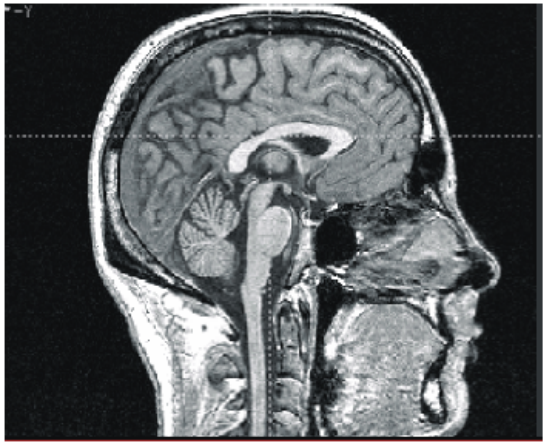
Magnetic Resonance Imaging (MRI)



MR sagittal image of human head

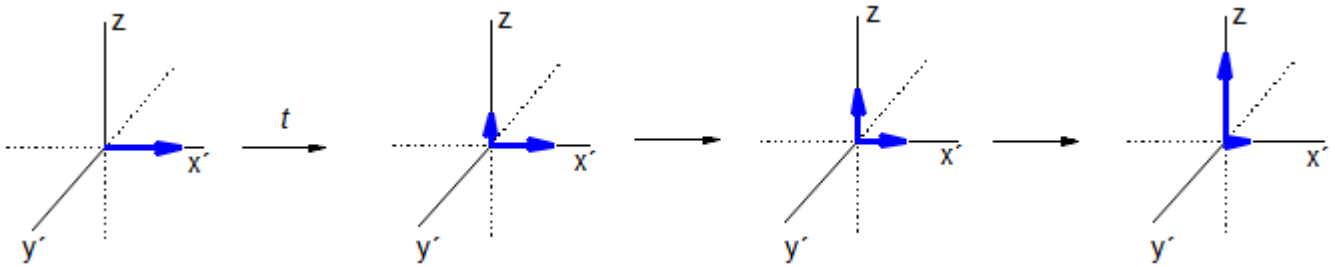
- Non-invasive and safe technique
- Great spatial resolution (μm scale)
- Outstanding diagnostic capability

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

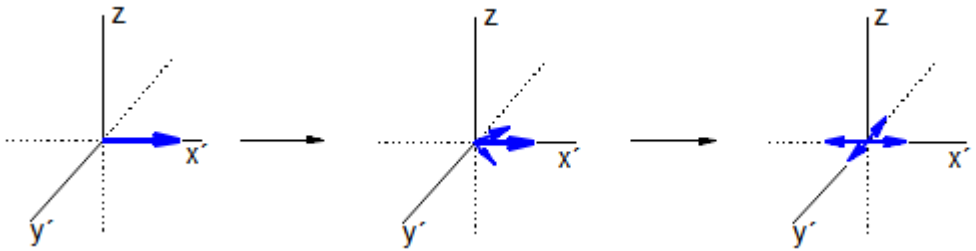
The contrast is mainly generated by difference in the relaxation times (T_1 and T_2) of water protons

Nuclear spin relaxation processes

T_1 Relaxation (Spin-Lattice Relaxation)



T_2 Relaxation (Spin-Spin Relaxation)



T_1 ca. 5 T_2

Contrast Agents (CA)

CA's contain paramagnetic atoms. 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.

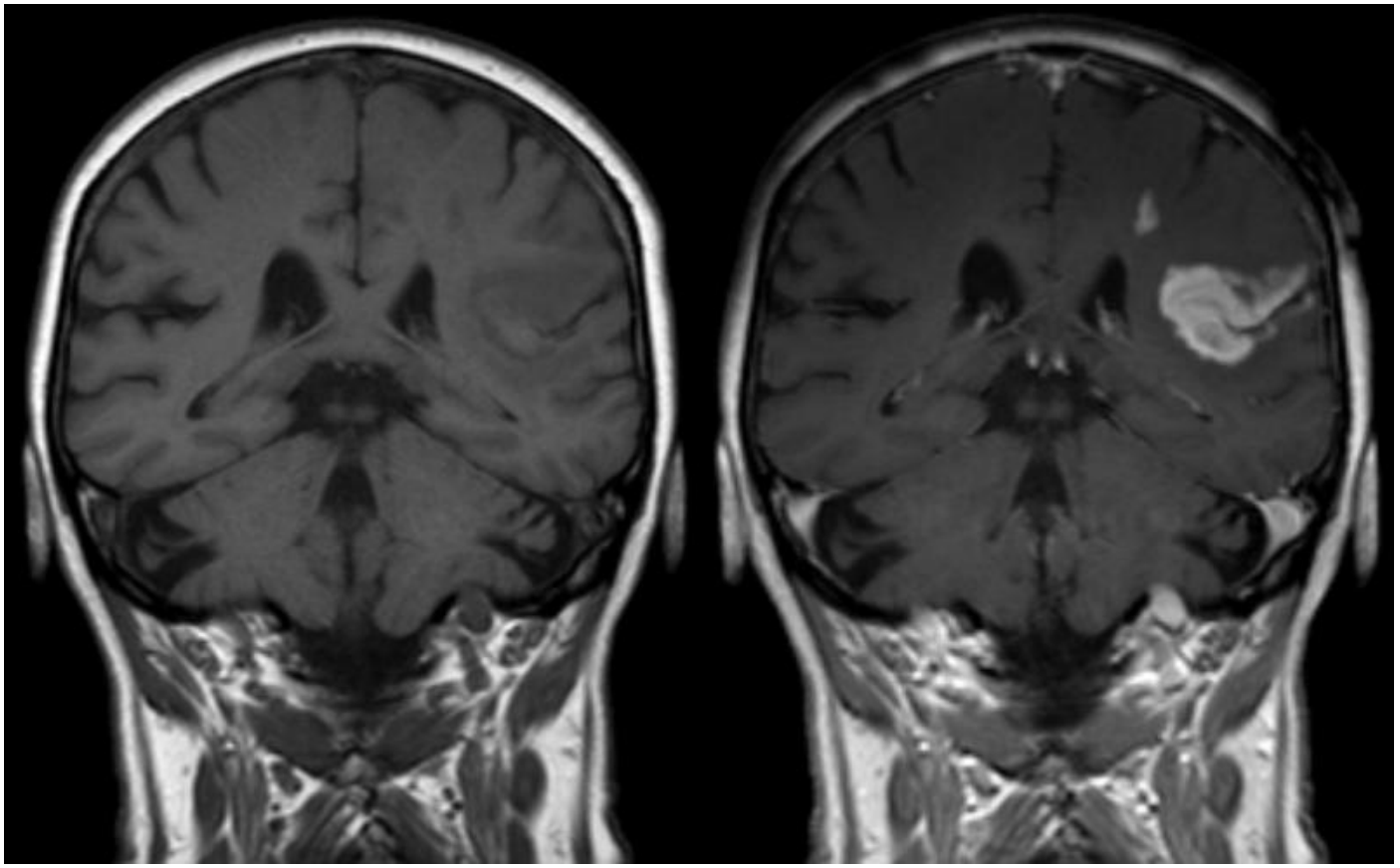
T_1 contrast agents (positive = hyper-intense signal): paramagnetic metal complexes Fe(III), Mn(II), Gd(III)

T_2 contrast agents (negative = ipo-intense signal): Small super-Paramagnetic Iron Oxide nanoparticles (SPIO) and Ultra-Small super-Paramagnetic Iron Oxide NPs (USPIO)

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

3 classes of CAs: non-specific extra-cellular agents, organ-specific agents, and blood-specific agents

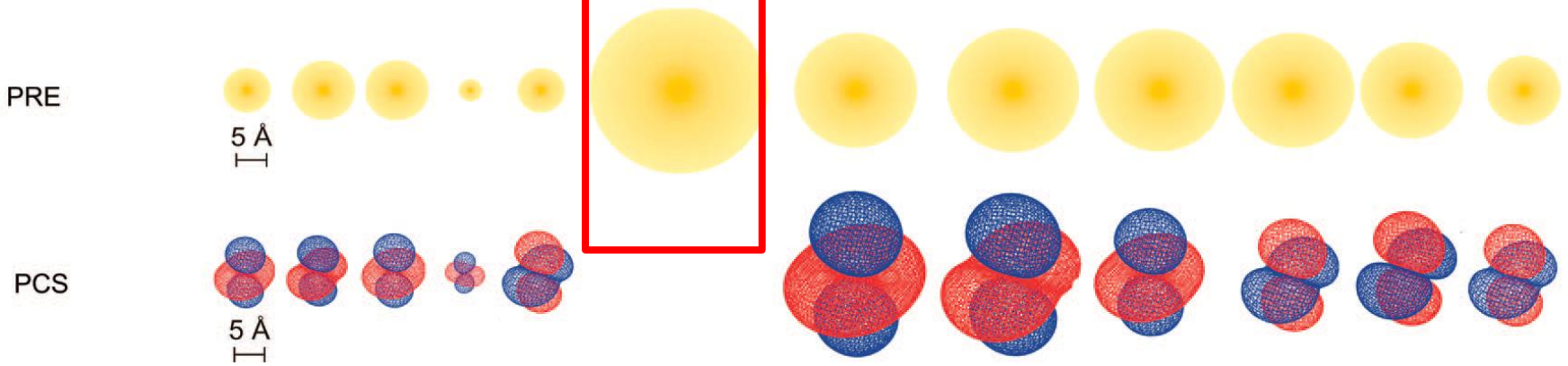
No CA extra-cellular CA



Defect of the blood-brain barrier after stroke shown in MRI.
T1-weighted images.

