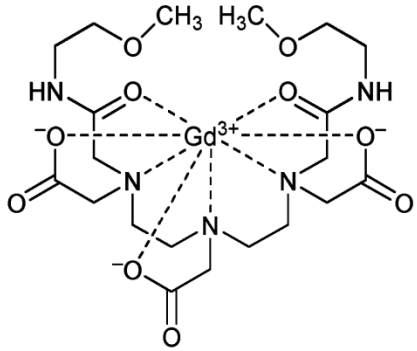
Gd-BT-DO3A
Gadovist®
(Schering)



Gd-DTPA
Magnevist®
(Schering)

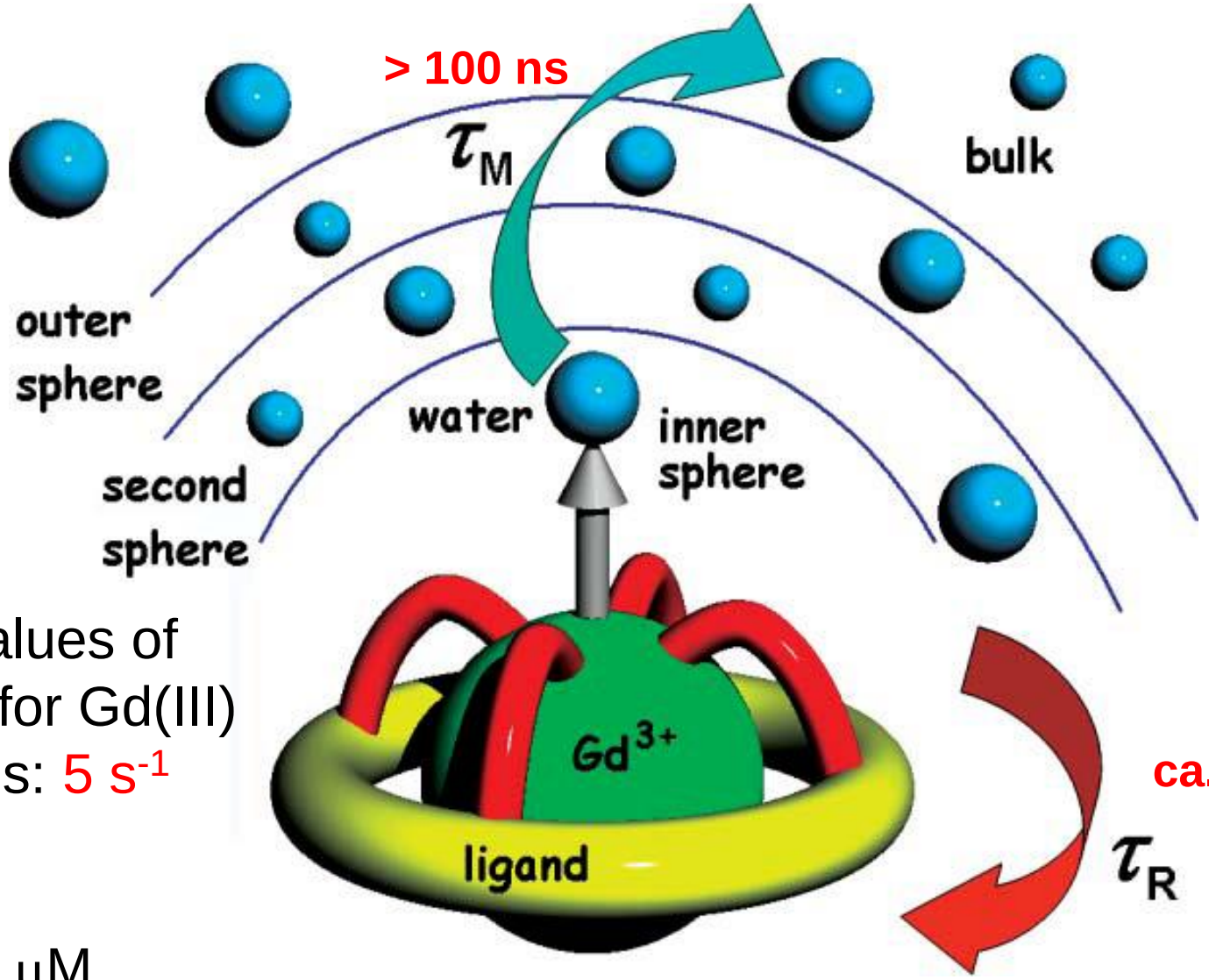


Gd-DTPA-BMA
Omniscan®
(Amersham)



Gd-DTPA-BMEA
OptiMARK®
(Mallinckrodt)

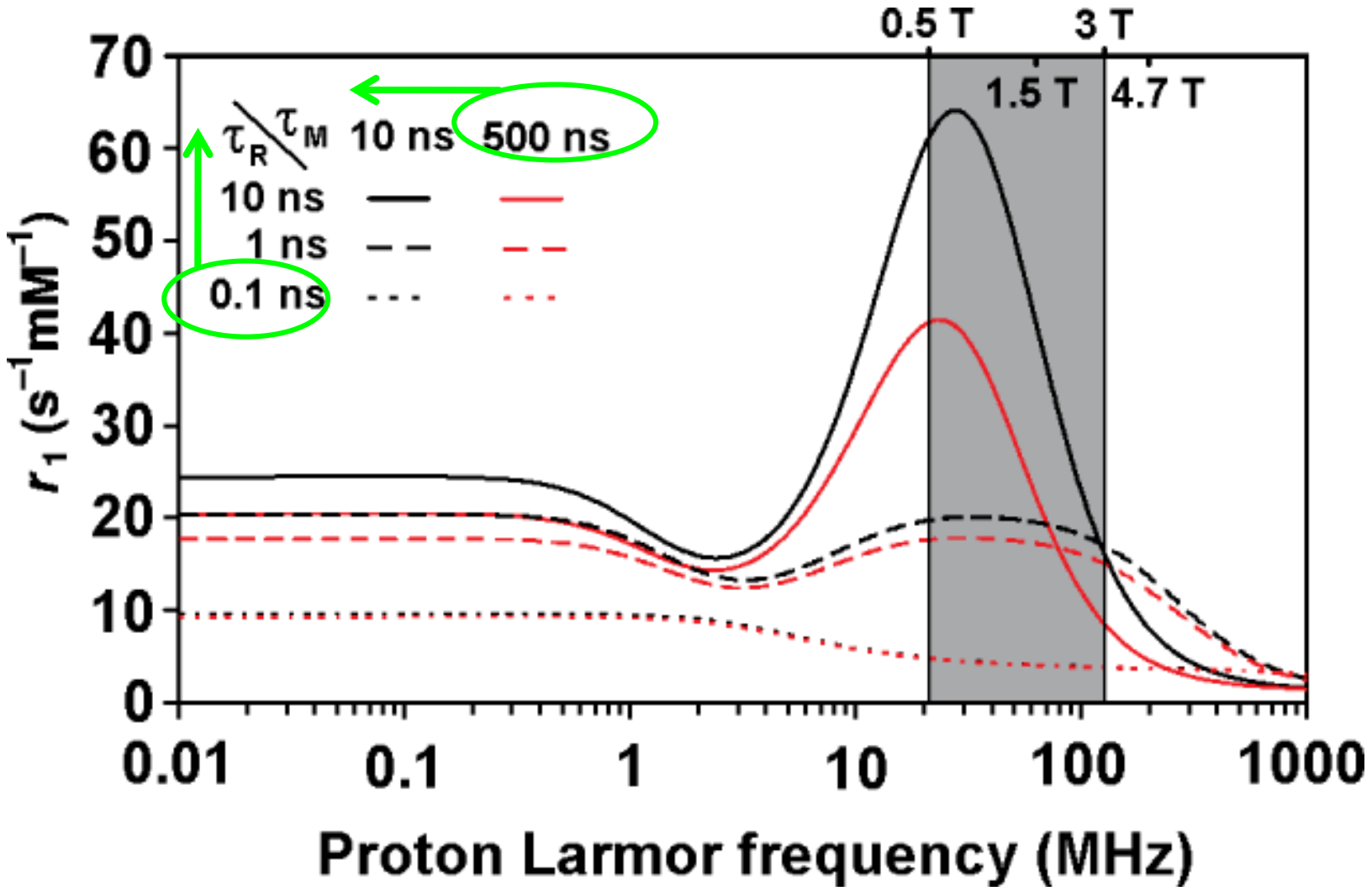
Parameters that affect Relaxivity



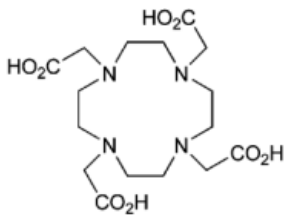
Typical values of relaxivity for Gd(III) complexes: 5 s^{-1} mM^{-1}

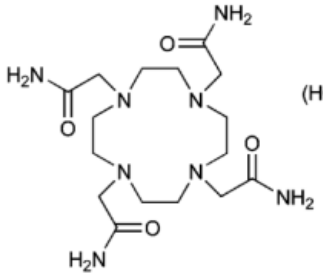
C > 125 μM

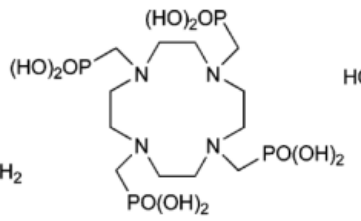
Teoria di Solomon-Bloembergen-Morgan (*SBM Theory*)

