Assemblage de copolymers diblocs à l'aide de gadolinium: vers de nouveaux agents de contraste pour l'IRM

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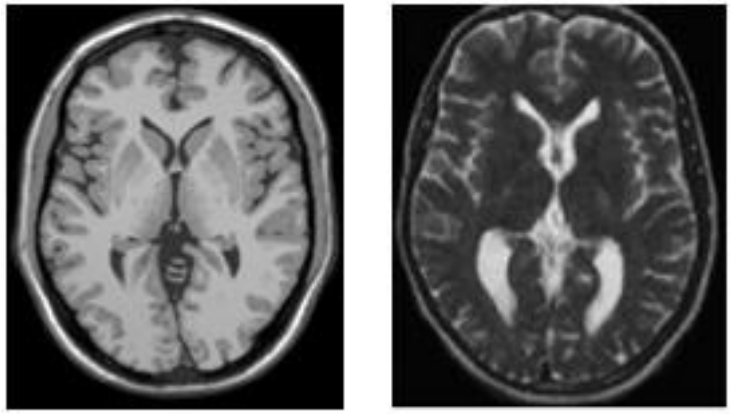
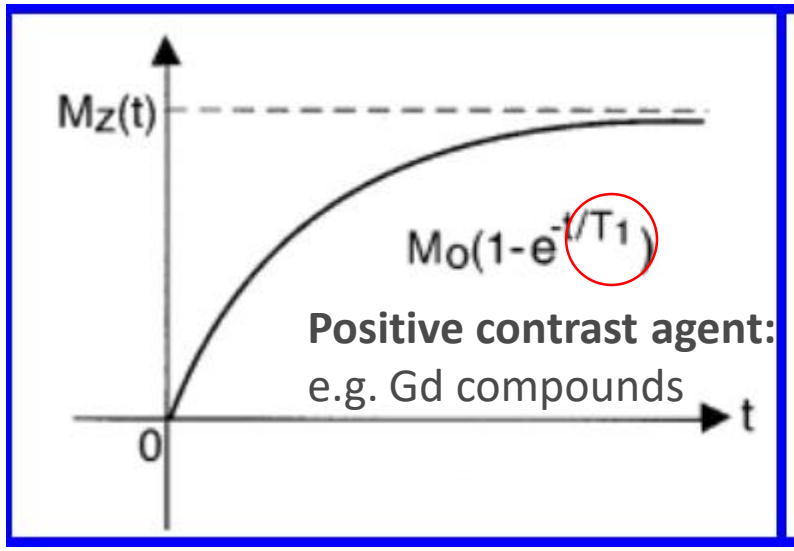
Université de Toulouse

Nanoparticles for MRI

Magnetic Resonance Imaging

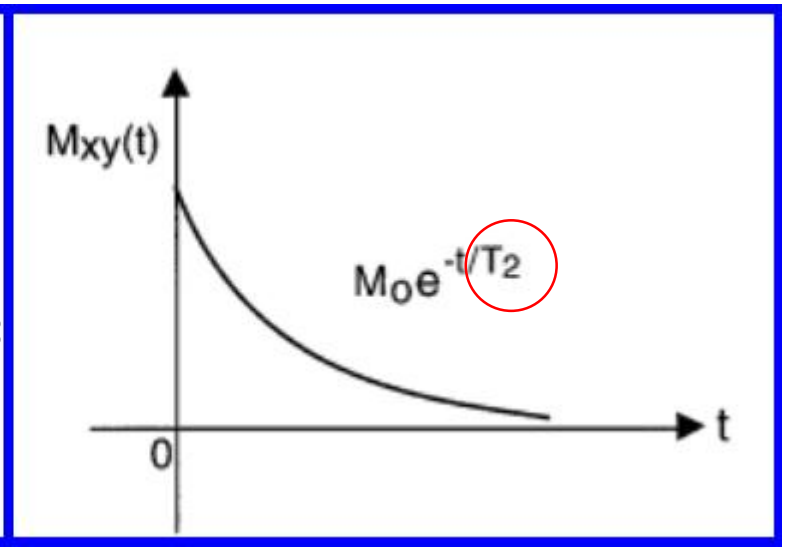


Longitudinal magnetization relaxation



Positive contrast agent:
e.g. Gd compounds

Transverse magnetization relaxation



Negative contrast agent:
e.g. superparamagnetic iron oxide

V. Pierre et al., *J. Biol. Inorg. Chem.* 2014, 19, 127

Nanoparticles for MRI

Name	Core Material	Diameter of core [nm]	Relaxivity based on concentration of whole atoms	
			r_1 [$mM^{-1}s^{-1}$]	r_2 [$mM^{-1}s^{-1}$]
Gd-DTPA	Gd	ion	4.1	4.9
Dextran-SPGO	Gd_2O_3		4.8	16.9
PEG-Gd_2O_3	Gd_2O_3	3	9.4	13.4
GadoSiPEG	Gd_2O_3	2.2	8.8	11.4
		3.8	8.8	28.8
		4.6	4.4	28.9
PGP/dextran-K01	$GdPO_4$		13.9	15
GdF_3:cit	GdF_3		3.17	
GdF_3/LaF_3:AEP	GdF_3/LaF_3		2.71	
PGP/dextran-K01	$GdPO_4$		13.9	15
MnO	MnO	7	0.37	1.74
		15	0.18	0.57
		20	0.13	0.52
		25	0.12	0.44
FeCo/GC	FeCo	4	31	185
		7	70	644