The relaxation time of the **electronic** spin moment of Gd(III) is much longer than for other lanthanide ions (*totally symmetrical spin state*), leading to a more efficient relaxation of nuclear spins of bulk water molecules.

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*

The diameter of the yellow sphere indicates the distance from the metal core at which the protons undergo a significant shortening of the nuclear spin relaxation time (i.e. the larger, the better).

~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

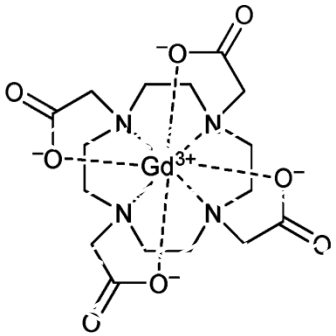
Market > 1 billion $/year

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

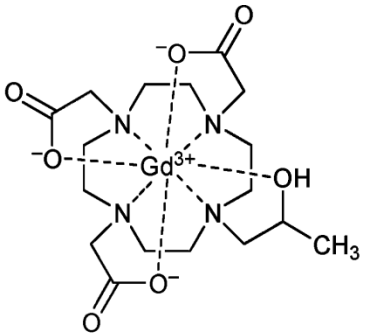
The Gd(III) ion is quite toxic (LD_{50} = 0.2 mmol·kg^{-1})

Some commercial T_1 contrast agents

(extracellular fluid CAs)

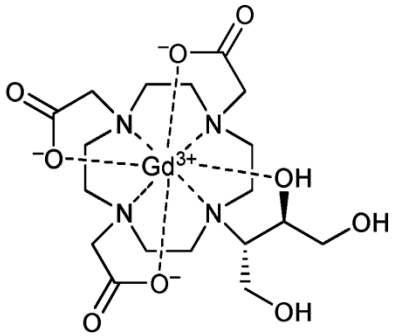


Gd-DOTA
Dotarem®
(Guerbet)

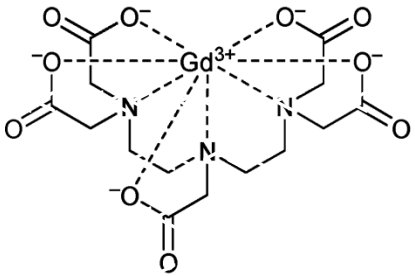


Gd-HP-DO3A
ProHance®
(Bracco)

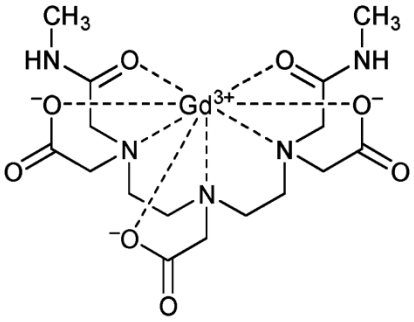
Typical dose =
0.1 – 0.3 mmoles/kg



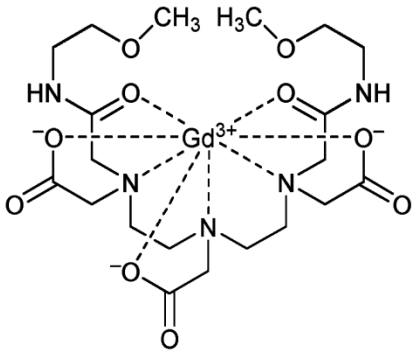
Gd-BT-DO3A
Gadovist®
(Schering)



Gd-DTPA
Magnevist®
(Schering)



Gd-DTPA-BMA
Omniscan®
(Amersham)



Gd-DTPA-BMEA
OptiMARK®
(Mallinckrodt)

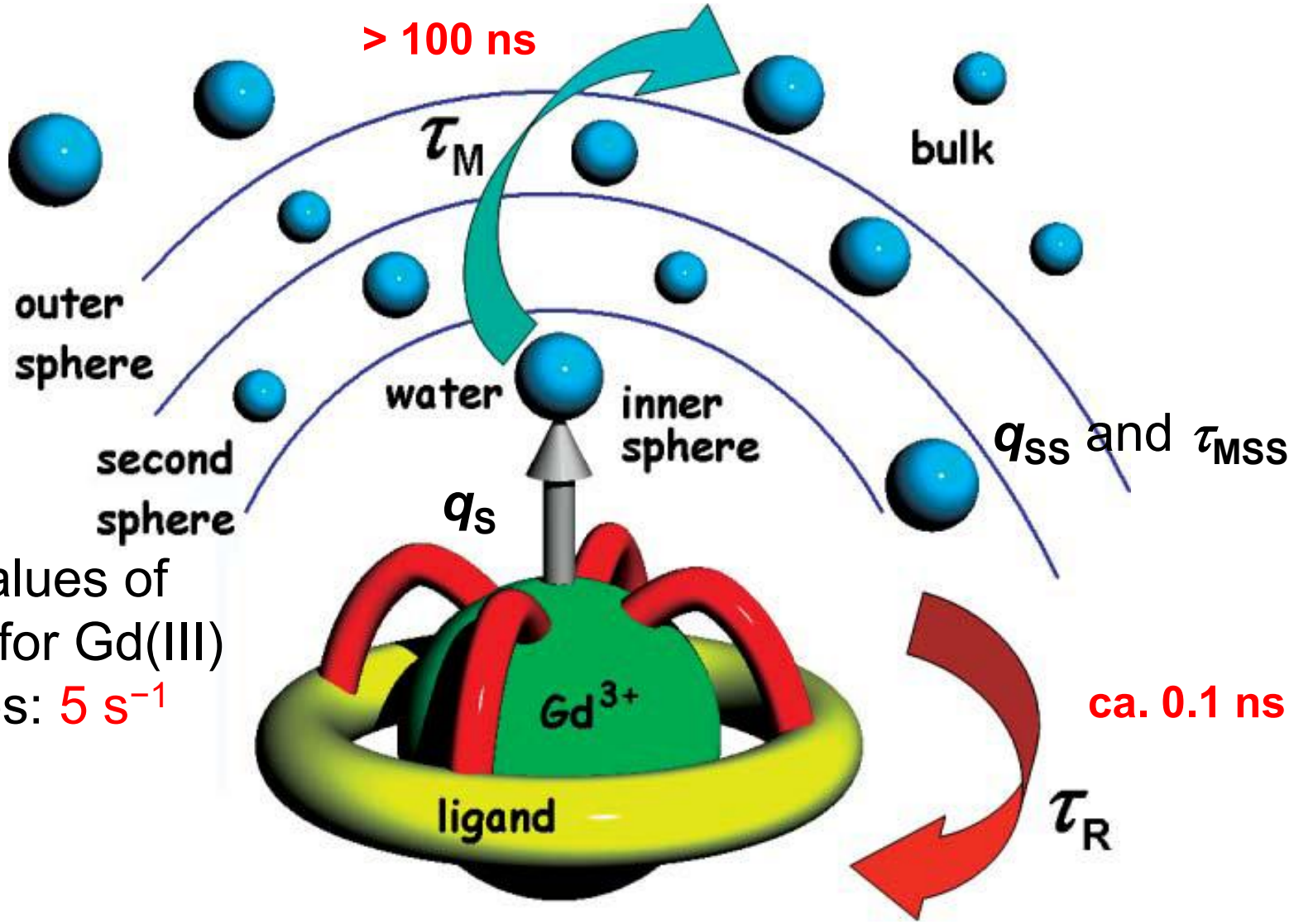
Typically, a pathology is identified because of **anatomical** (e.g., narrower arteries) or **physiological** (e.g., permeable, damaged blood-brain barrier) changes.

