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PARACEST Agents: Optimization for Human MR Imaging

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imagination at work

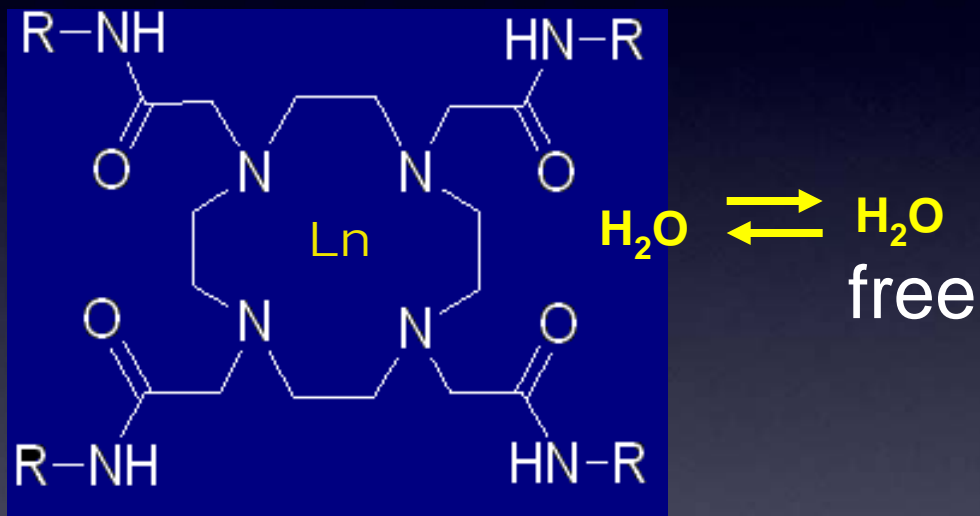


PARACEST agents

(paramagnetic chemical exchange saturation transfer)

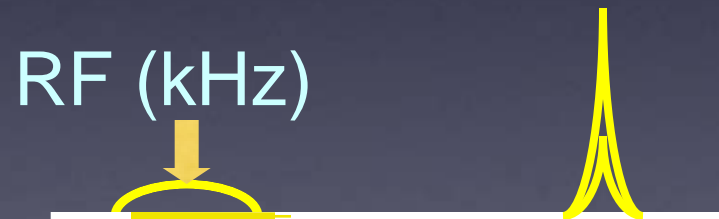
Lanthanide complexes with slow water exchange

DOTA-Tetraamide complexes



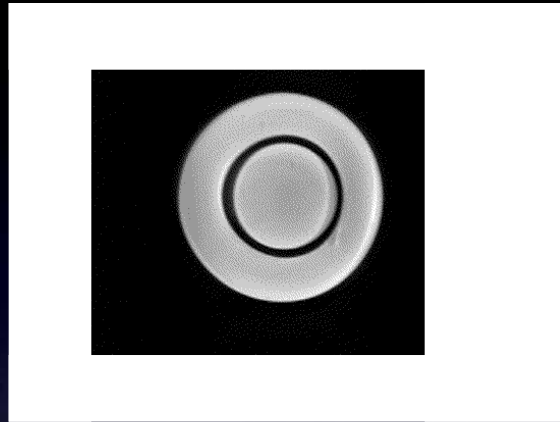
bound

Lanthanide ion	T_B (μ)	Δ (^1H) (ppm)
Eu^{3+}	382	50
Dy^{3+}	17	-720
Tm^{3+}	3	500



Aime S, et.al., *MRM* 47:639(2002)
Zhang S, et.al., *JACS* 123:1517(2001)
Zhang S, et.al., *JACS* 124:4226(2002)

PARACEST EFFECT



$$I_f M_b^0 = I_b M_f^0$$

$$M_z^f / M_z^0 \sim I_f / T_{1f} \quad (\text{Assuming full saturation of the bound protons !})$$

Free water signal

Exchange lifetime

- Fast kinetics (but still slow exchange regime)
- Big chemical shift difference => no direct saturation
- Detection of multiple agents simultaneously
 - No MT effects for some of the agents

Aims:

Develop an understanding of which structural factors modulate the water exchange lifetimes of the chelates.