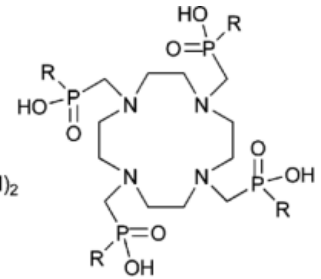


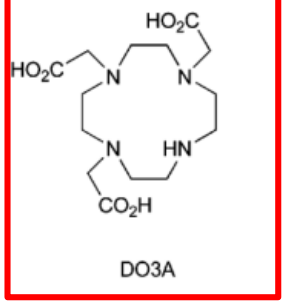
DOTA family

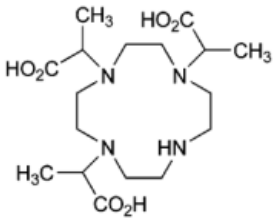

DOTA

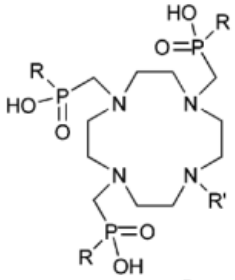

DOTAM

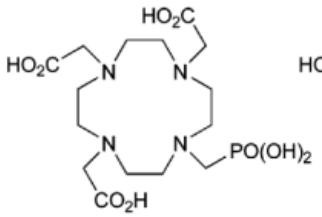

DOTP

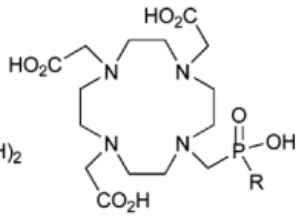

$DOTP^{R}$

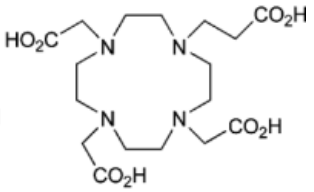

DO3A

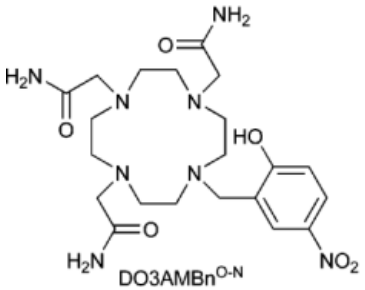

DO3MA

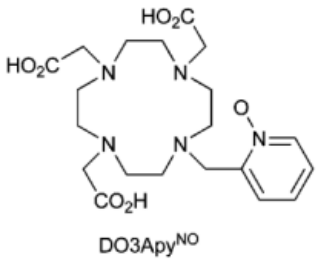

$DO3P^{R}$

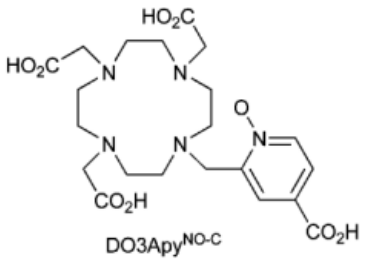

DO3AP

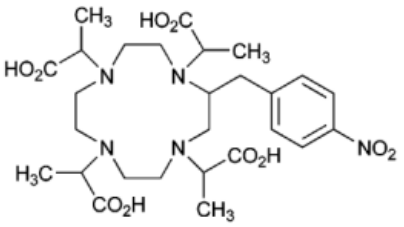

$DO3AP^{R}$


DO3ACE


$DO3AMBn^{O-N}$


$DO3Apy^{NO}$


$DO3Apy^{NO-C}$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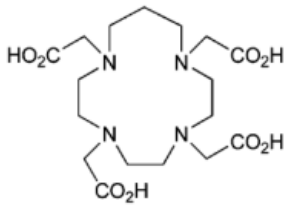
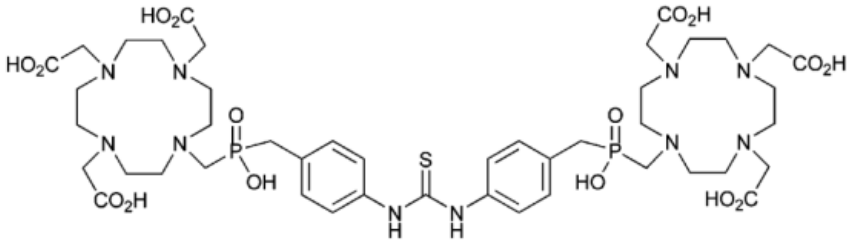
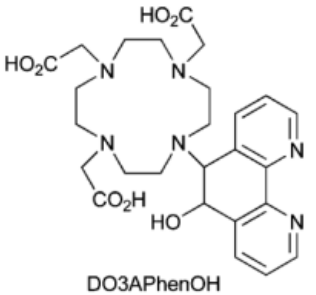
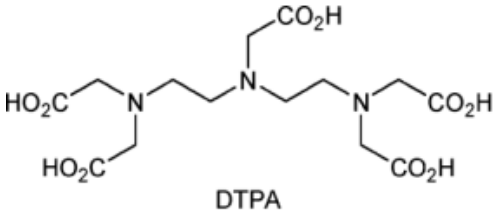

TRITA

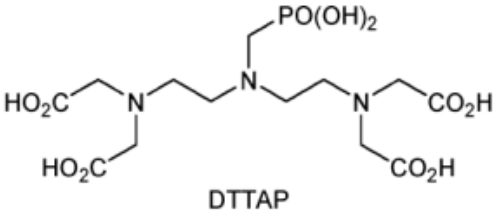

$(DO3AP^{ABn})_2CS$


DO3APhenOH

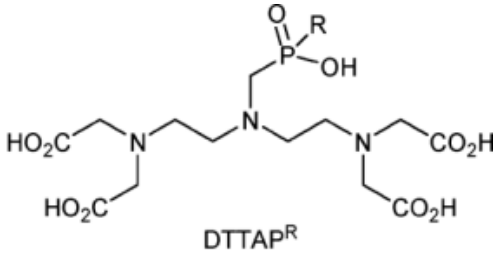
DTPA family



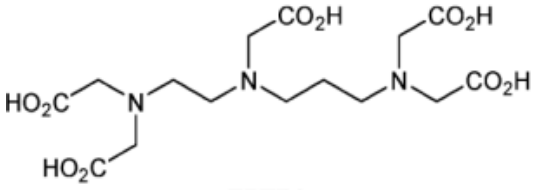
DTPA



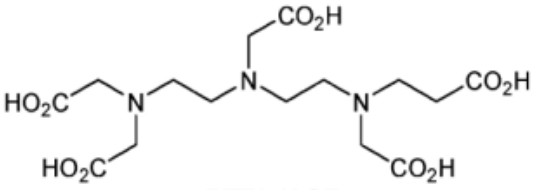
DTTAP



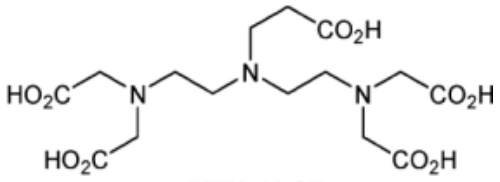
DTTAP^{R}



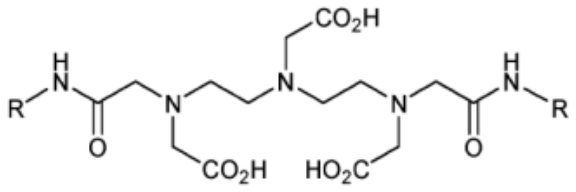
EPTPA



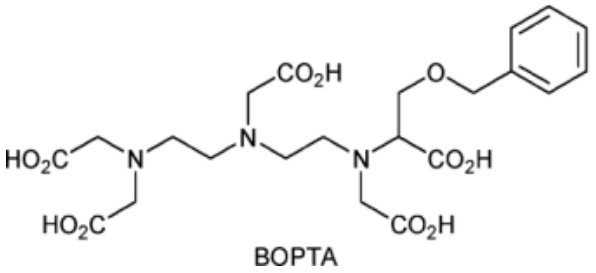
DTTA-*N*-CE



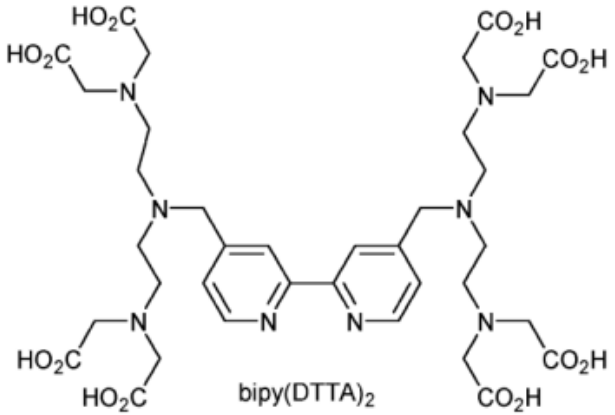
DTTA-*N'*-CE



DTPA-bis(amide)

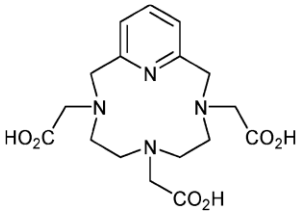


BOPTA

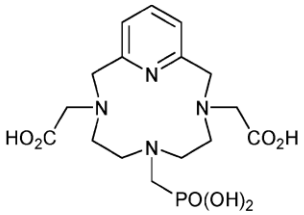


bipy(DTTA)$_2$

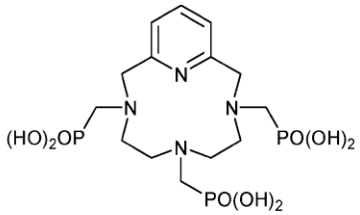
Nuovi leganti polidentati per CA di Gd(III)