Relaxivity

Relaxivity r_1 ($mM^{-1}\ s^{-1}$) of a CA is the ability of its 1 mM solution to **increase** the longitudinal relaxation rate R_1 (= $1/T_1$) of the nuclear spin moment of water protons.
The higher the relaxivity, the better is the CA.

Parameters that affect relaxivity

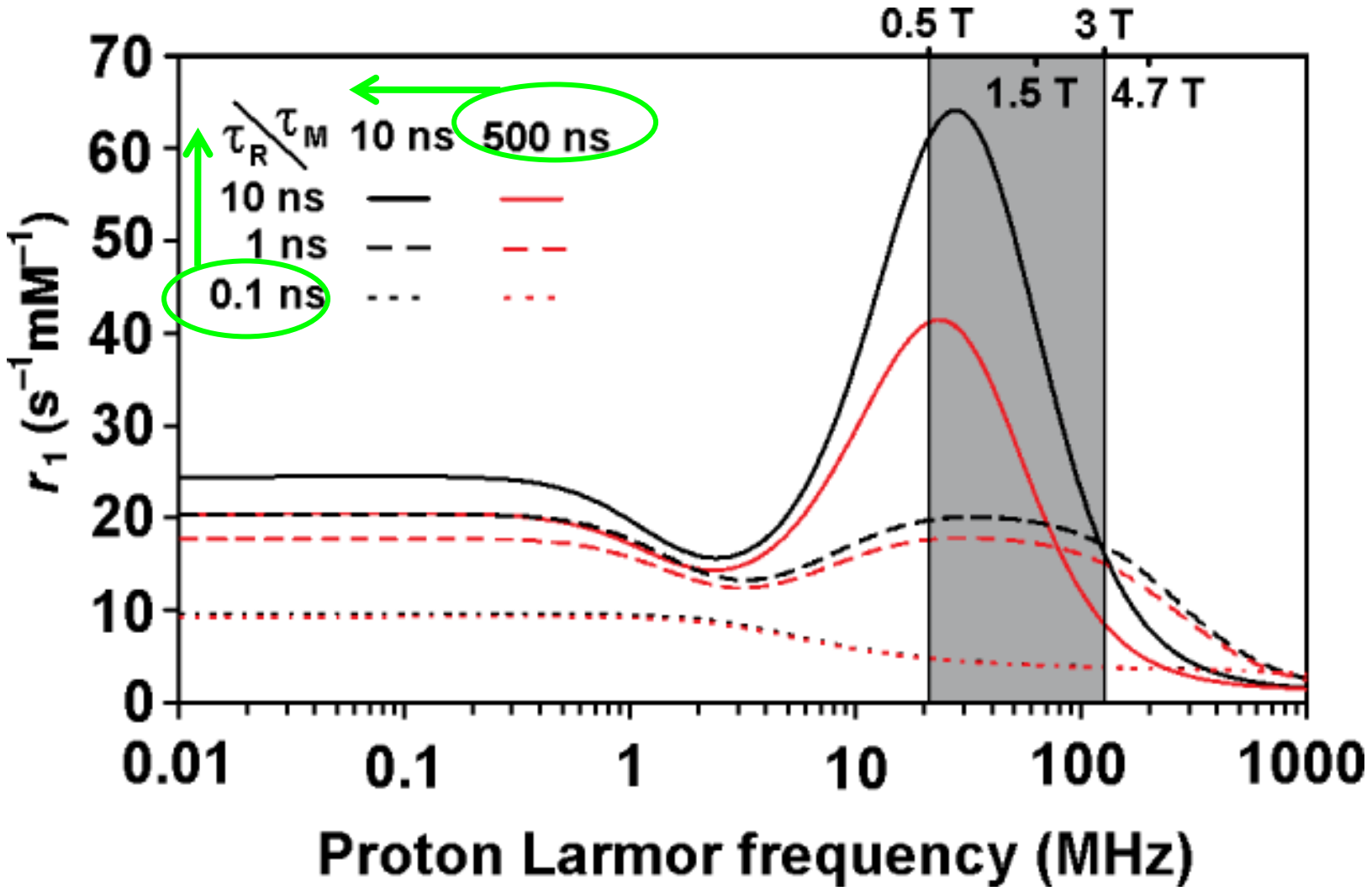
Solomon-Bloembergen-Morgan Theory (*SBM Theory*)



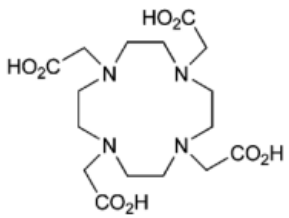
Typical values of relaxivity for Gd(III) complexes: 5 s^{-1} mM^{-1}

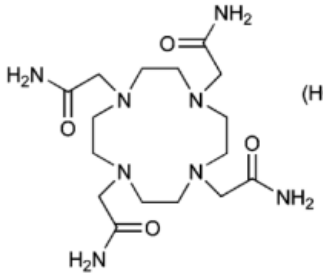
[Gd] > 125 μM for affording a visible contrast

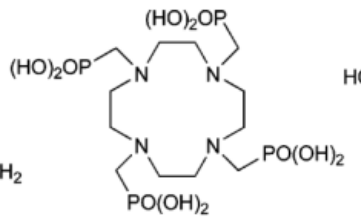
Optimal water-exchange and tumbling times

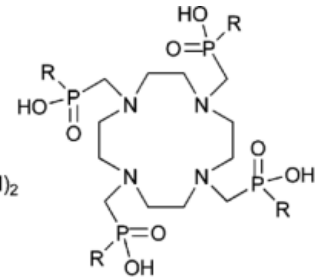


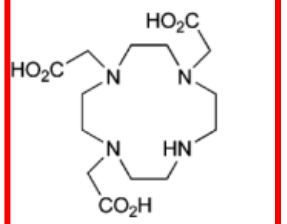
DOTA family

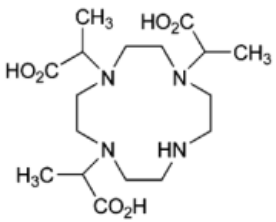

DOTA

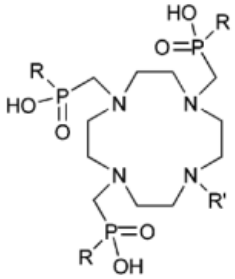

DOTAM

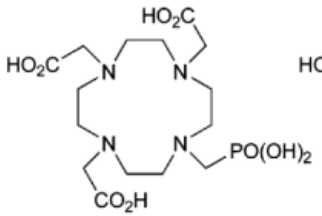

DOTP

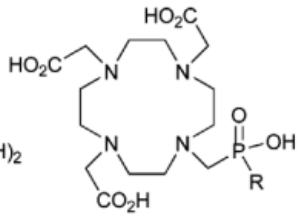

$DOTP^{R}$

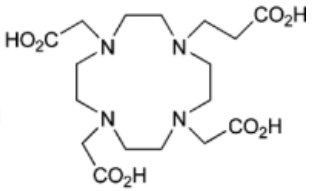

DO3A


DO3MA


$DO3P^{R}$


DO3AP


$DO3AP^{R}$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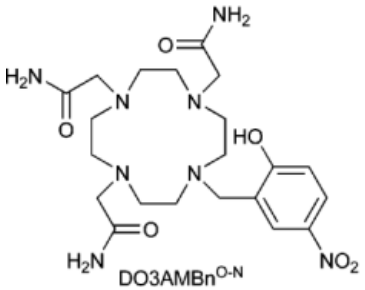
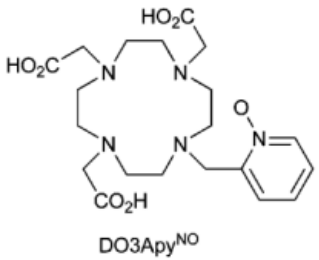
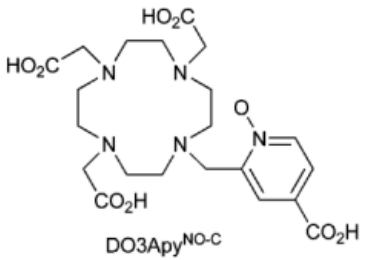
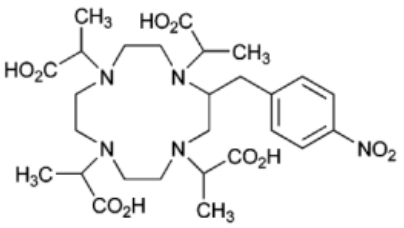