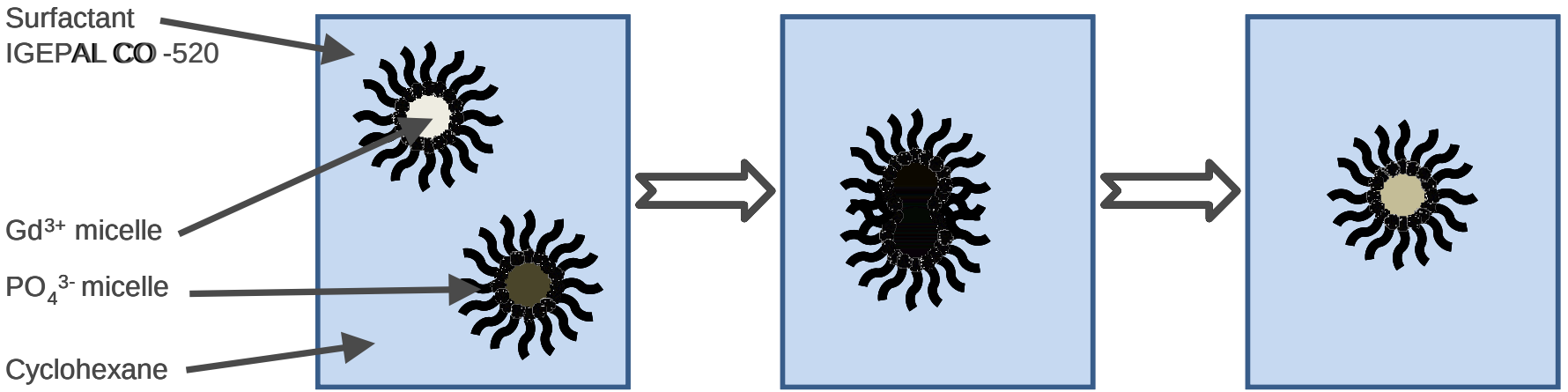
pK_s = 26 at 21°C

F. Poitrasson et al., *Geochim. Cosmochim. Acta* 2004, 68, 2207

H. B. Na et al., *Adv. Mat.* 2009, 21, 2133

Nanoparticles for MRI

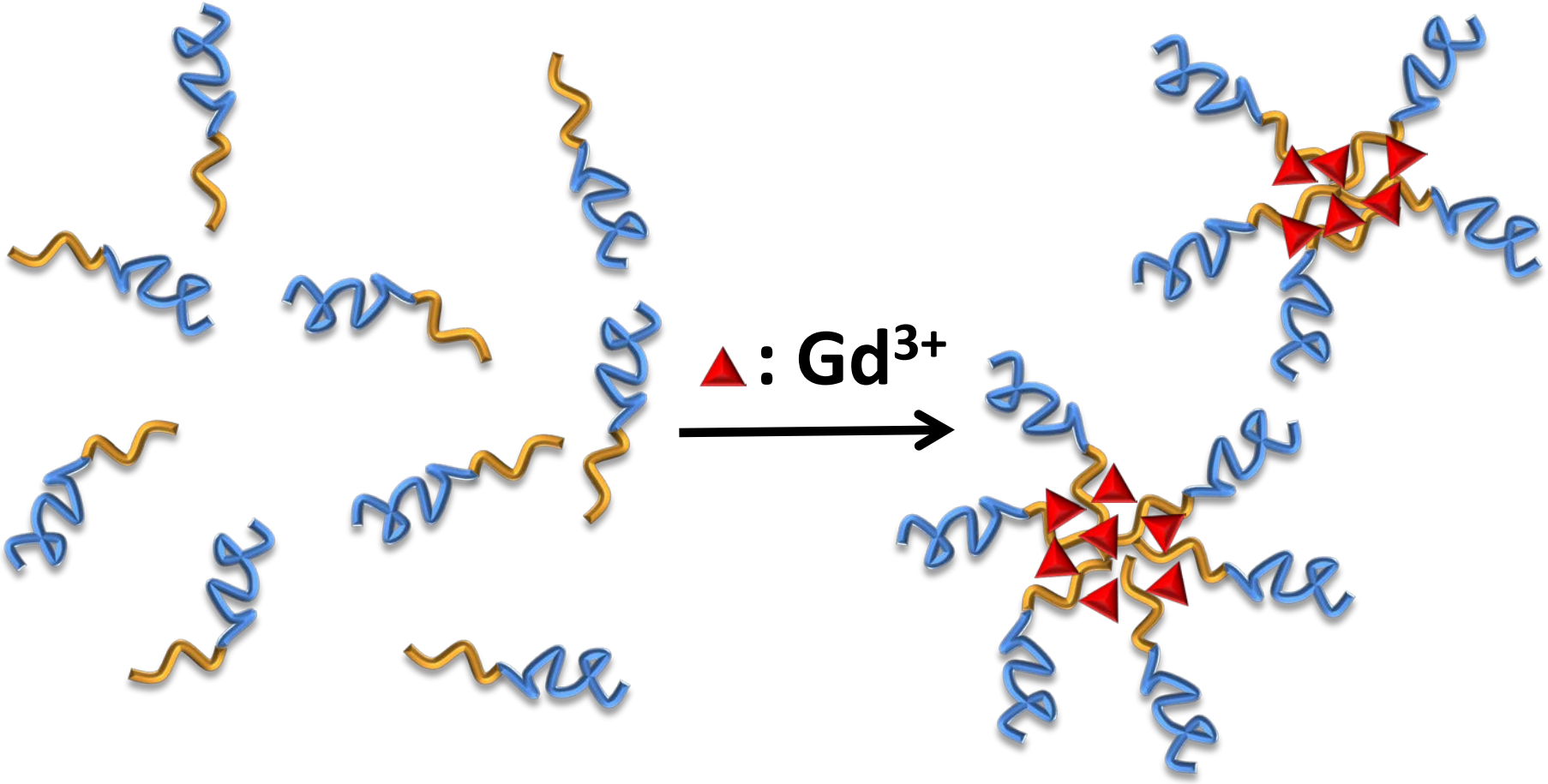
$$Gd(NO_3)_3 + Na_2HPO_4 \longrightarrow GdPO_4 \cdot H_2O$$



Large quantities of surfactants for few nanoparticles !