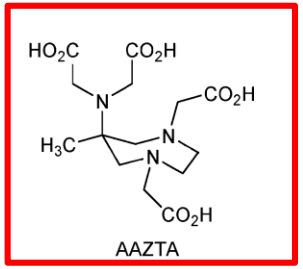
pyDO3A



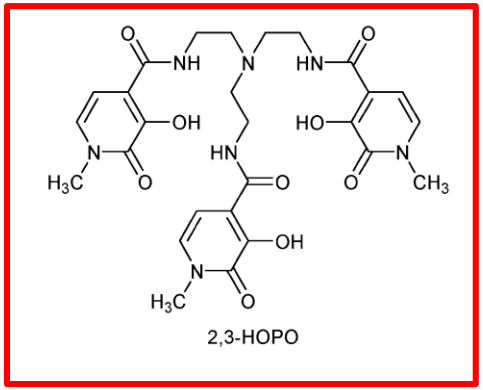
pyDO2AP



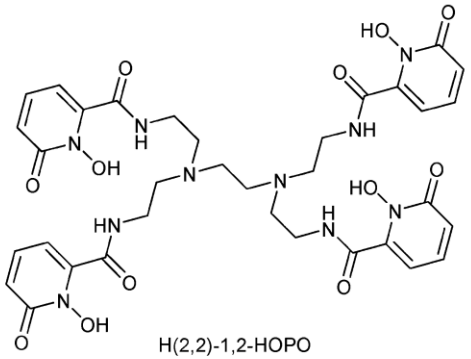
pyDO3P



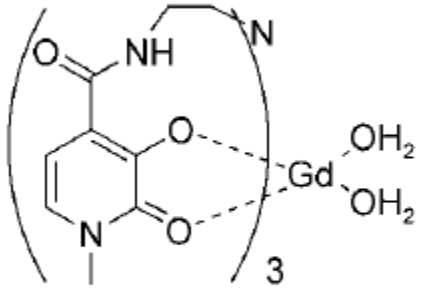
AAZTA



2,3-HOPO

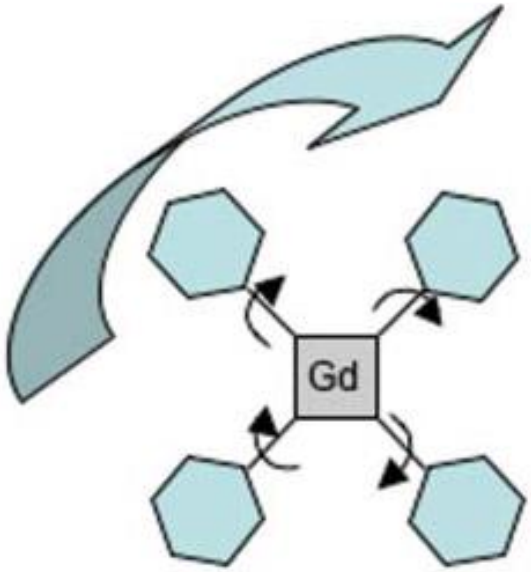


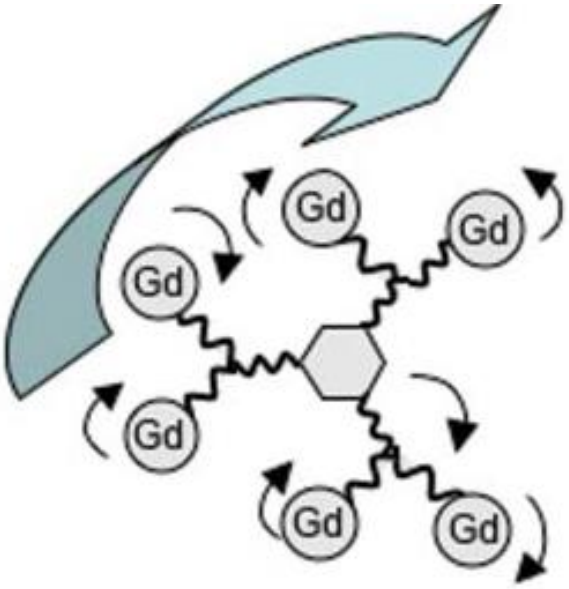
H(2,2)-1,2-HOPO



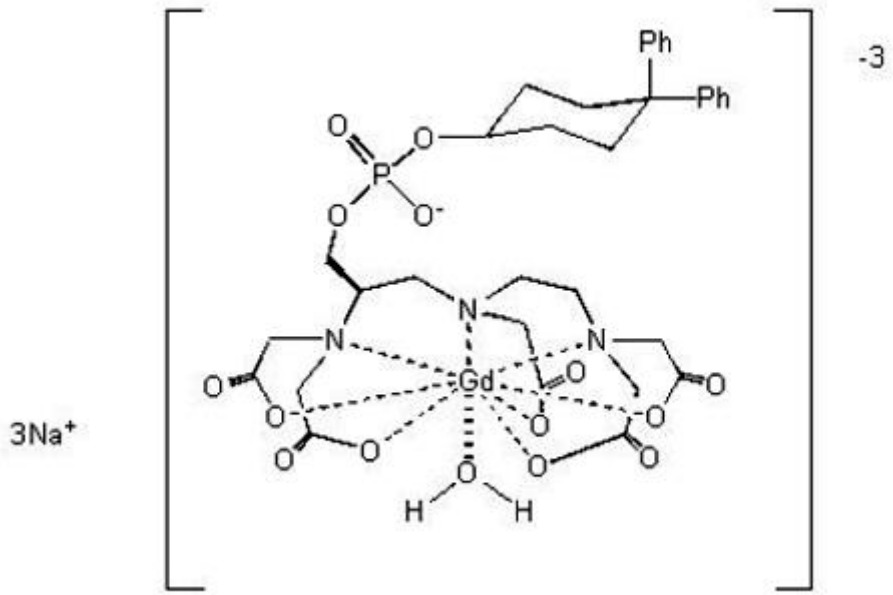
[Gd{tren(1-Me-3,2-hopo)$_3$}(H_2O)$_2$]

Strategie per aumentare τ_M

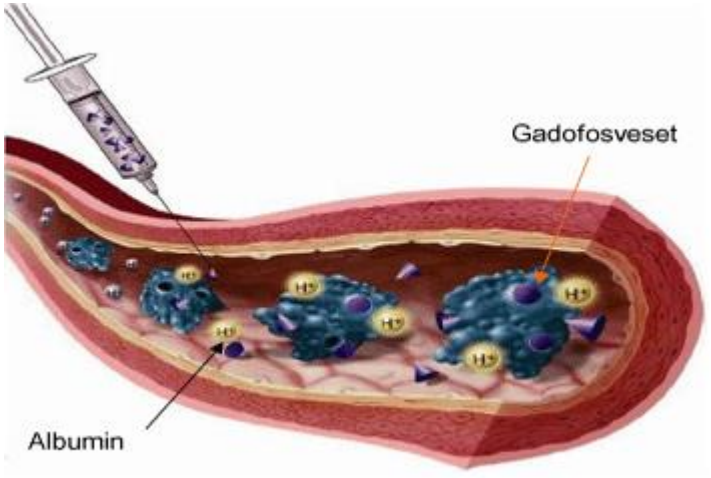




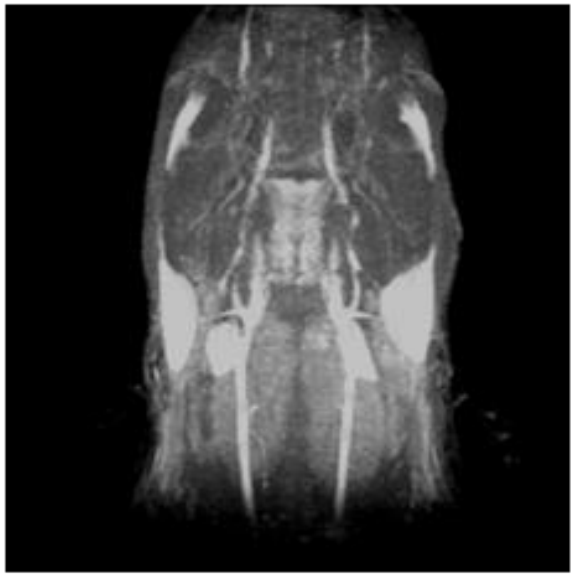
Blood pool contrast agents



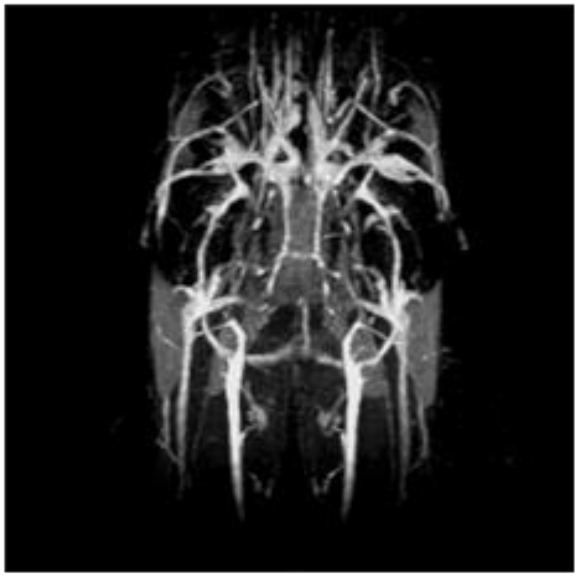
Vasovist®



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

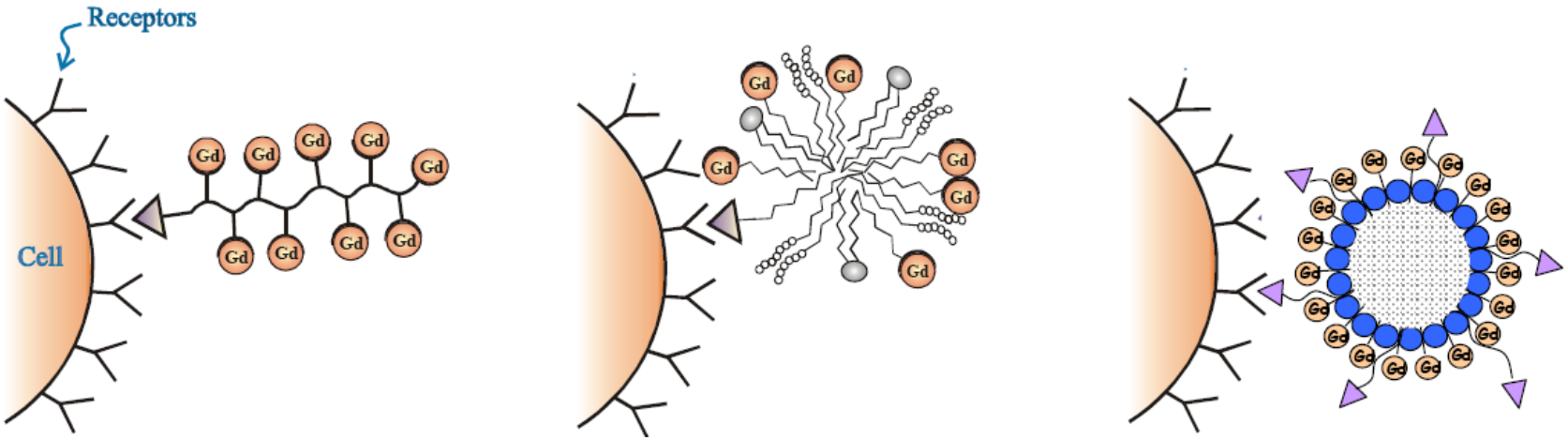
Towards molecular imaging with MRI

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

C > 125 μM

Several strategies can be adopted

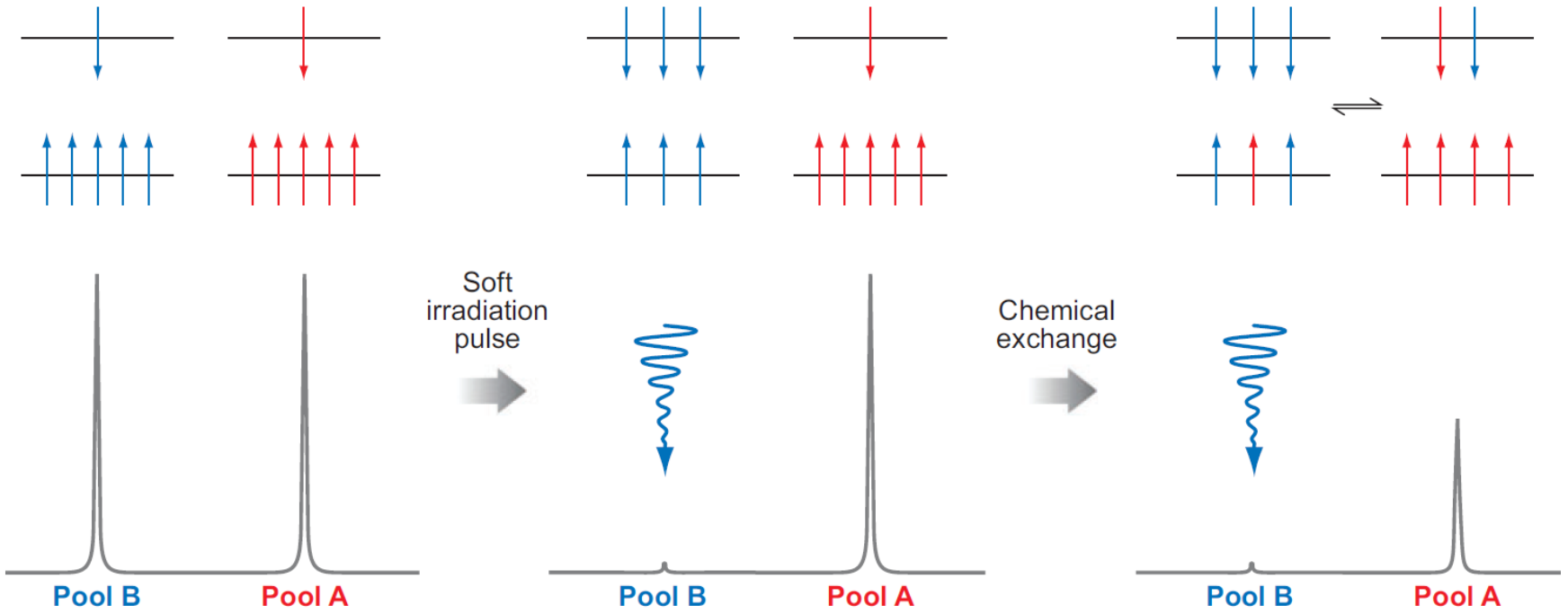
- Gd-chelates covalently or non-covalently linked to biocompatible polymer (proteins, polysaccharides, etc…)
- Self-assembling of complexes (e.g. micelles)
- Use of Gd-loaded nanoparticles (e.g. liposomes,…)