$DO3AMBn^{O-N}$


$DO3Apy^{NO}$


$DO3Apy^{NO-C}$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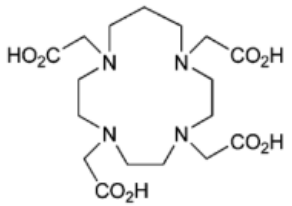
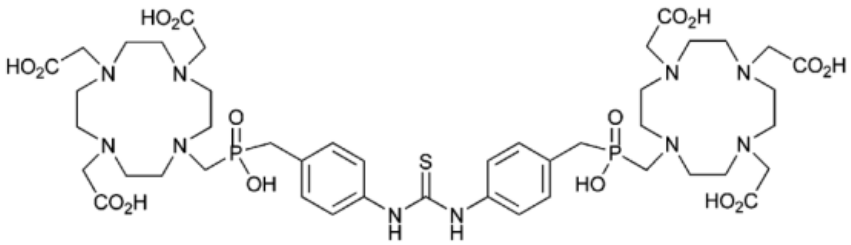
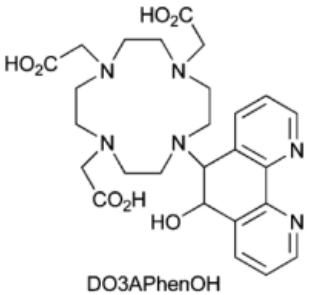
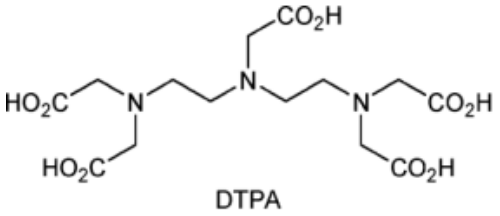

TRITA

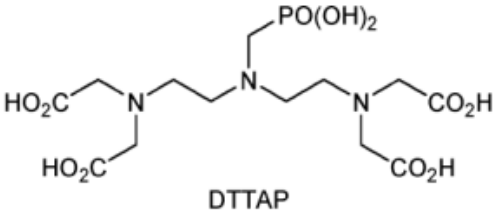

$(DO3AP^{ABn})_2CS$


DO3APhenOH

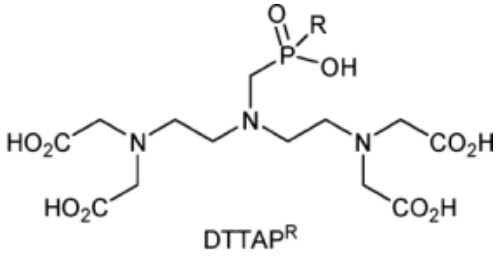
DTPA family



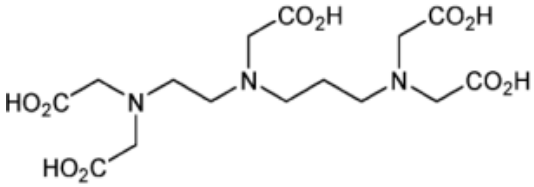
DTPA



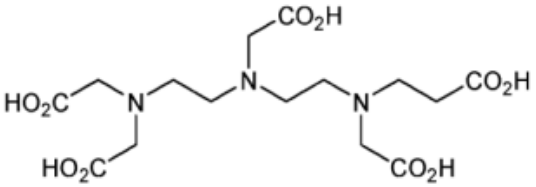
DTTAP



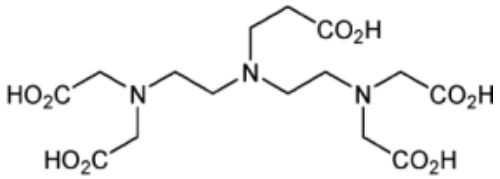
DTTAP^{R}



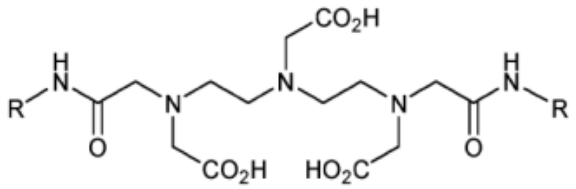
EPTPA



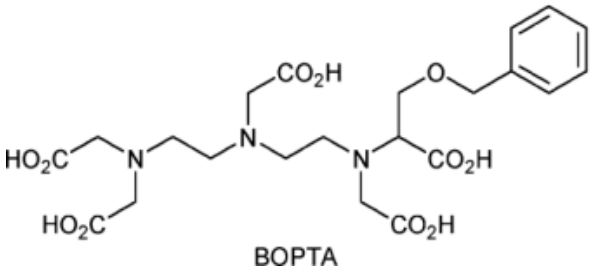
DTTA-*N*-CE



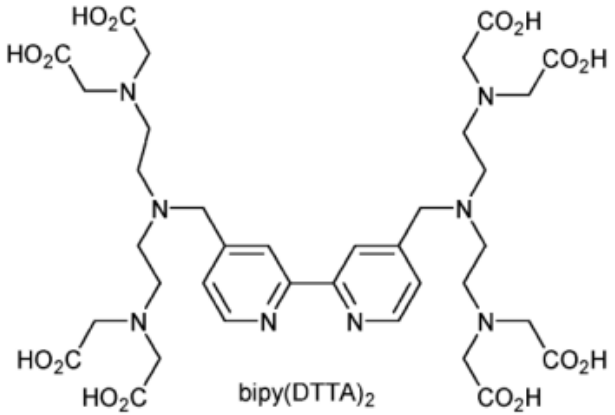
DTTA-*N'*-CE



DTPA-bis(amide)

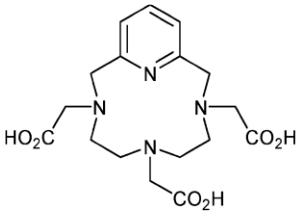


BOPTA

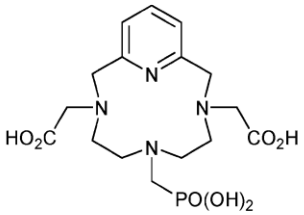


bipy(DTTA)$_2$

New polidentate chelators for Gd(III) CA's



pyDO3A



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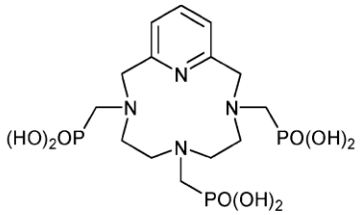

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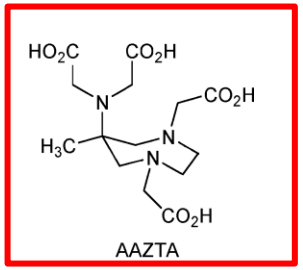
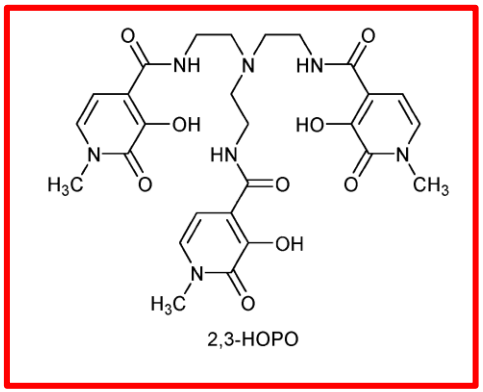
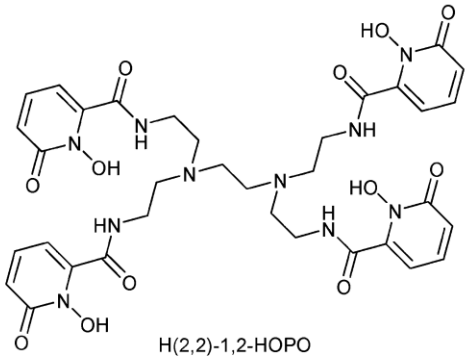