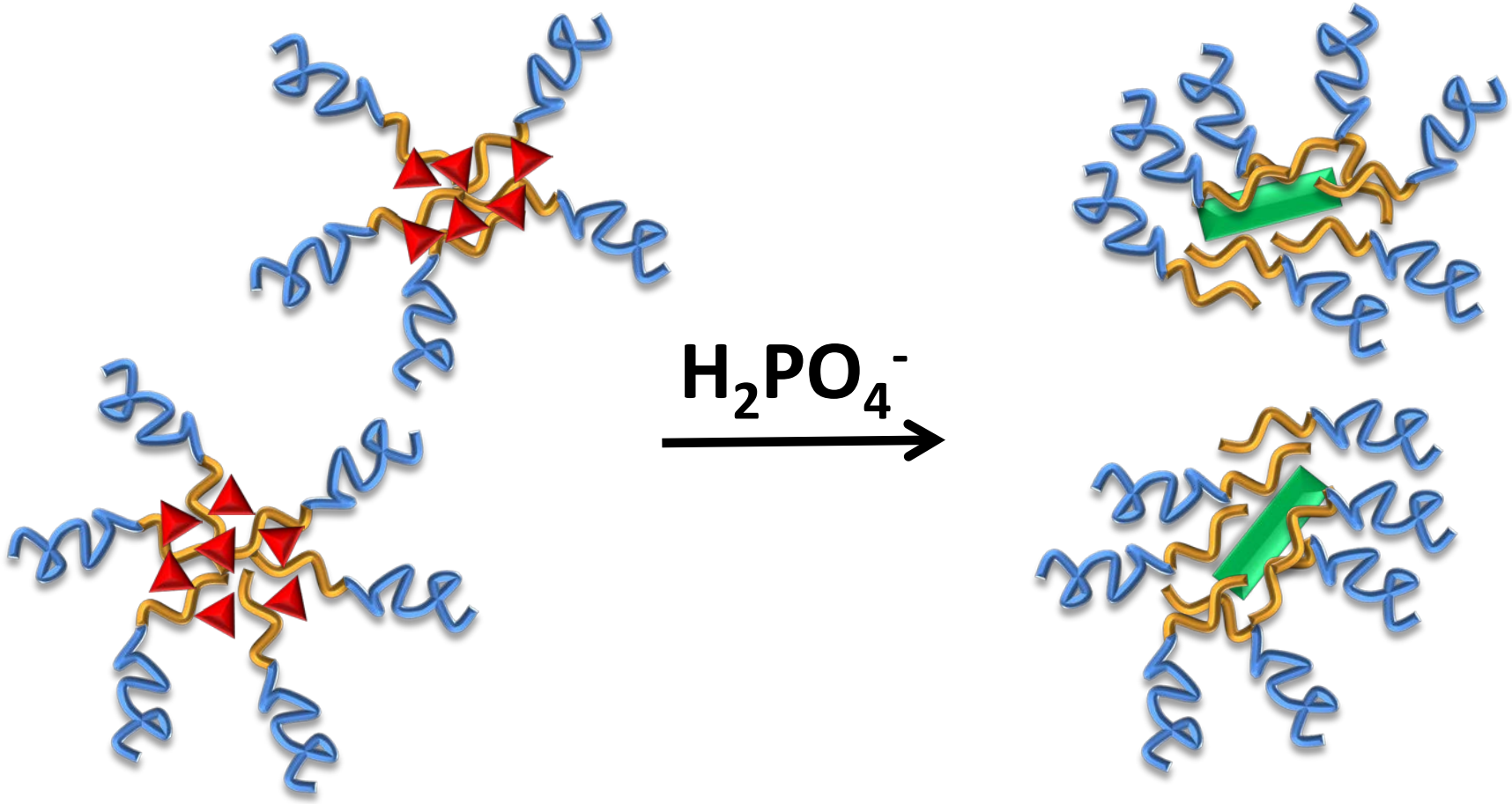
M. F. Dumont et al., *Bioconjugate Chem.* 2012, 23, 951