CEST Contrast Agents

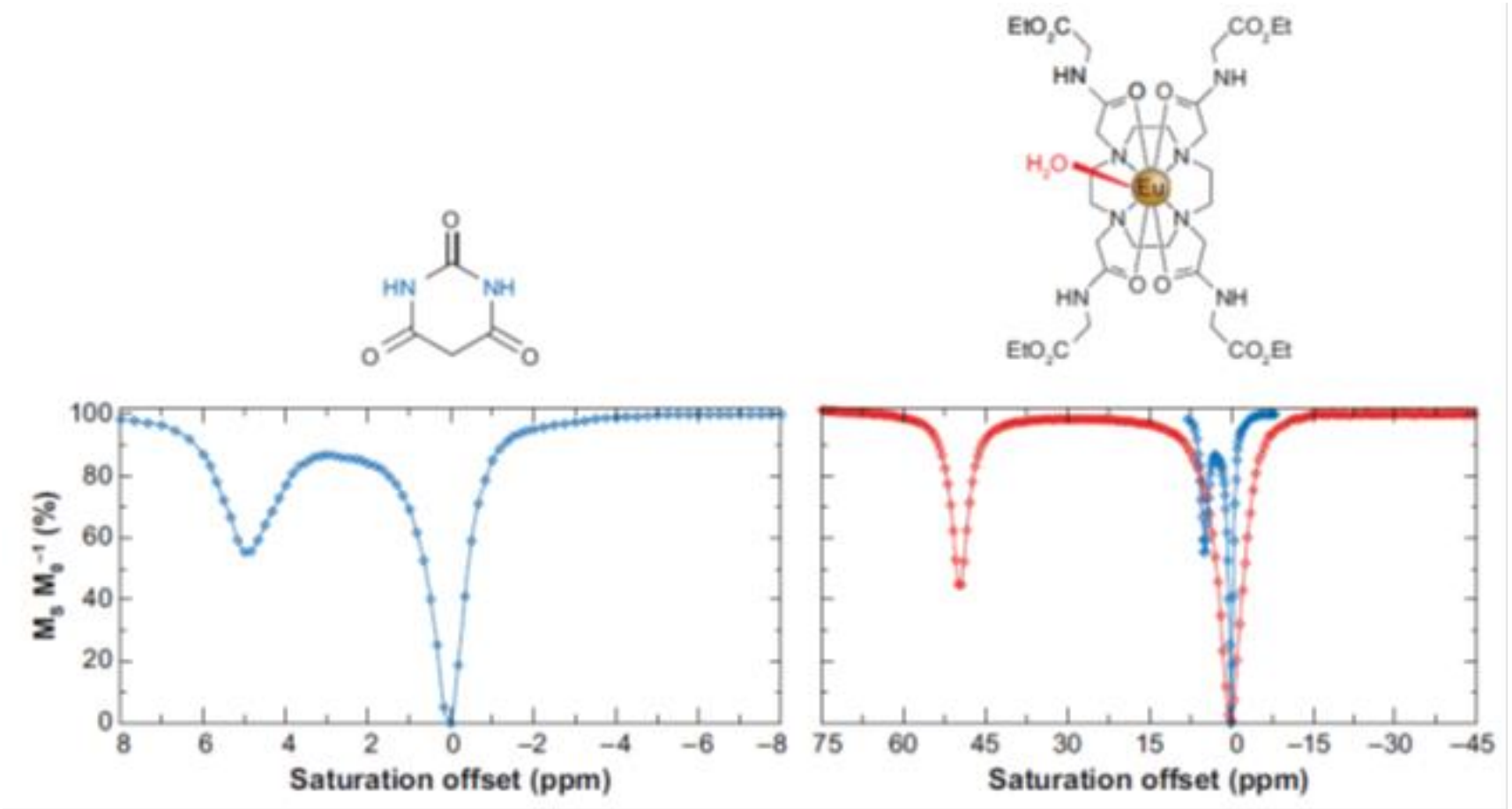
Chemical Exchange Saturation Transfer

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



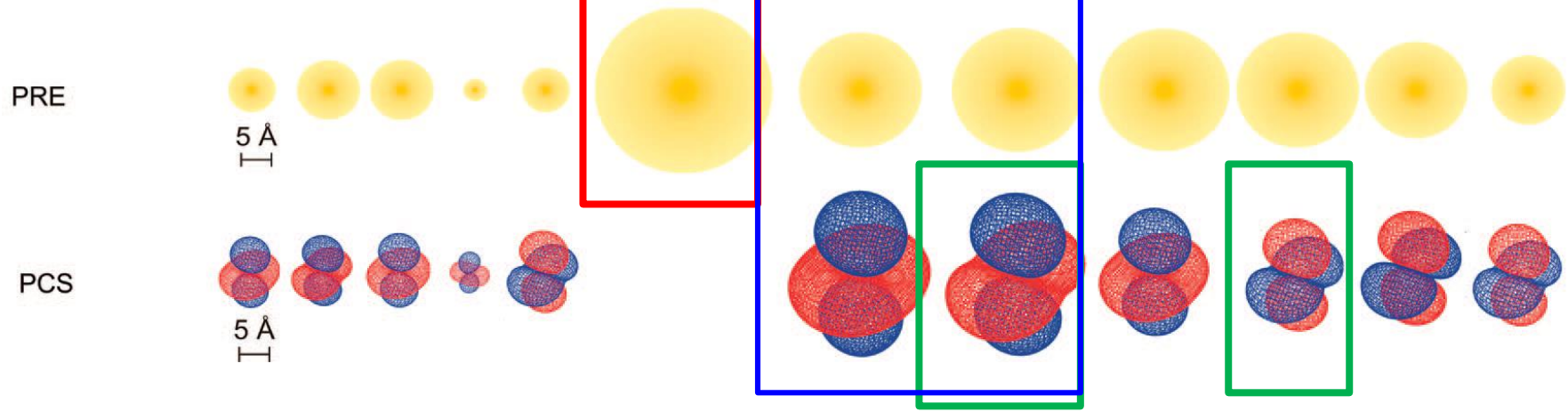
$$k_{CEST} < \Delta\omega$$

CEST and PARACEST agents: saturation offset



isotropo

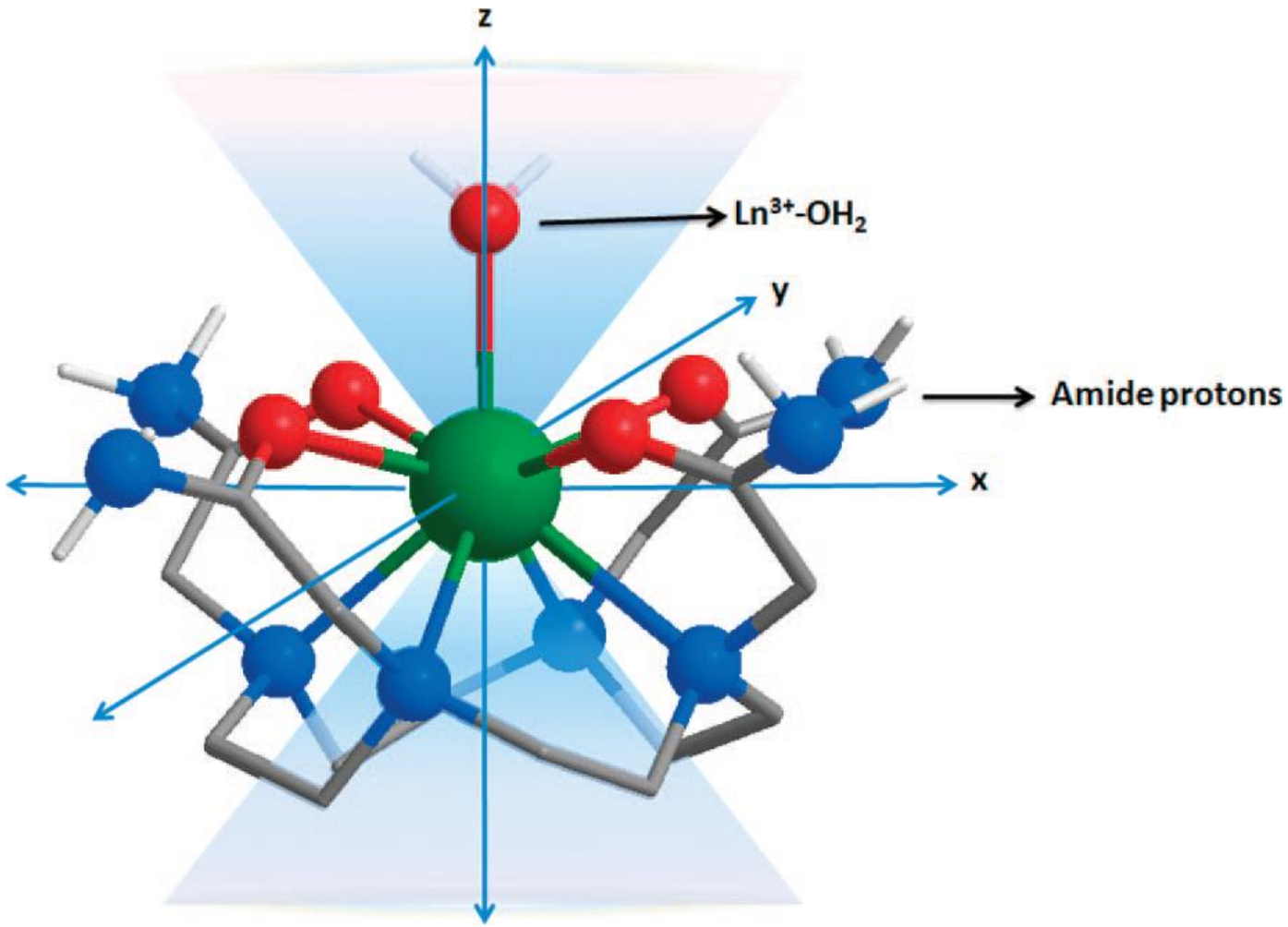
Ln	La^{3+}	Ce^{3+}	Pr^{3+}	Nd^{3+}	Sm^{3+}	Eu^{3+}	Gd^{3+}	Tb^{3+}	Dy^{3+}	Ho^{3+}	Er^{3+}	Tm^{3+}	Yb^{3+}	Lu^{3+}
$\mu_{eff}/\mu B$ cald.	0.00	2.54	3.58	3.68	0.85	0.00	7.94	9.72	10.63	10.60	9.59	7.57	4.53	0.00
$\chi/10^{-32}m^3$	0.0	5.6	11.2	11.4	0.6	6.0	55.1	82.7	99.2	98.5	80.3	50.0	18.0	0
$\Delta\chi_{ax}/10^{-32}m^3$	0	2.1	3.4	1.7	0.2	-2.3	0	42.1	34.7	18.5	-11.6	-21.9	-8.3	0
$\Delta\chi_{rh}/10^{-32}m^3$	0	0.7	2.1	0.4	-0.1	-1.6	0	11.2	20.3	5.8	-8.6	-20.1	-5.8	0