AAZTA

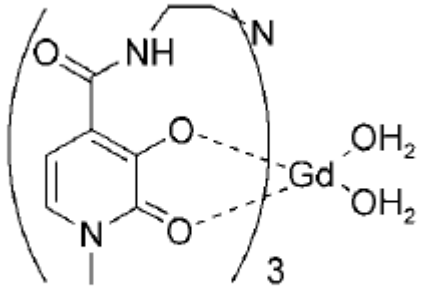
mesocyclic



2,3-HOPO

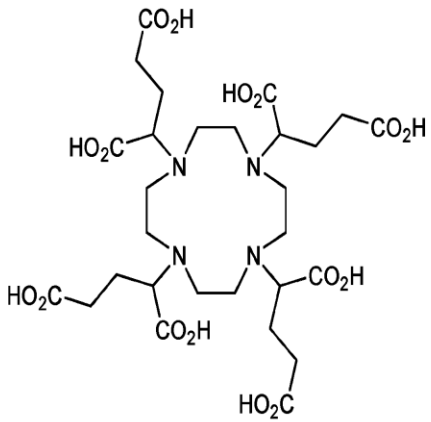


H(2,2)-1,2-HOPO

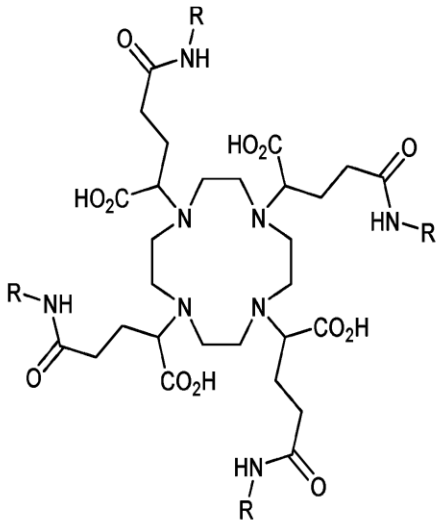


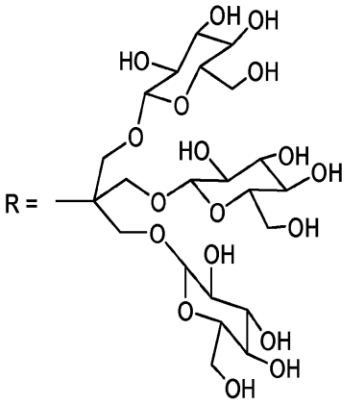
[Gd{tren(1-Me-3,2-hopo)$_3$}(H_2O)$_2$]

Strategies for increasing q_{SS} and τ_M

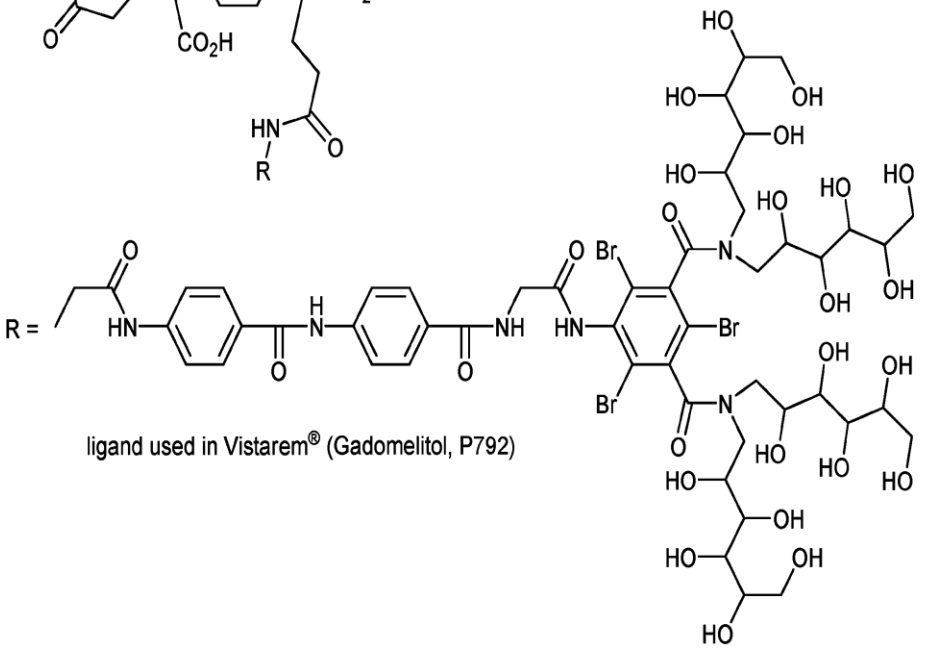


TCED



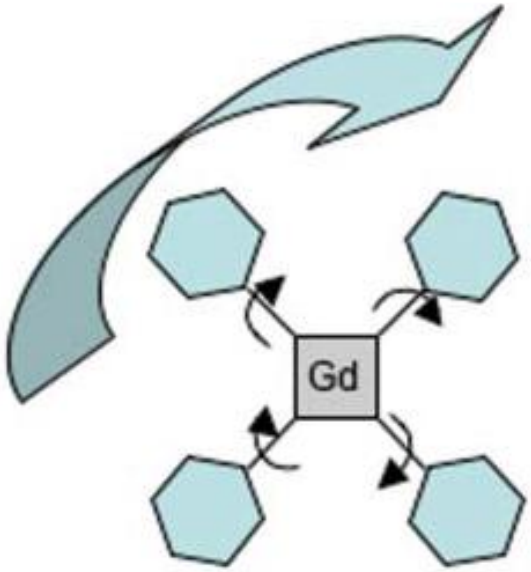


DOTA-Glu$_{12}$

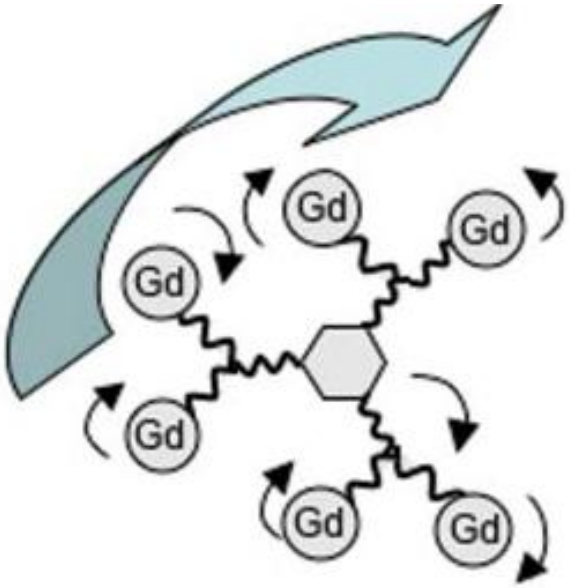


ligand used in Vistarem® (Gadomelitol, P792)