Diblock copolymers and $GdPO_4$ NPs



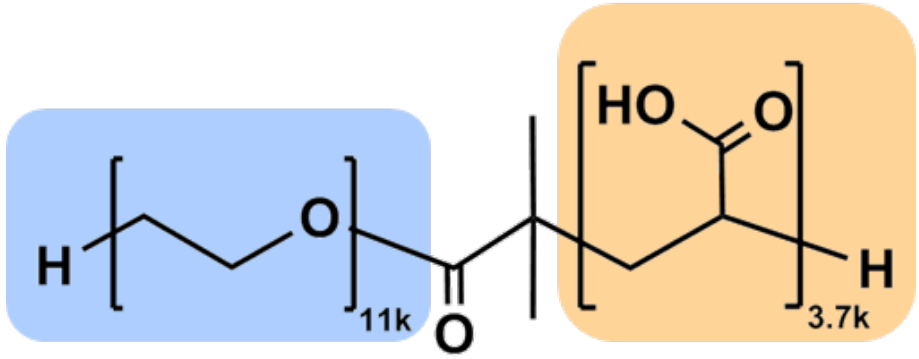
Hybrid Poly-Ion Complexes

Diblock copolymers and $GdPO_4$ NPs

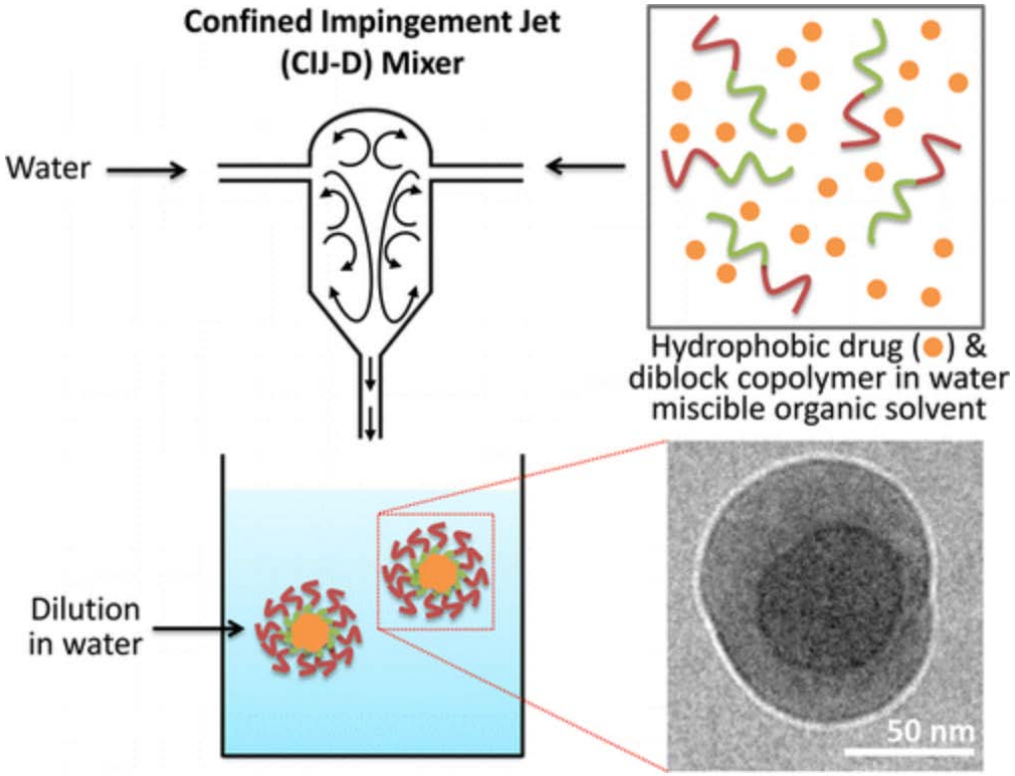


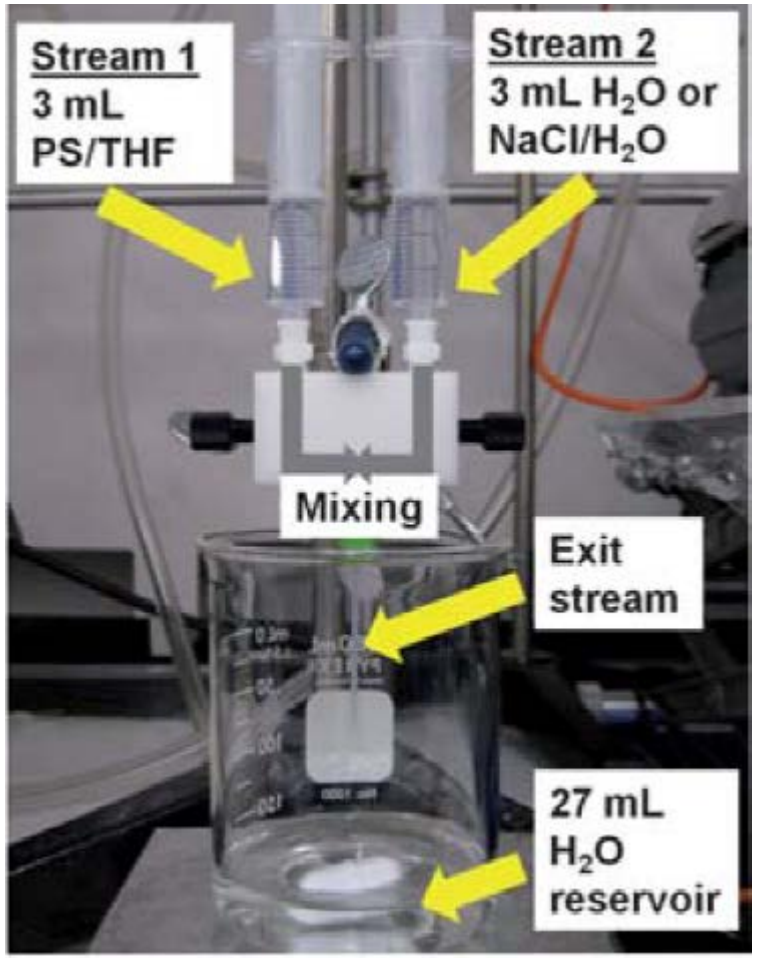
Diblock copolymers and $GdPO_4$ NPs

PEO_{11k}-$PAA_{3.7k}$



NanoPrecipitation and $GdPO_4$ nanoparticles





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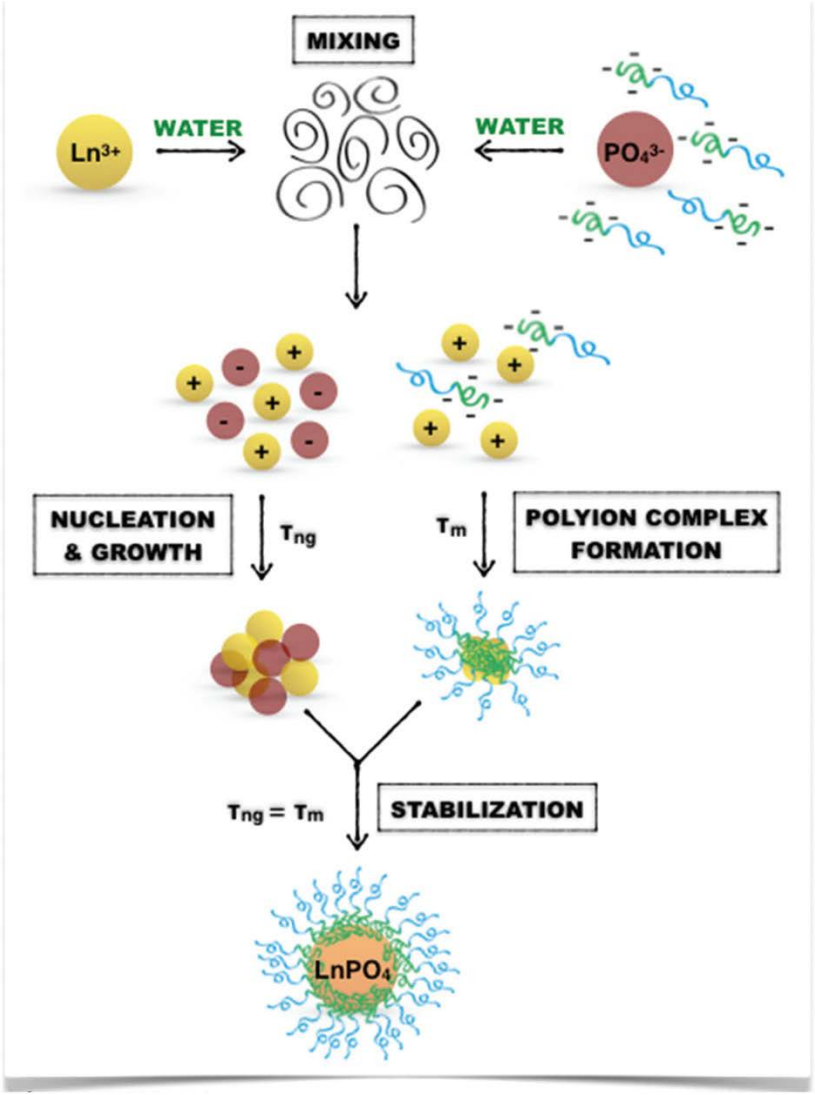