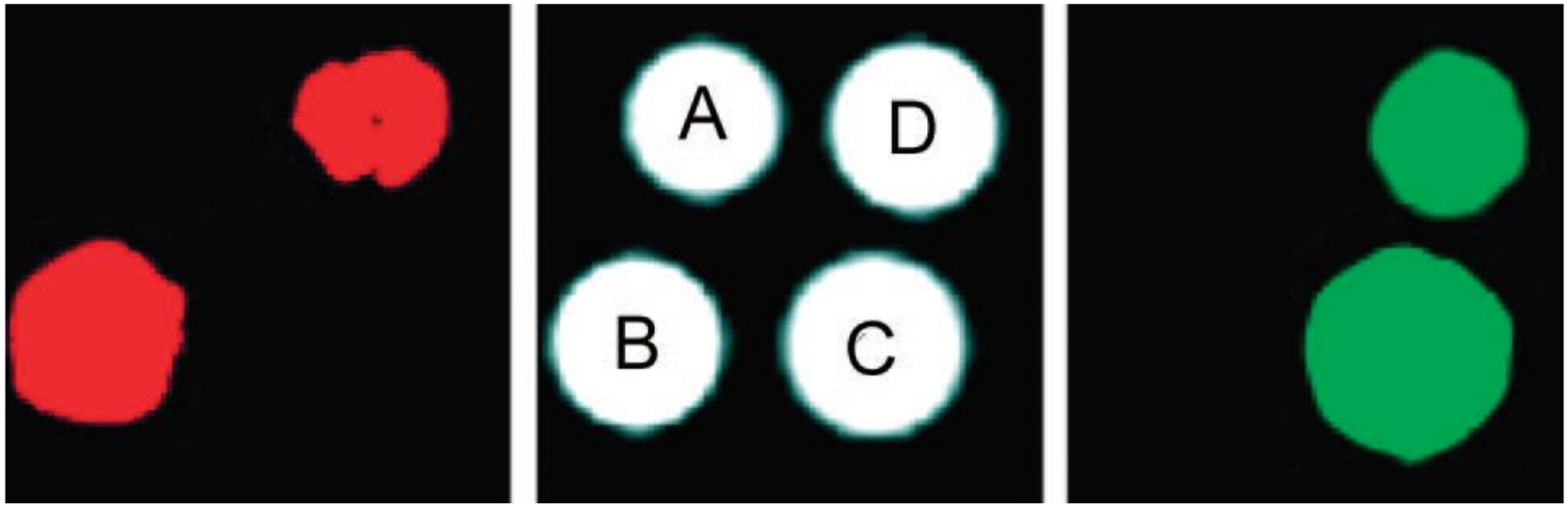


PRE = *Paramagnetic Relaxation Enhancement*

PCS = *Pseudo-Contact Shift*

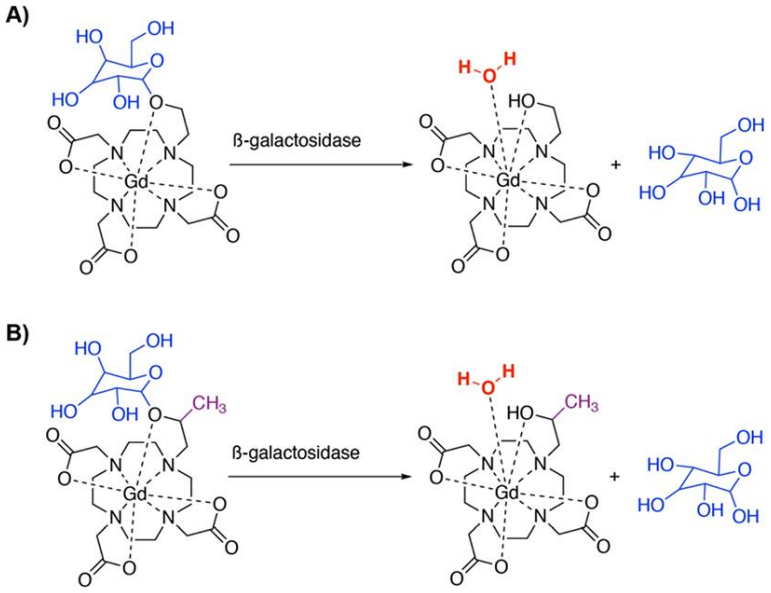
determina la variazione di chemical shift indotta da ciascuno ione sui nuclei vicini e le iso-superfici rappresentano la grandezza e il segno del chemical shift

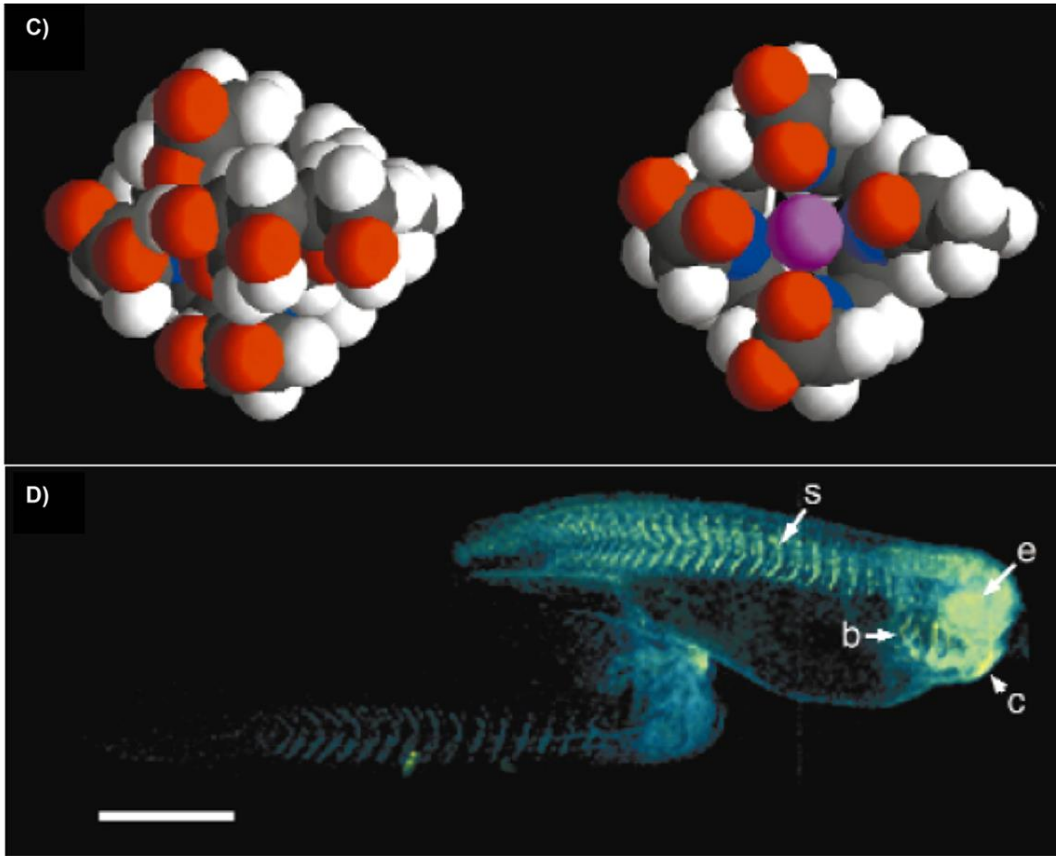

z
Ln^{3+}-OH_2
y
Amide protons
x



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

Responsive (*smart*) CA





55 M water signal was imaged and this signal was augmented by 0.5 mM contrast agent which in turn was augmented by a 4 µM enzyme concentration (right image)

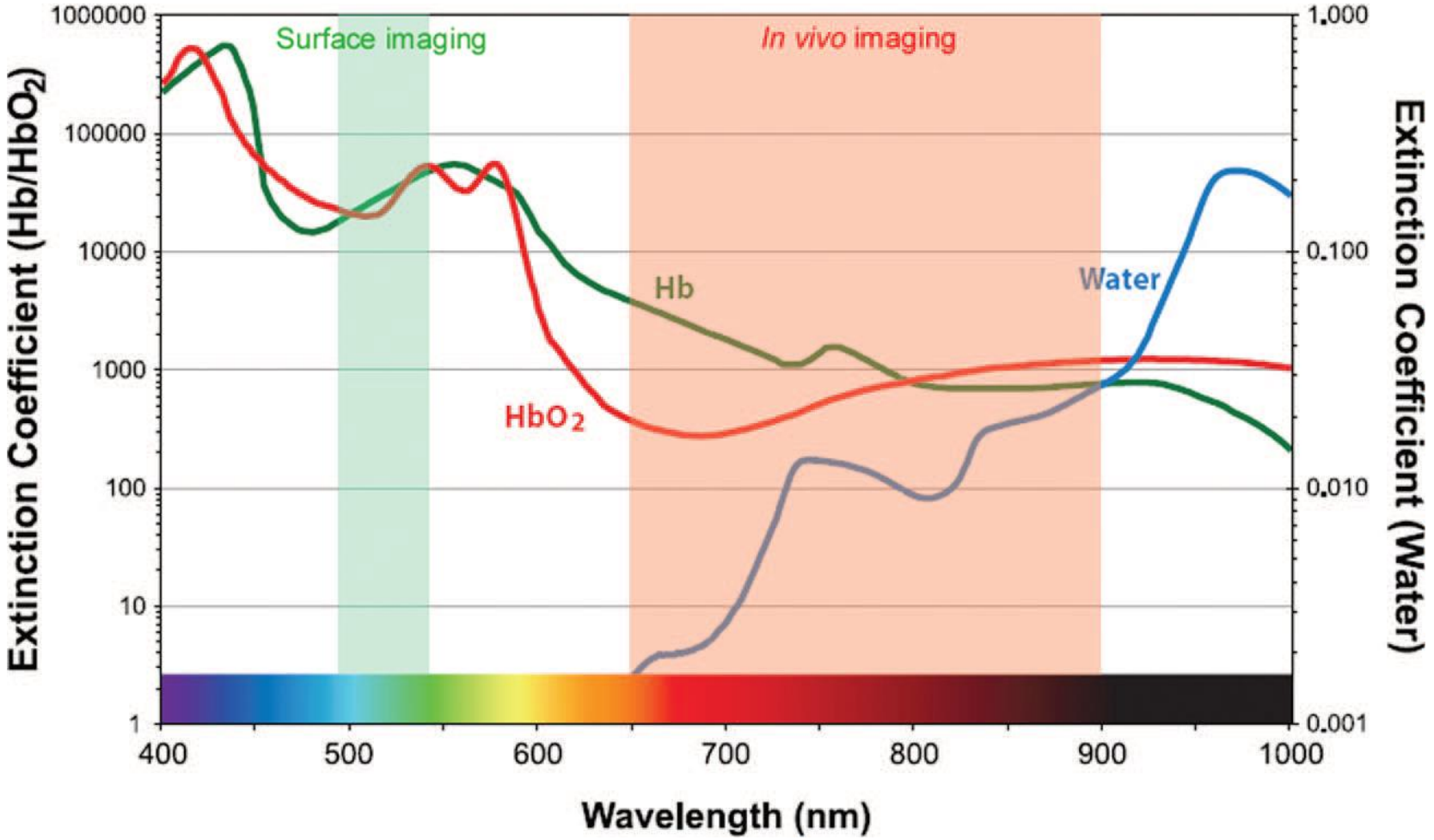
T_2 contrast agents
super-paramagnetic iron oxide particles (SPIO)
d = 60 – 250 nm