Strategies for increasing the tumbling time τ_M

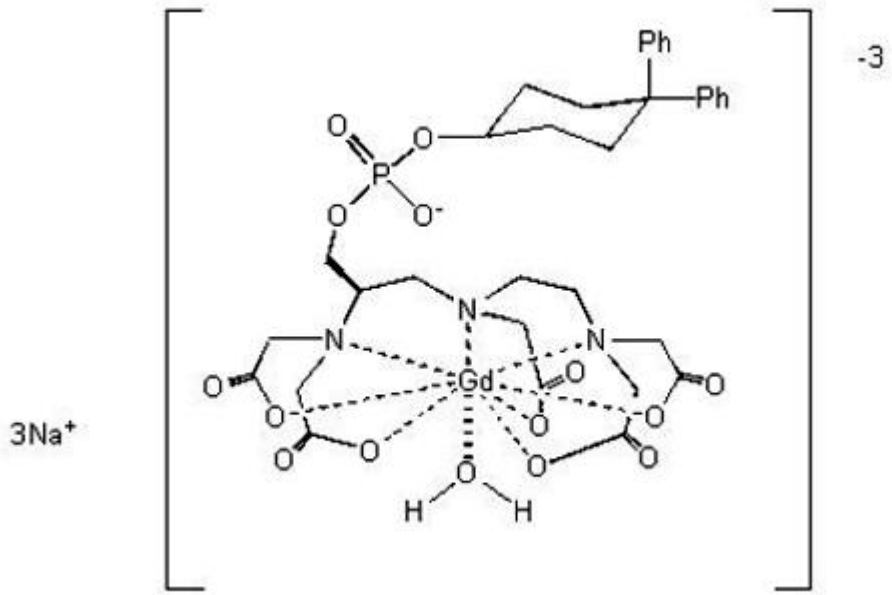


baricenter approach

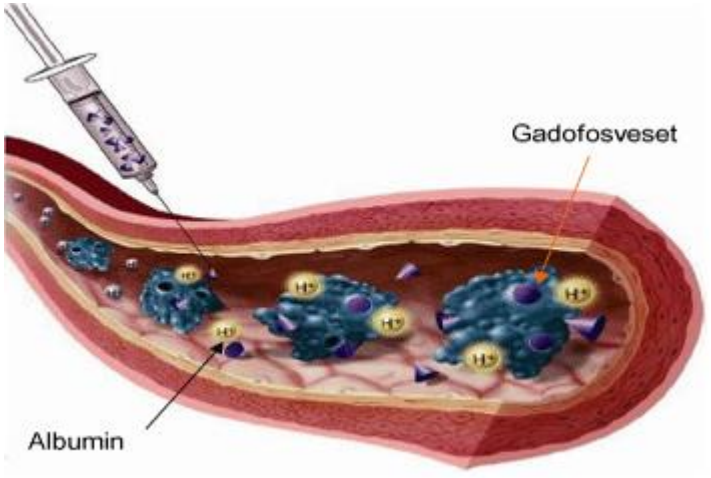


dendrimer approach

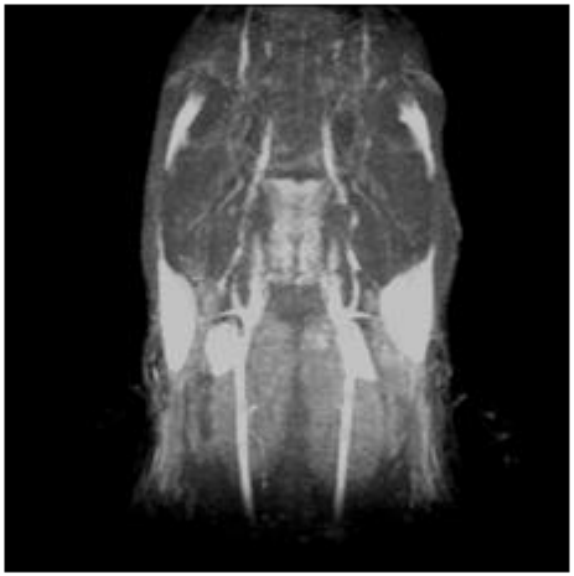
Blood pool (angiographic) contrast agents



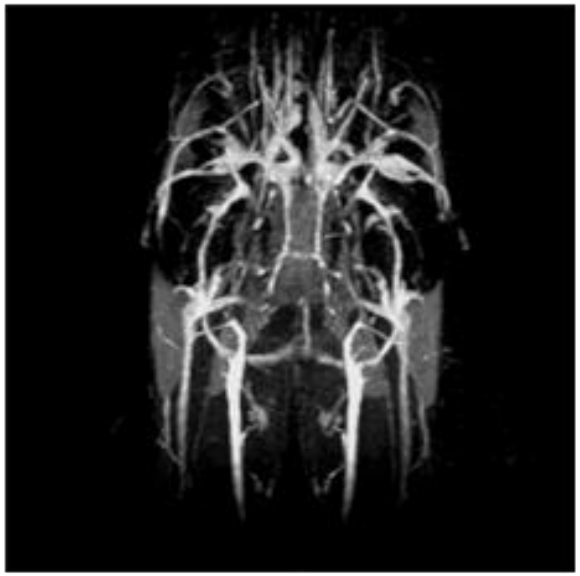
Vasovist®



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

Targeted CA's for MRI

A commercial CA of Gd, with a relaxivity of about 5 $mM^{-1} \cdot s^{-1}$, must reach a **concentration of at least 125 μM** to give visible contrast. This concentration is much higher than that of typical biological receptors: no 1:1 Gd – targeting vector strategy allowed.

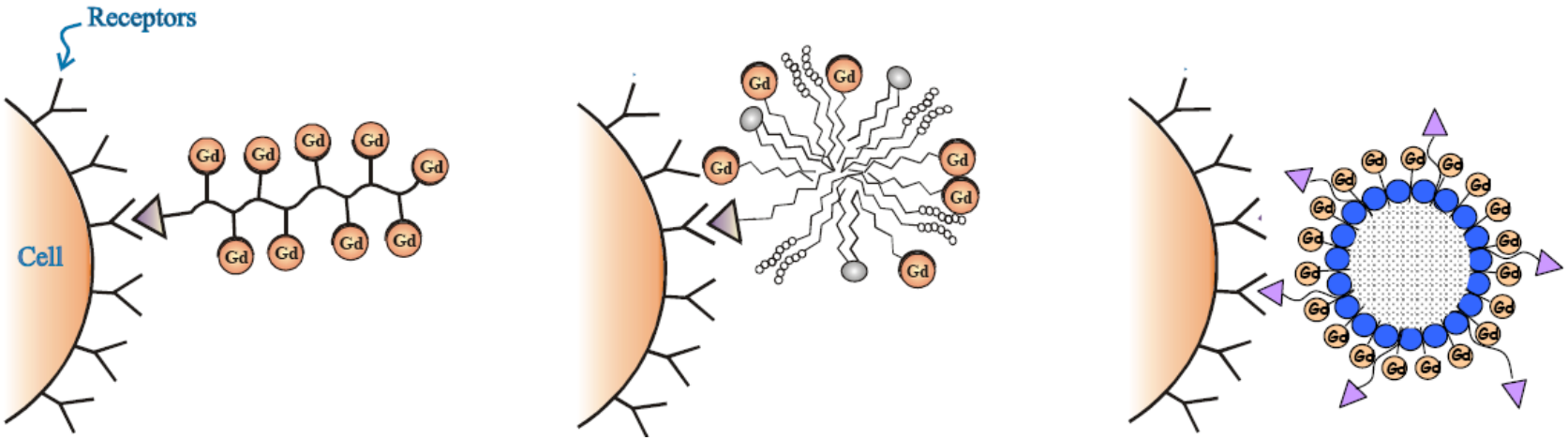
Towards molecular imaging with MRI

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

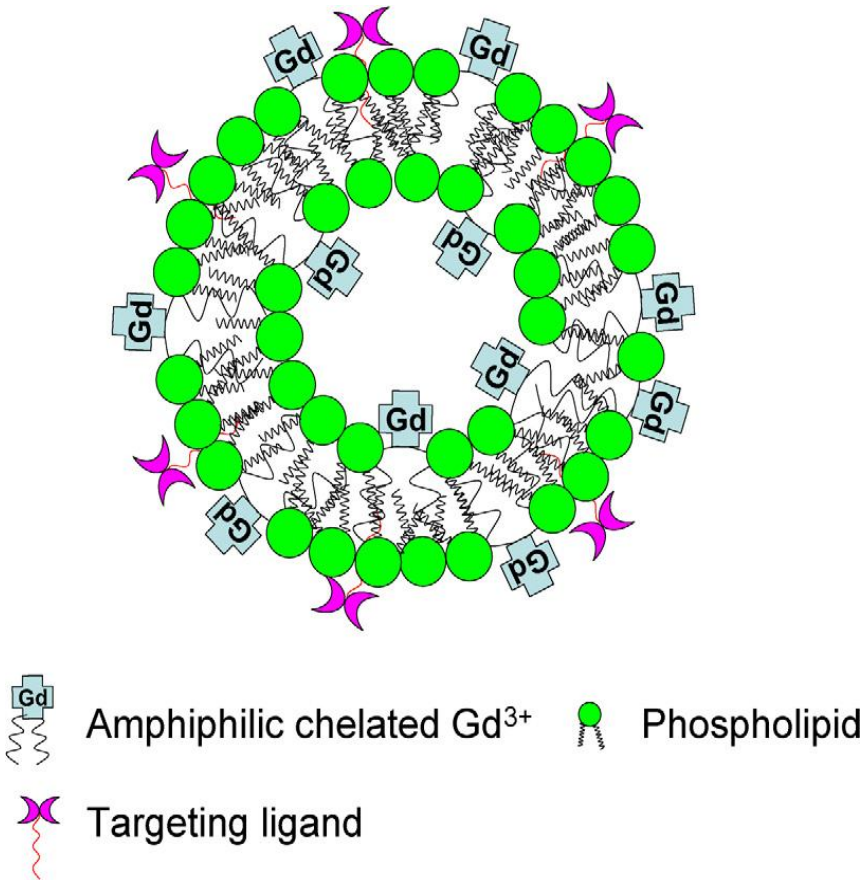
C > 125 μM

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,…)