Dr S. Chassaing

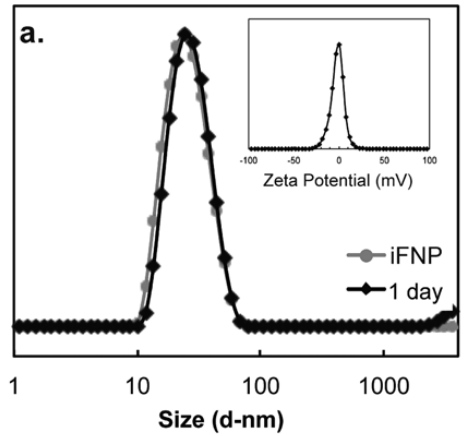
K. M. Pustulka et al., *Mol. Pharmaceutics,* 2013, 10, 4367

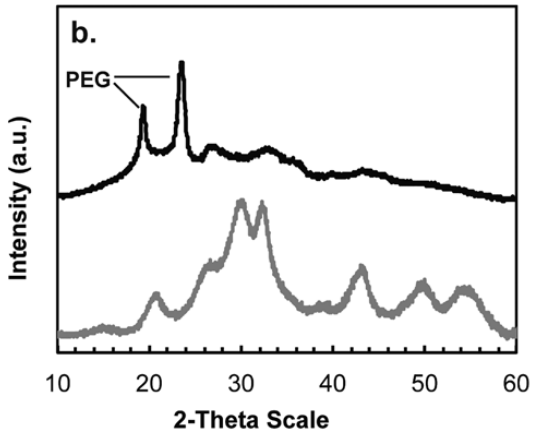
C. Zhang et al., *Soft Matter,* 2012, 8, 86
W. S. Saad, R. K. Prud'homme , *Nanotoday,* 2016, 2, 212

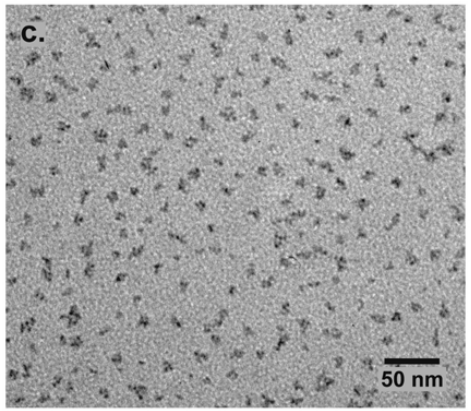
NanoPrecipitation and $GdPO_4$ nanoparticles