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

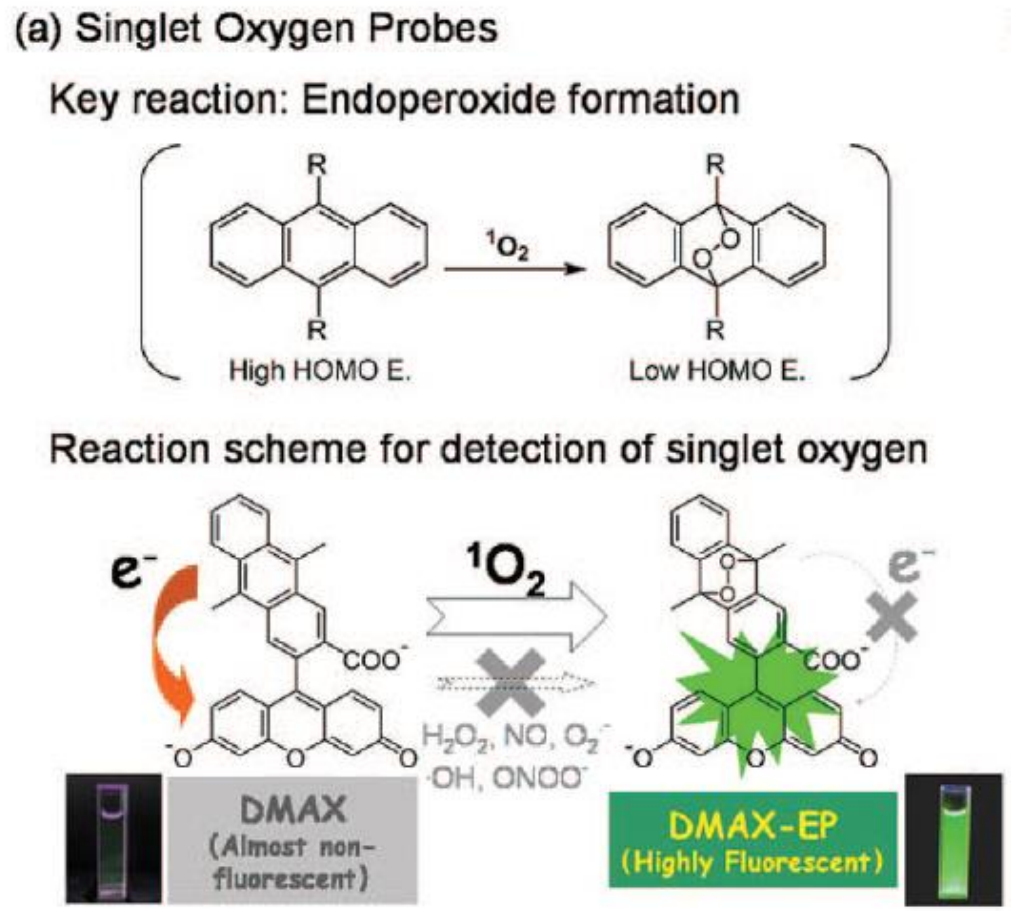
Imaging ottico

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

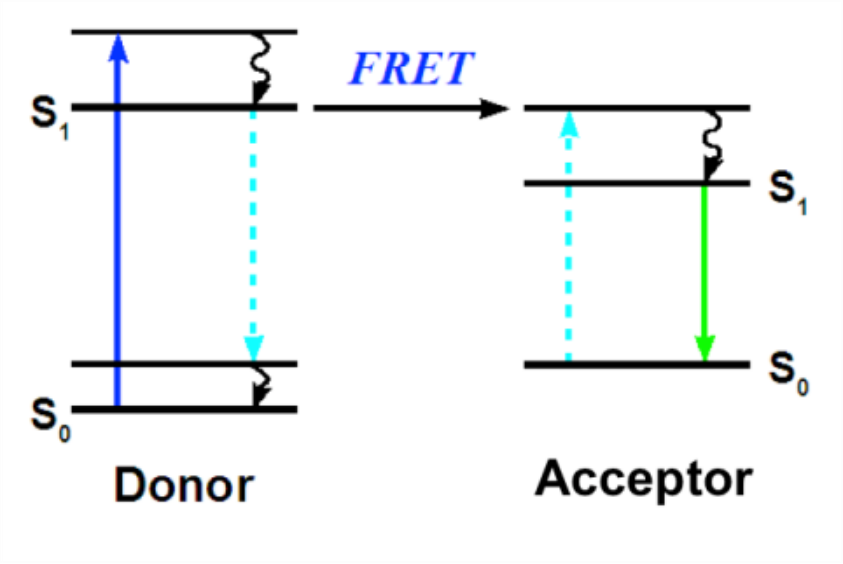
- Window
- Stokes shift
- Brightness
- Stability



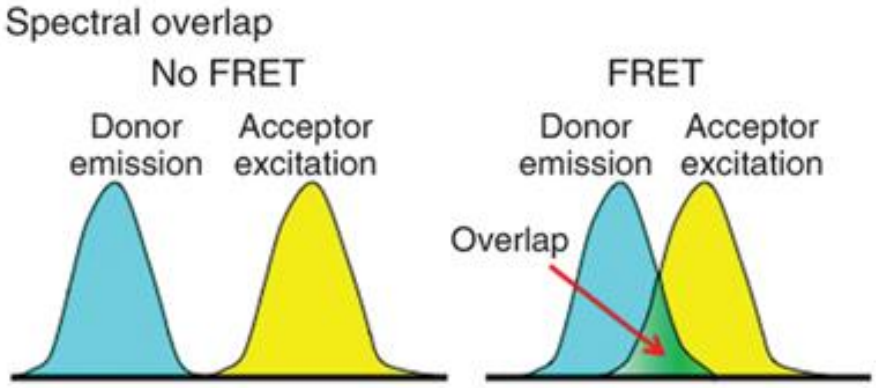
Esempio di *switchable fluorescent probe* sensore di $^1O_2$

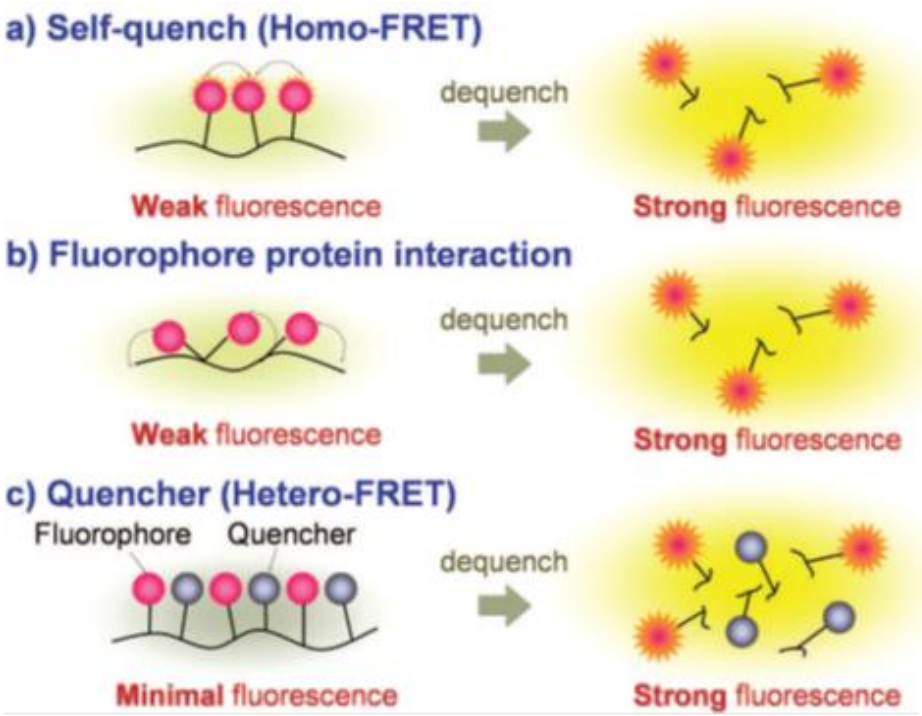


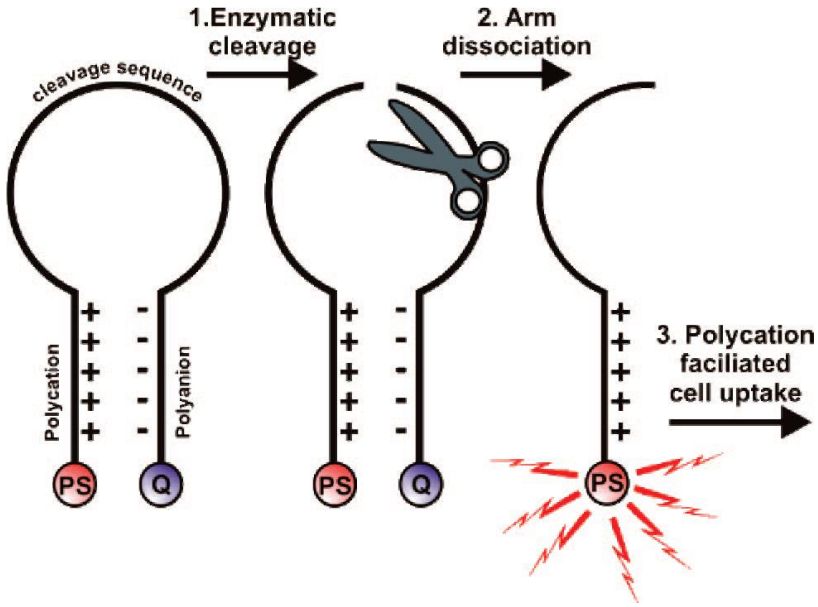
FRET *fluorescence – resonance energy transfer*