Determine the bio-distribution and pharmacokinetics of PARACEST agents.

Derive theoretical models and experimental methods for determining the water exchange lifetimes *in vivo*.

Optimize the detection of PARACEST effects *in vivo* under practical limits for power deposition.

Aim 2

The PARACEST DOTA amide derivatives have toxicity, bio-distribution, and pharmacokinetic properties that are almost identical to those for Gd-DOTA (Dotarem). DOTA chelates are kinetically inert and there have been no reported cases of NSF with Dotarem.

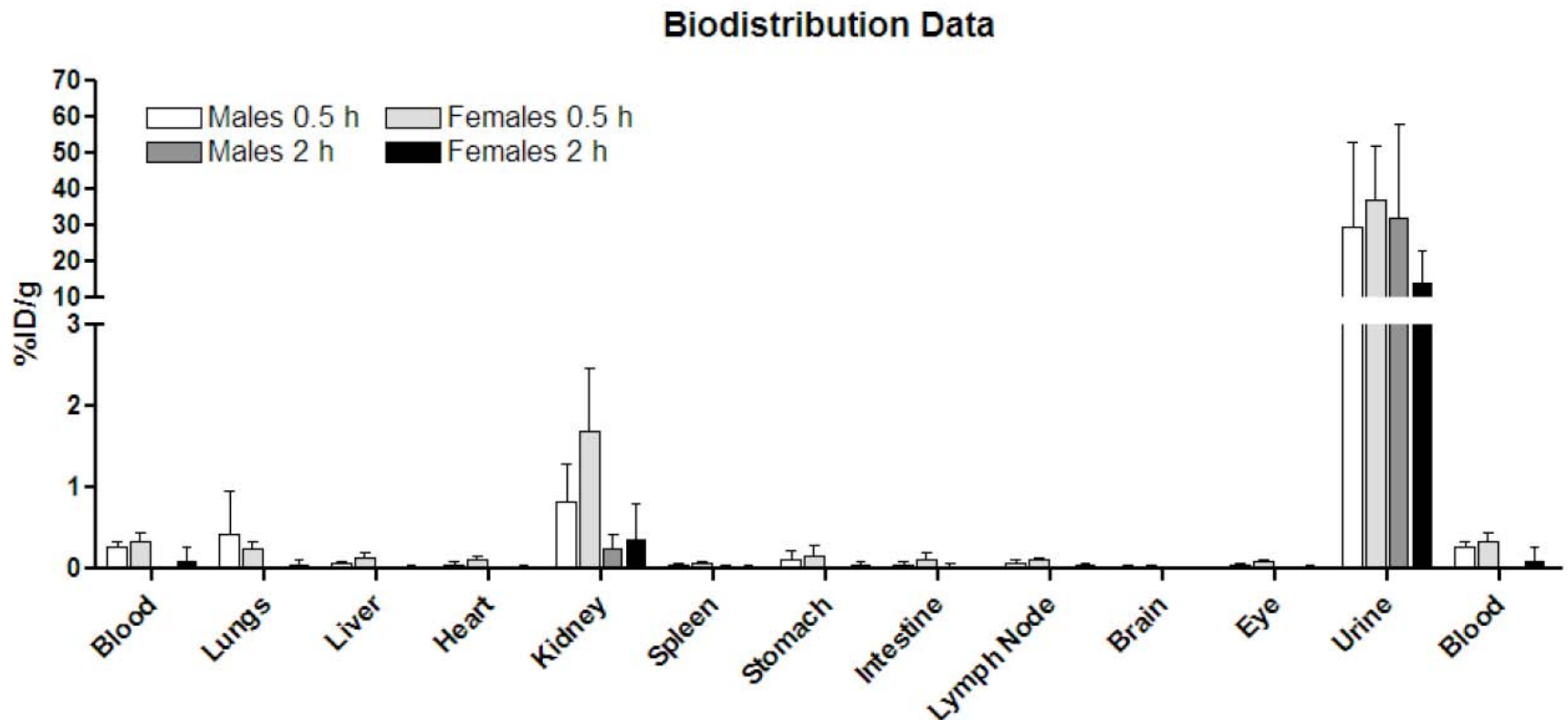
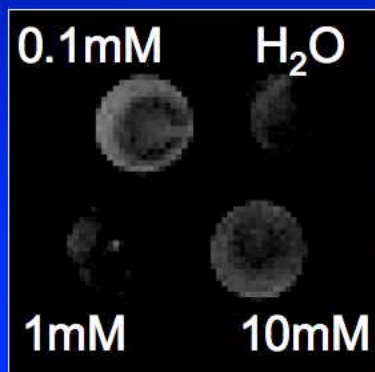