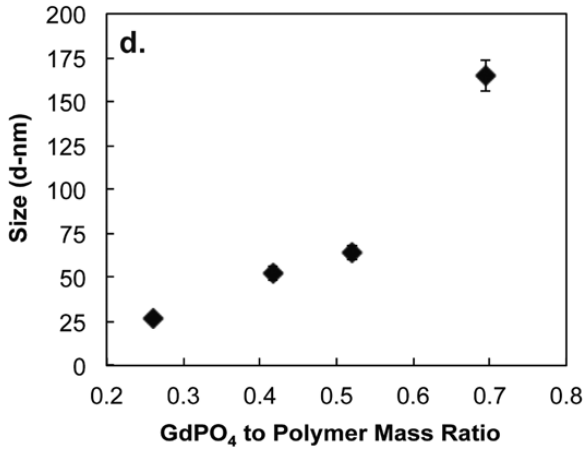


ca 30 nm





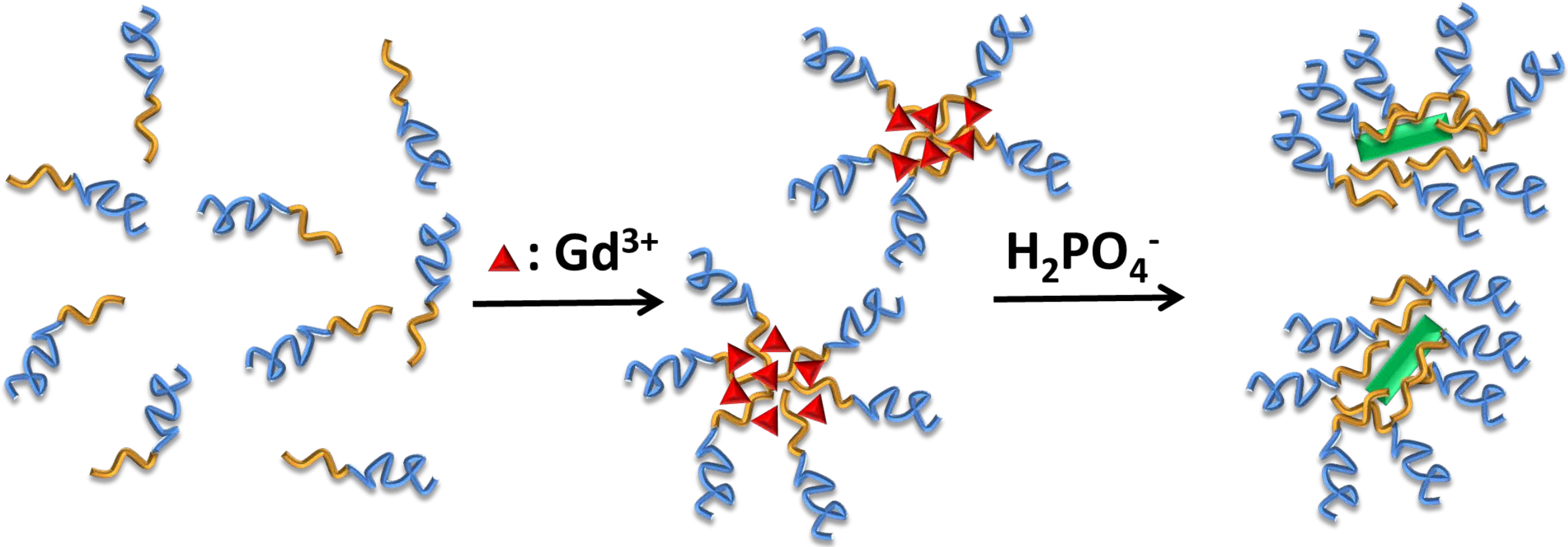




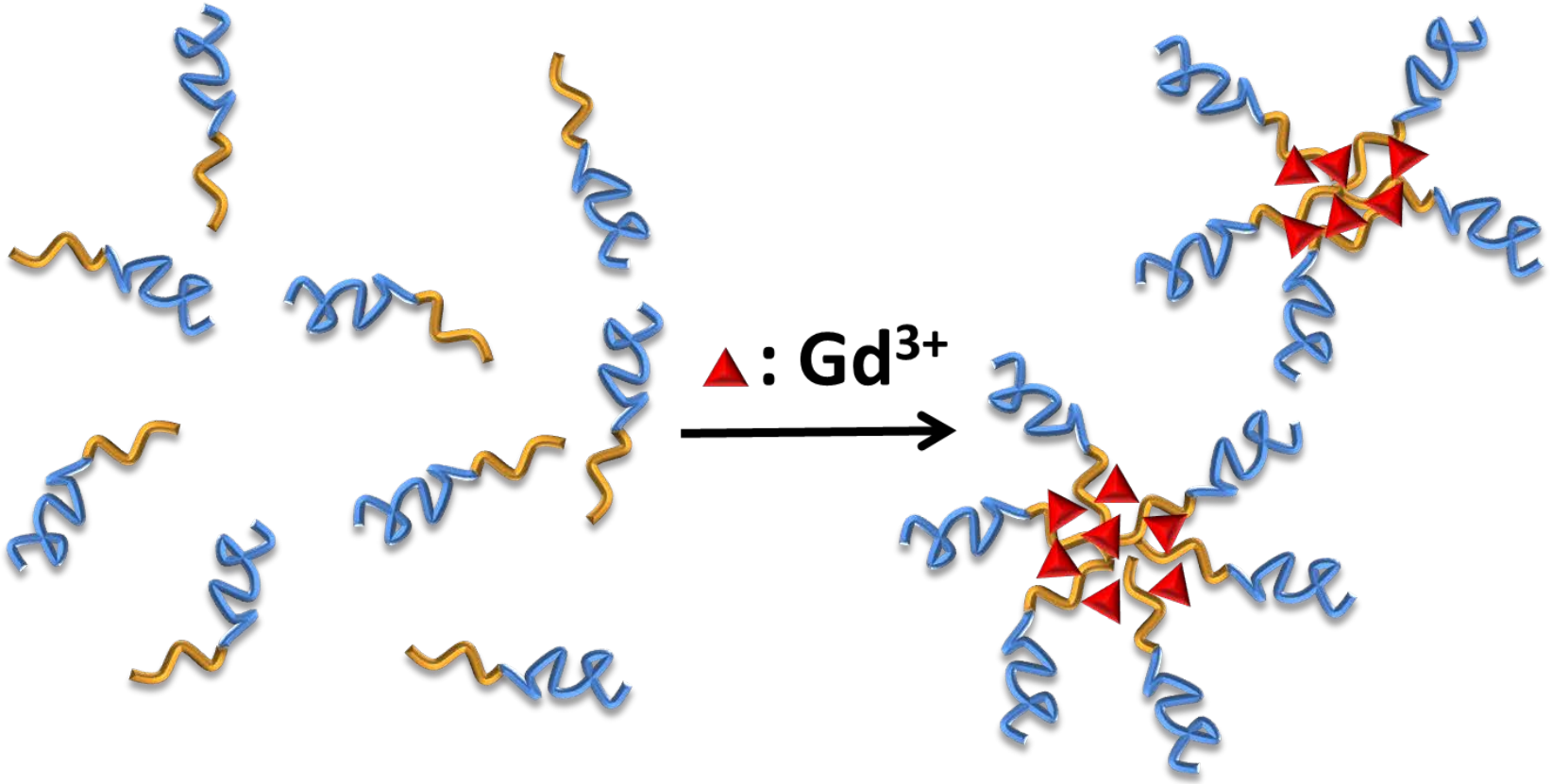
$r_1 = 18\ mM^{-1}s^{-1}$ and $r_2 = 22\ mM^{-1}s^{-1}$ at 1.4 T