Hypothetical targeted liposome for MRI

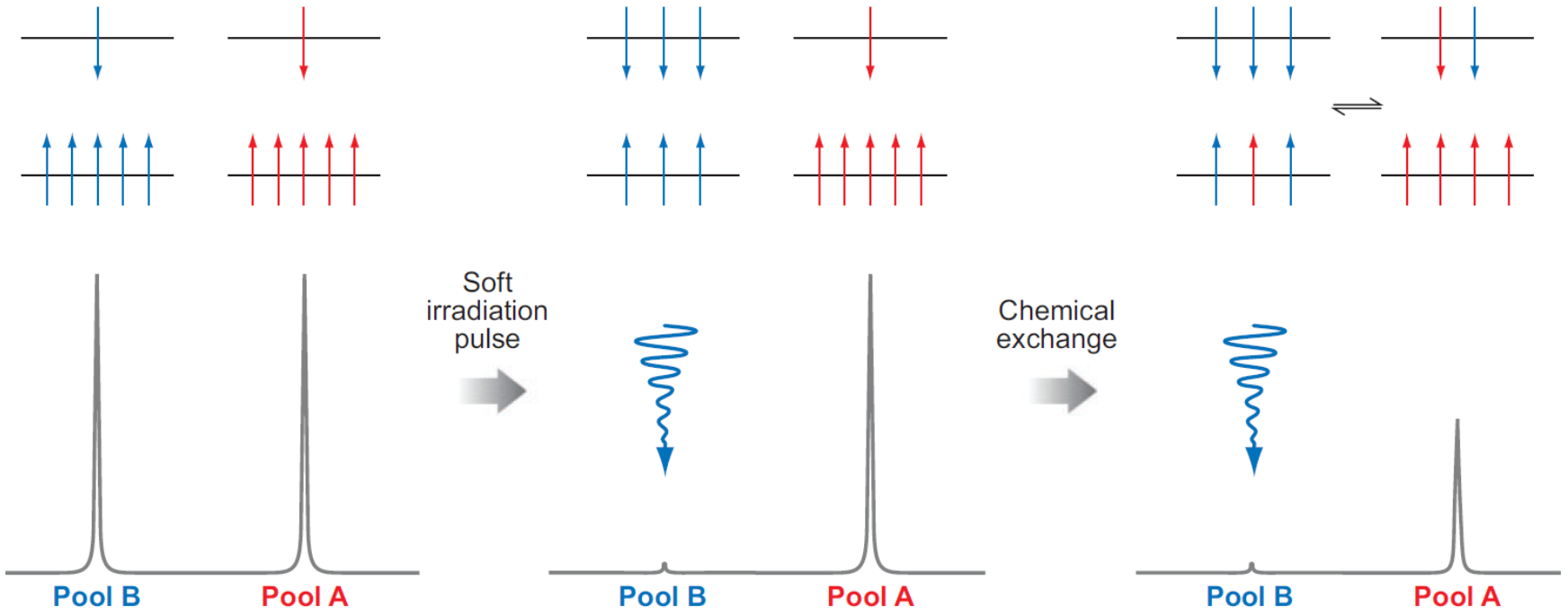


CEST Contrast Agents

Chemical Exchange Saturation Transfer

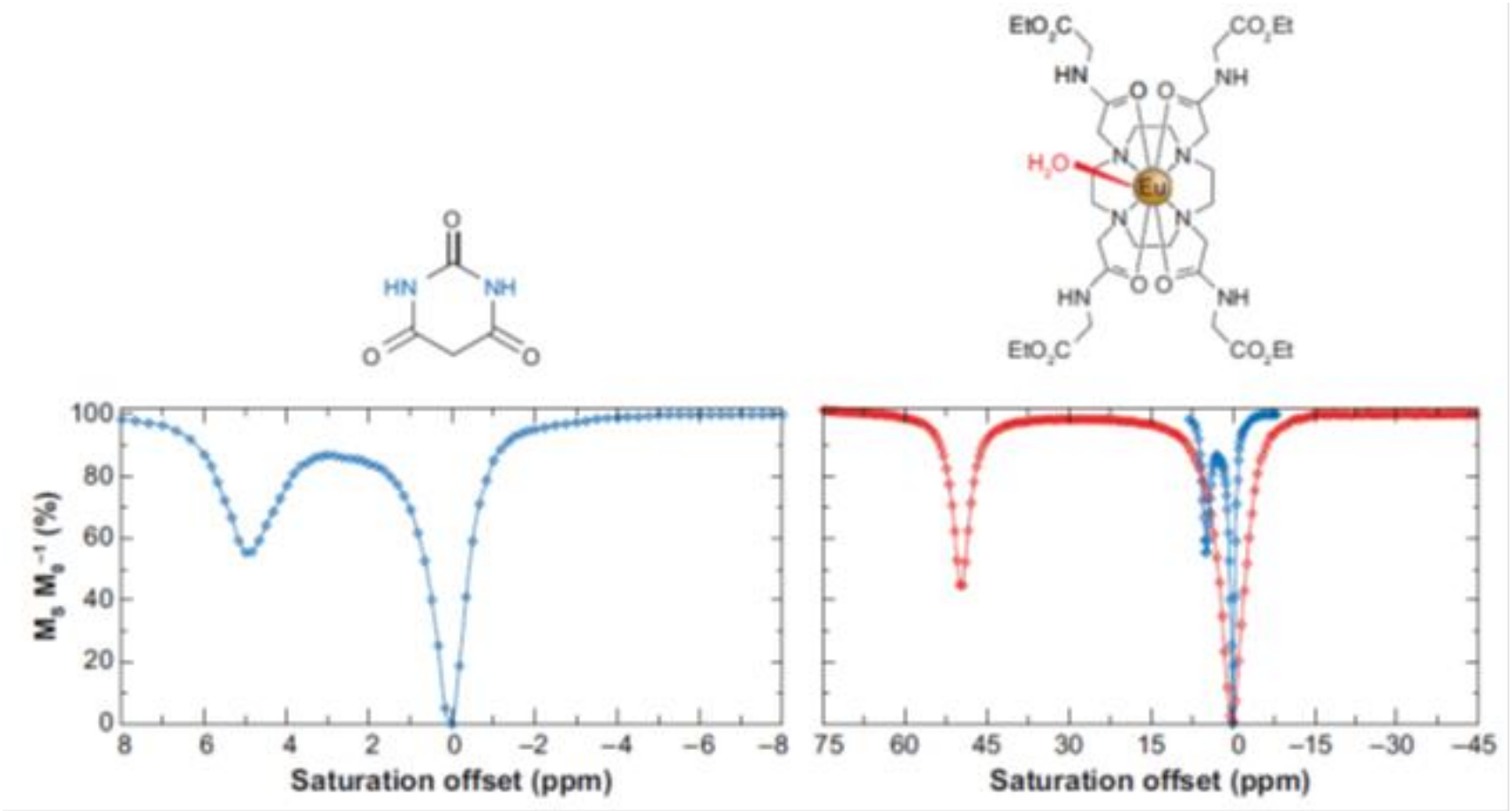
CEST technique exploits the resonance frequency for imaging