Figure 2: Biodistribution of DOTAM-4AmC. Shown is the biodistribution of ^{177}Lu labeled DOTAM-4AmC. The percent of initial dose per gram of tissue (%ID/g) is plotted for each tissue. White bars = Group 1 males (0.5 h time point), light grey bars = Group 1 females (0.5 h time point), dark grey bars = Group 2 males (2 h time point), black bars = Group 2 females (2 h timepoint). Error bars represent standard deviations.

EuDOTA-4AmC

PARAPCEST

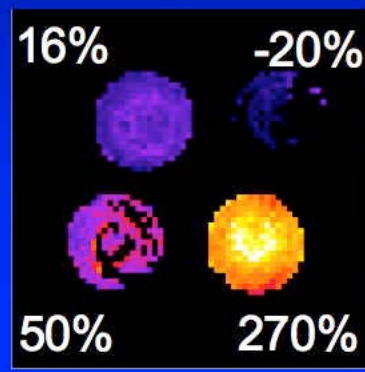
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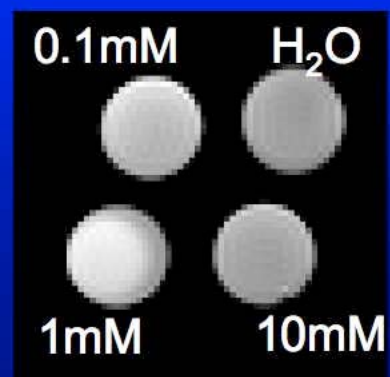


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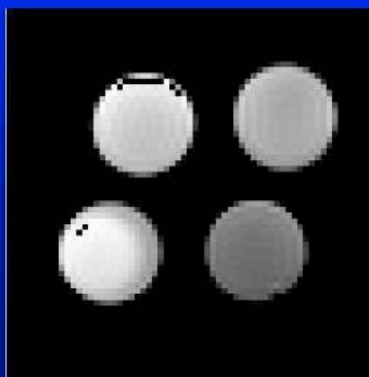


PARACEST

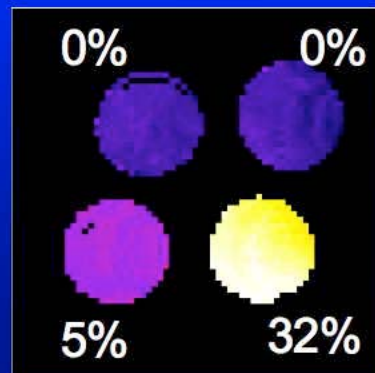
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Conclusions

Chemical exchange based effects provide a new route of MRI contrast, and it is possible to chemically “tune” PARACEST agents.

These PARACEST agents have very favorable toxicities, bio-distributions, and pharmacokinetics for clinical applications.

Quantitation is possible *in-vivo*.

Further development is required to fully utilize the possibilities in *in-vivo* research and clinical studies, particularly in the area of maximizing the effect size while managing SAR.