N. M. Pinkerton et al. , *Nanoscale* 2017, 9, 1403

Diblock copolymers and $GdPO_4$ NPs



Gd Hybrid Poly-Ion Complexes



???

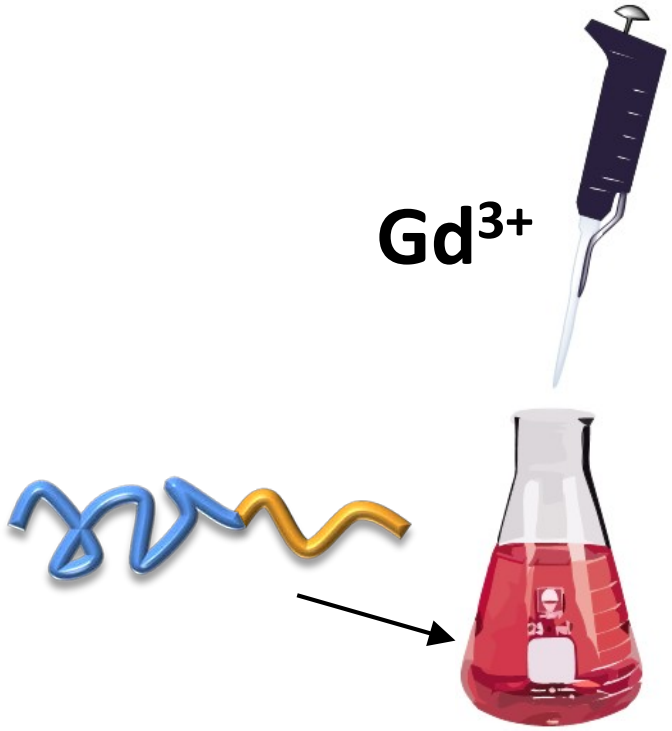
Hybrid Poly-Ion Complexes

Gd Hybrid Poly-Ion Complexes

Metal ion / Inorganic material	Polymer	Reference
La^{3+} / lanthanide hydroxide	poly(acrylic acid)/ poly(acrylamide) (PAA-b-PAM)	F. Bouyer, C. Gérardin et al. *Colloid Surf. A* **2003**, 217, 179
Al_{13}^{7+}/ aluminium hydroxide	poly(acrylic acid)-b-poly(hydroxyethylacrylate) (PAA-b-PHEA)	C. Gérardin, N. Sanson et al. *Angew. Chem. Int. Ed.* **2003**, 42, 3681
Cd^{2+}/ CdS	poly(ethylene oxide)-*b*-polystyrene-*b*-poly(acrylic acid) (PEO-*b*-PS-*b*-PAA)	N. Duxin et al. *J. Am. Chem. Soc.* **2005**, 127, 10063