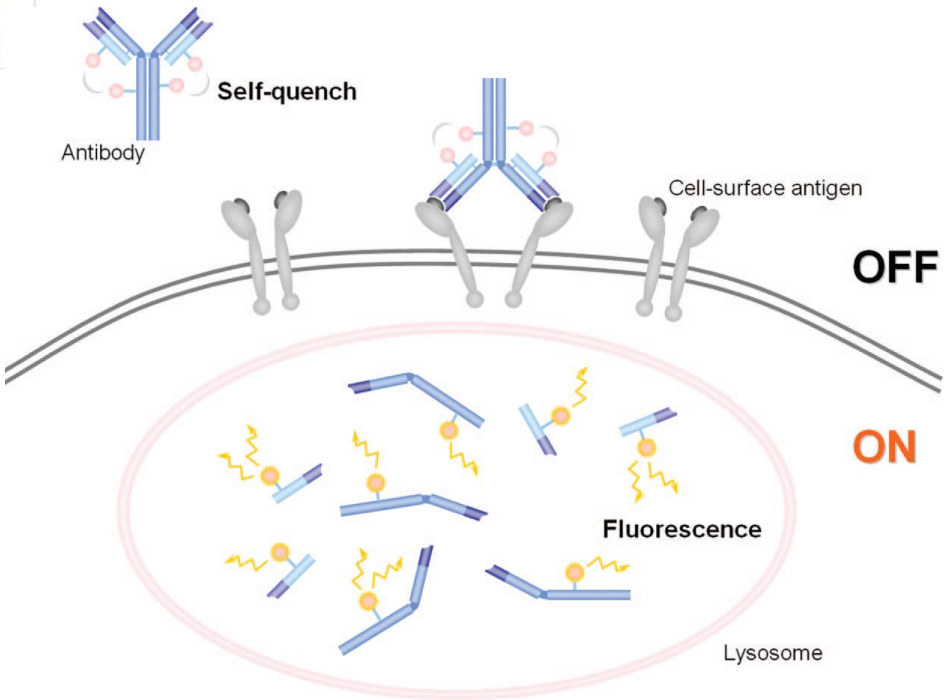


$1/r^6$

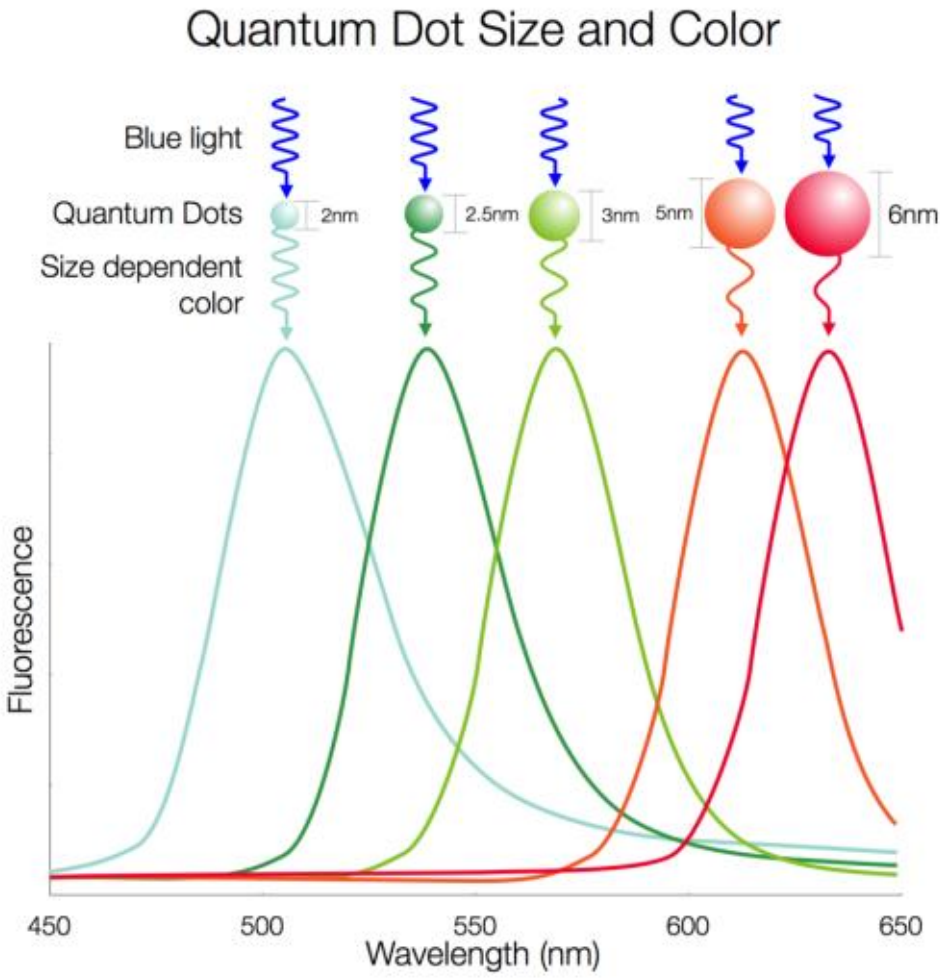



a) Self-quench (Homo-FRET)
dequench
Weak fluorescence
Strong fluorescence
b) Fluorophore protein interaction
dequench
Weak fluorescence
Strong fluorescence
c) Quencher (Hetero-FRET)
Fluorophore
Quencher
dequench
Minimal fluorescence
Strong fluorescence


1.Enzymatic cleavage
2. Arm dissociation
cleavage sequence
Polycation
Polyanion
PS
Q
3. Polycation faciliated cell uptake


Antibody
Self-quench
Cell-surface antigen
OFF
ON
Fluorescence
Lysosome

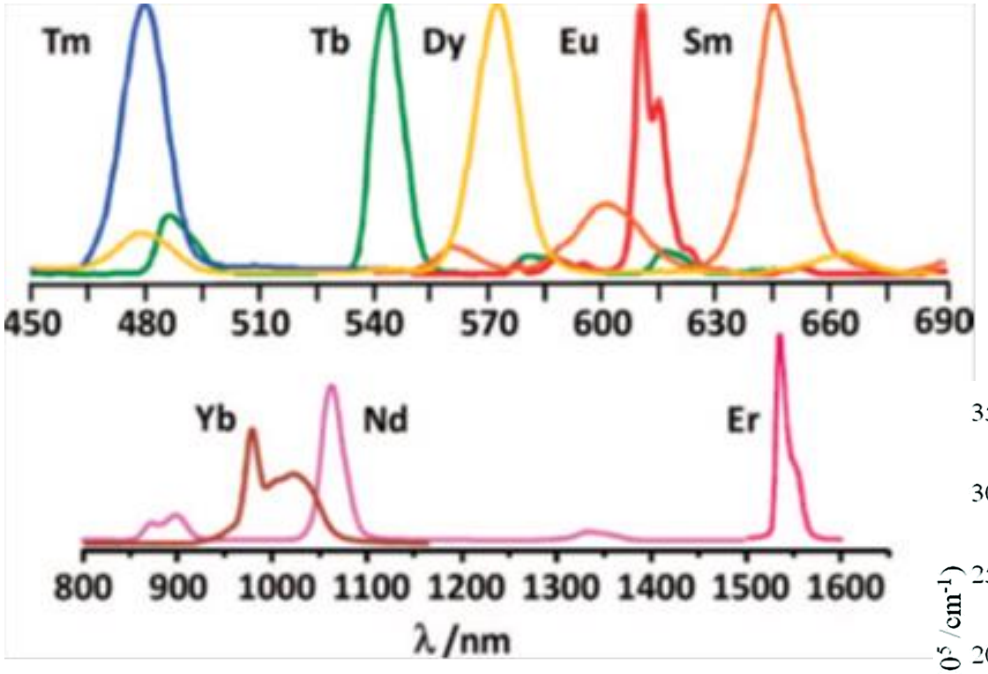
quantum dots (QD)
nano-cristalli di semiconduttori (e.g. CdSe)