Mobile compounds with protons in slow exchange with bulk water



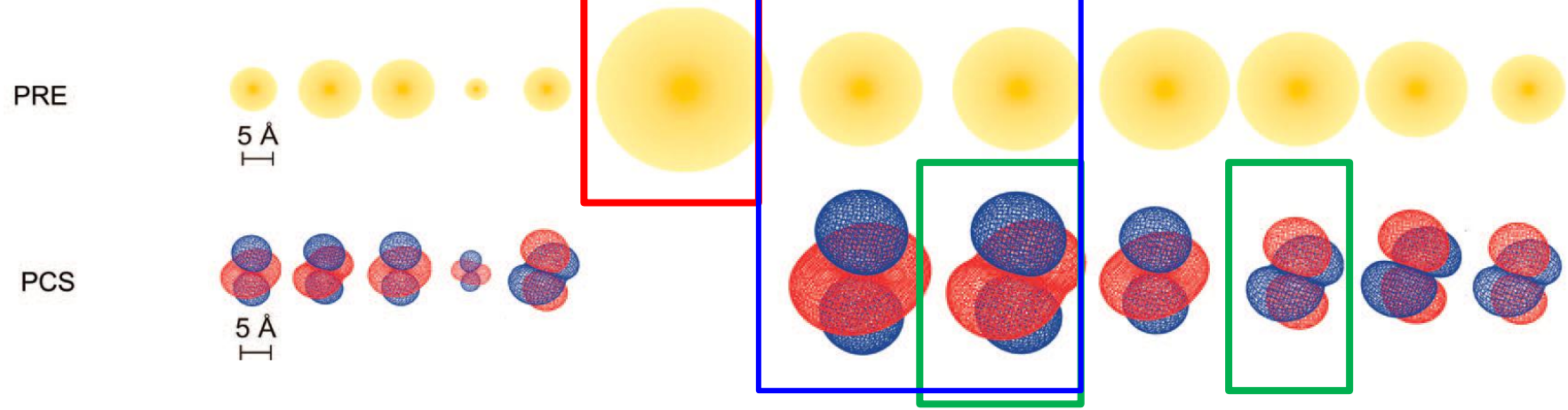
$$k_{CEST} < \Delta\omega$$

CEST and PARACEST agents: saturation offset



isotrope

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



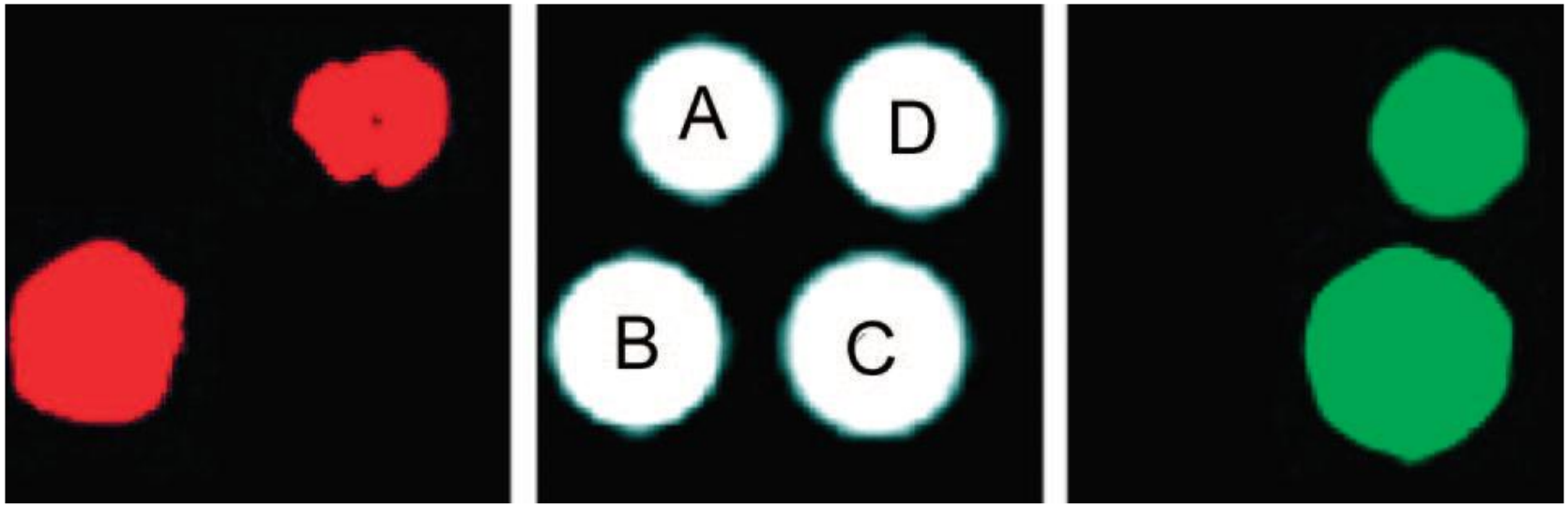
PCS = *Pseudo-Contact Shift*

determines the chemical shift change induced by each ion on neighboring nuclei, and the iso-surfaces represent the magnitude and sign of the chemical shift

At the time being, the sensitivity of exogenous CEST agents is still too low for applications. CEST MRI is primarily used clinically to visualize **endogenous** molecules (proteins, glycogen) without injecting external agents.
Key clinical applications include mapping amide proton transfer (APT) in tumors. APT imaging allows clinicians to distinguish between tumor progression and radiation necrosis.

CEST CA's are potentially responsive agents: in principle, any change in a parameter that might affect the exchange kinetics (e.g. pH, O_2 concentration, temperature,….) will affect the CEST signal.

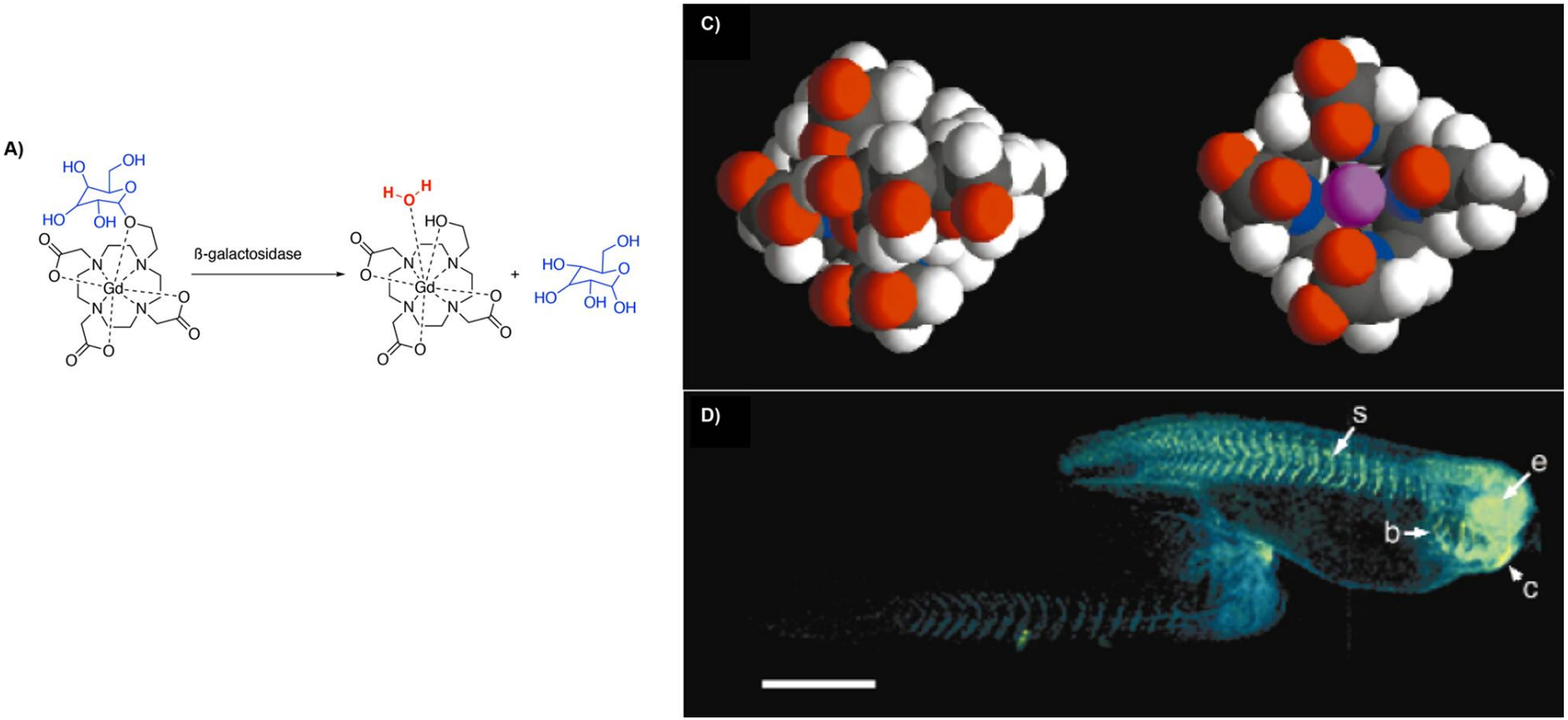
Flexibility of CEST imaging



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

Responsive (*smart*) CA

Sensor of β-galactoxidase



The addition of 0.5 mM CA alone (left) increases contrast slightly in the embrio, but the addition of β-galactoxidase enzyme 4 mM (right) generates a significant increase in contrast (*q* goes from 0 to 1).

T_2 contrast agents
super-paramagnetic iron oxide particles (SPIO)
Ø = 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

Biocompatible coating biocompatibile: dextran, starch, glycosamino-glycan, organic siloxanes, sulfonated styrene-divinylbenzene copolymers,….

Future developments

Multimodal imaging agents and theranostics