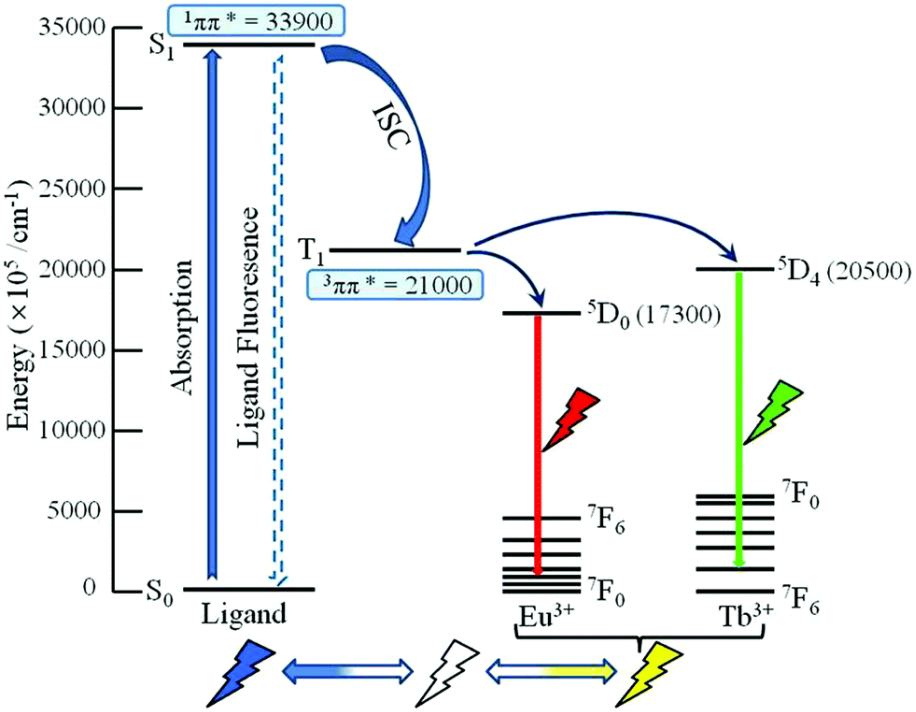
Ø 2 – 10 nm

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

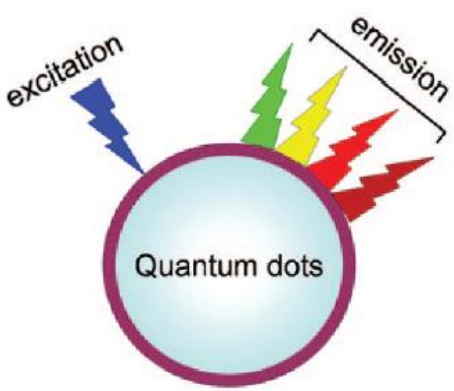
Complessi dei lantanidi

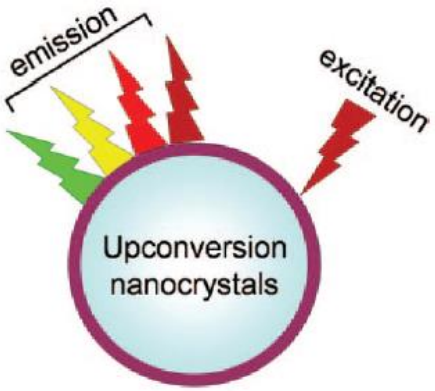


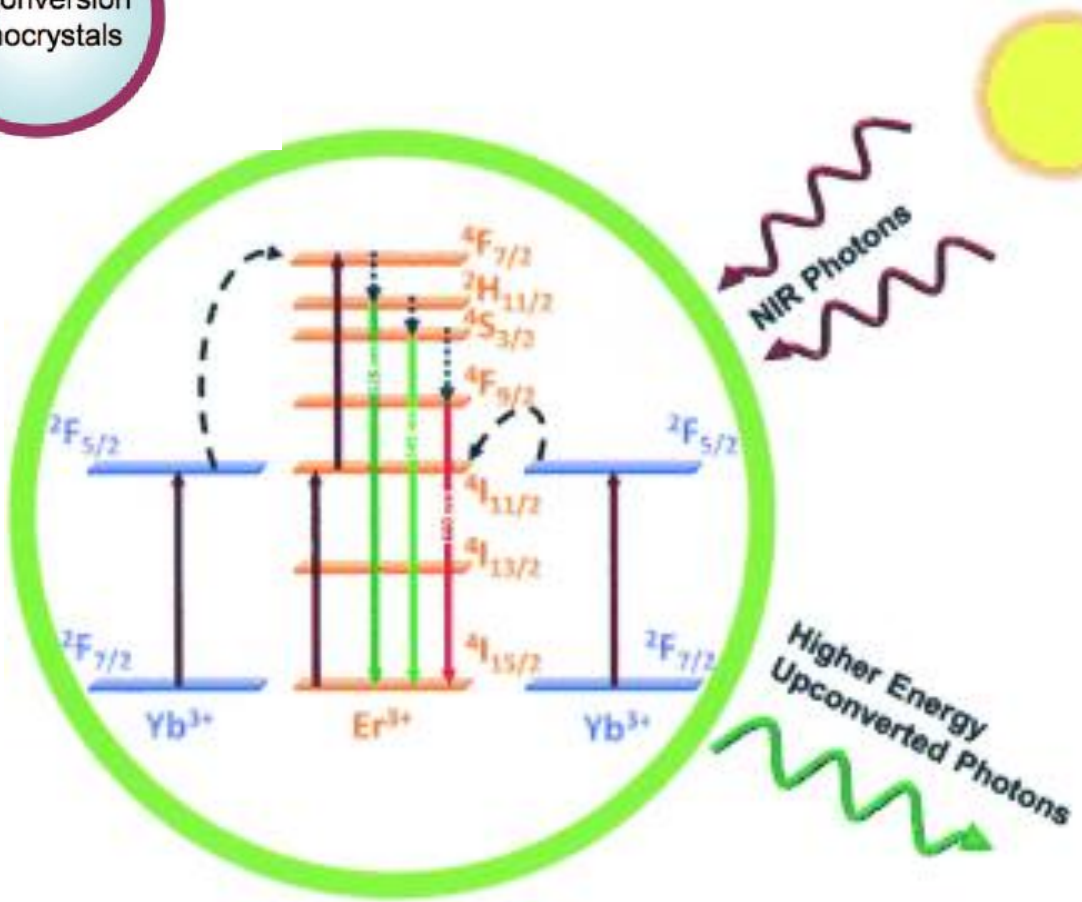
Effetto antenna dei leganti



Upconverting QDs e LnNPs

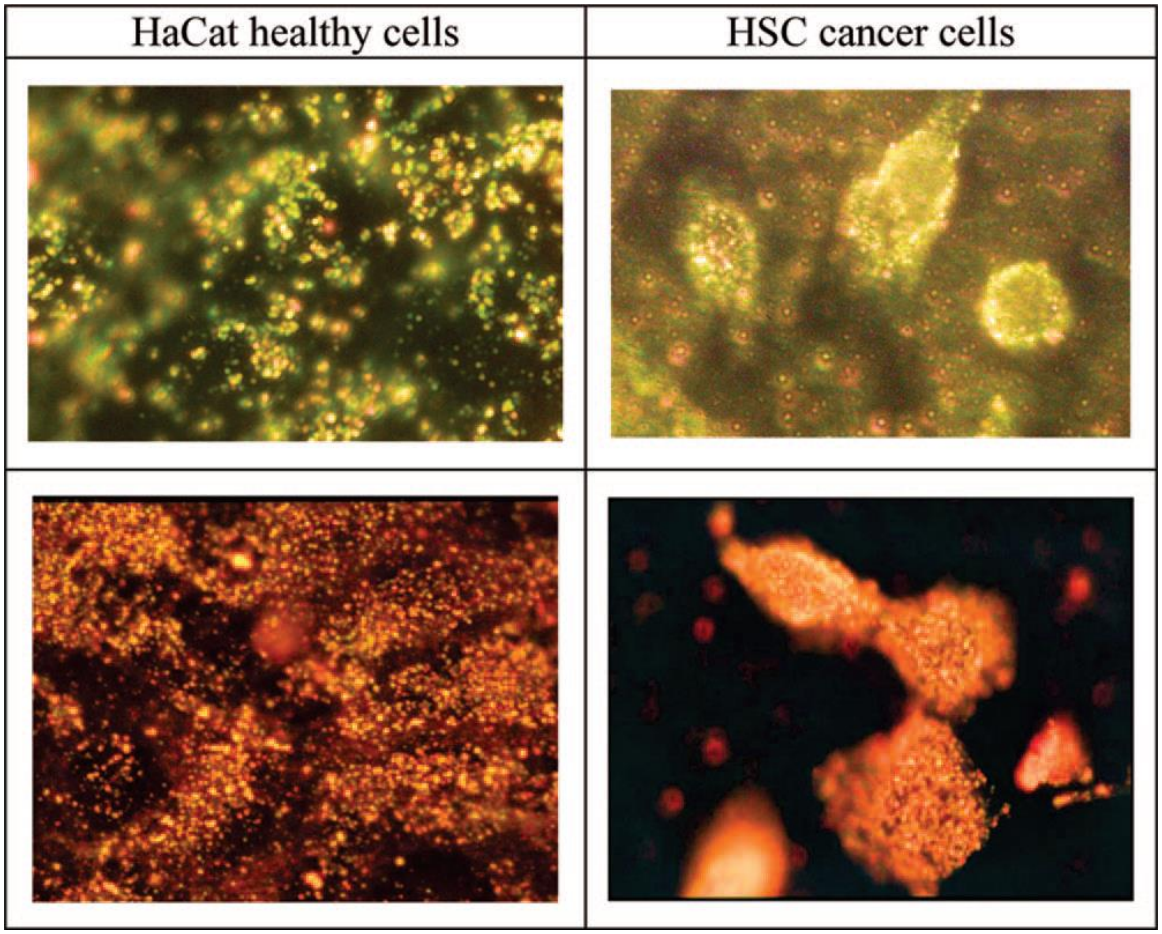






Dark-field fluorescence imaging con AuNP

scattered light



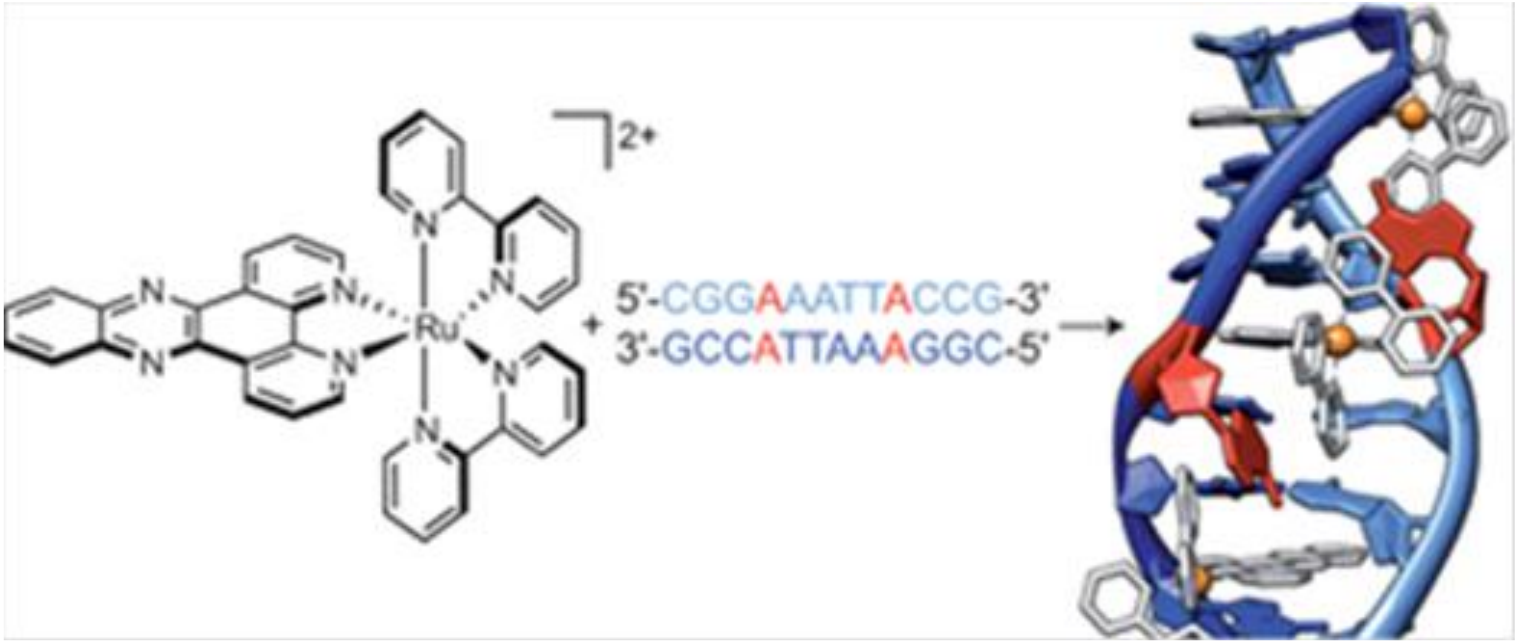
Au nanospheres

Au nanorods

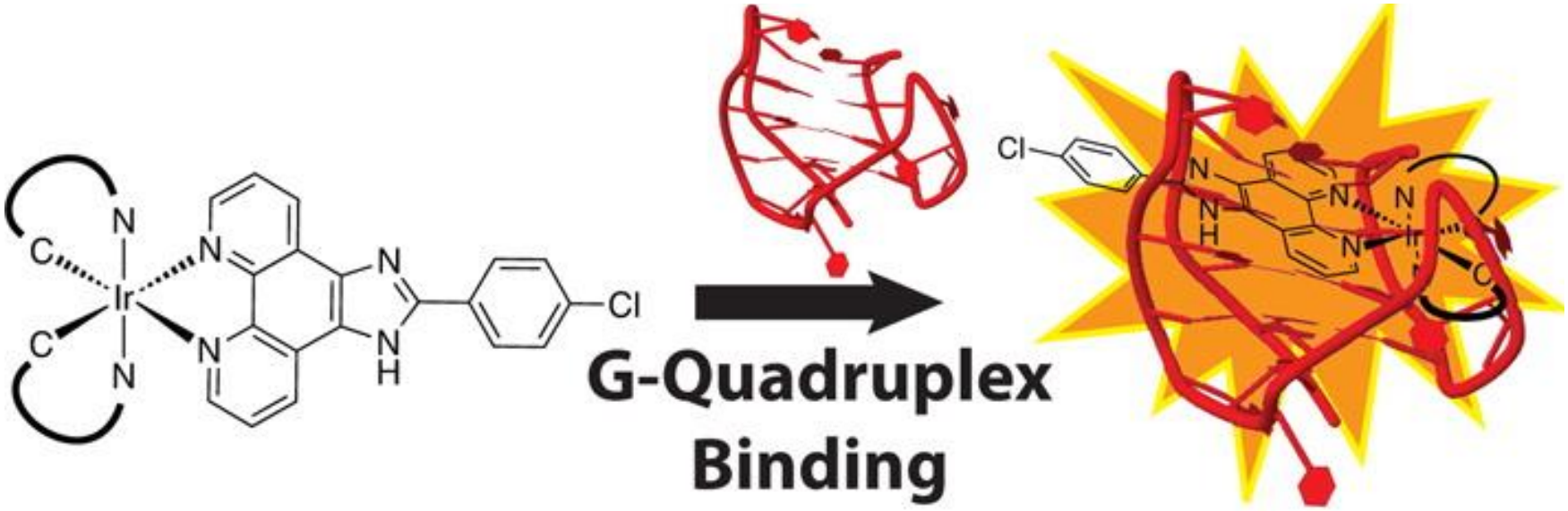
AuNP coniugate a anticorpi anti-EGFR

EGFR = *epidermal growth factor receptor*, marcatore tumorale

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



G-quadruplex sensing



Sviluppi futuri

Multimodal imaging agents and theranostics