J.F. Berret *Adv. Colloid Int. Sci.* **2011**, 167, 38

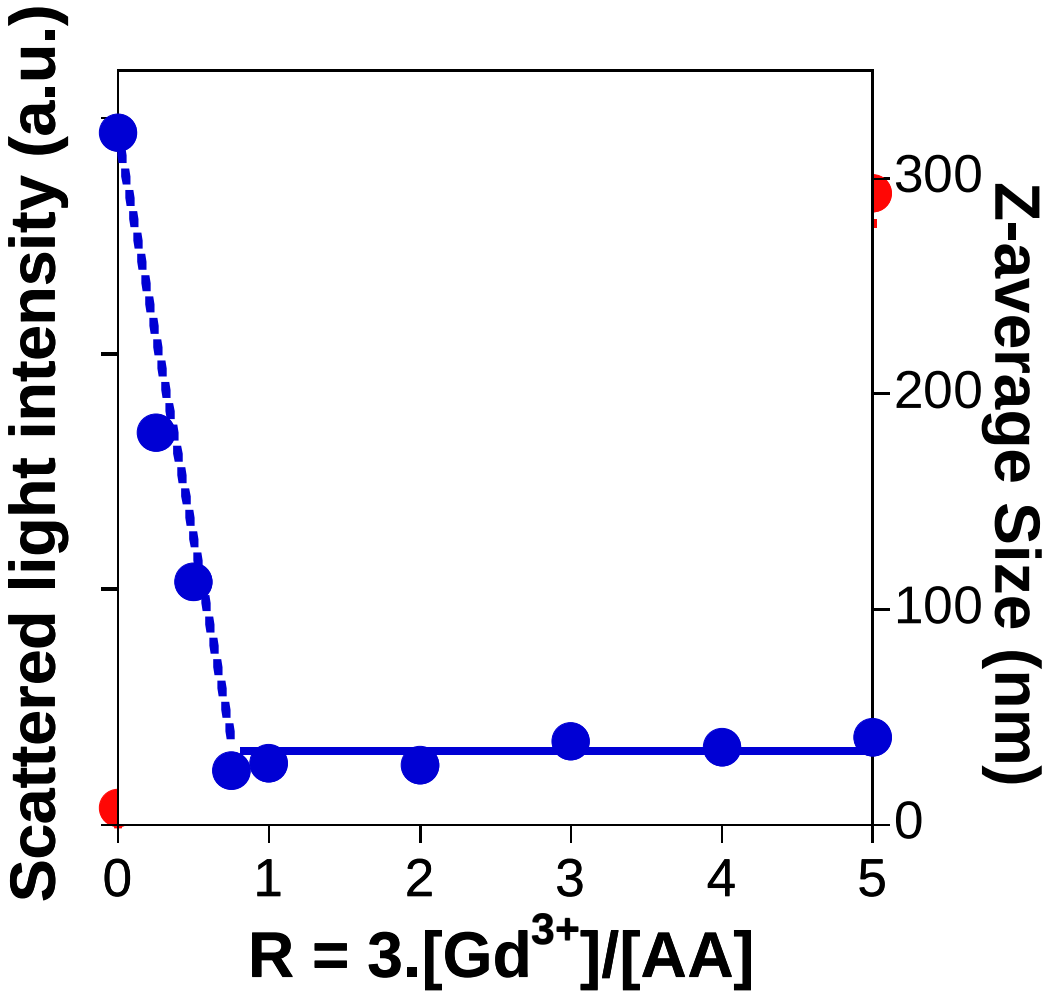
Gd Hybrid Poly-Ion Complexes



$$R = \frac{charges\ due\ to\ Gd^{3+}}{charges\ due\ to\ the\ AA} = \frac{3.[Gd^{3+}]}{[AA]}$$

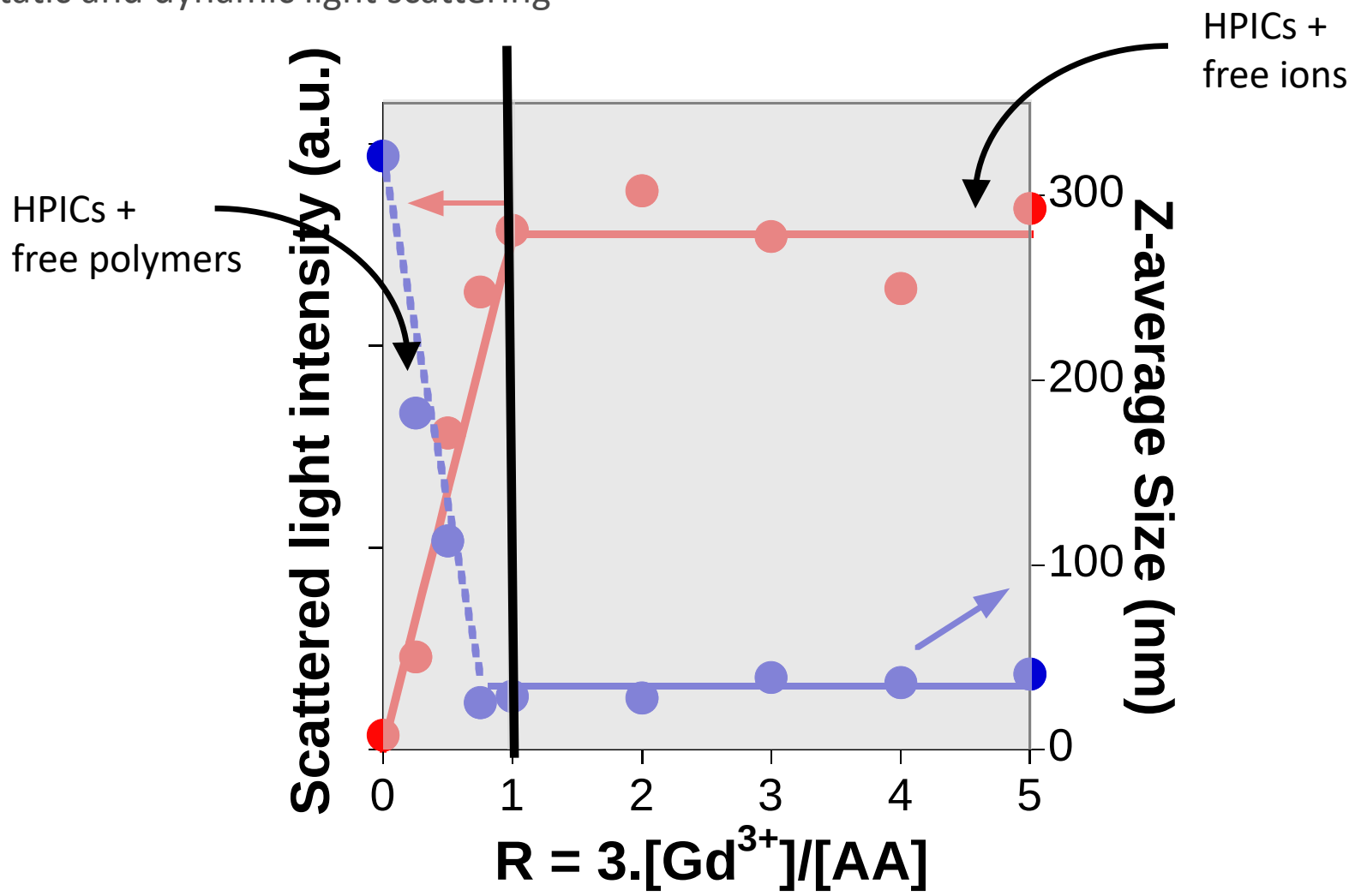
Gd Hybrid Poly-Ion Complexes

Static and dynamic light scattering



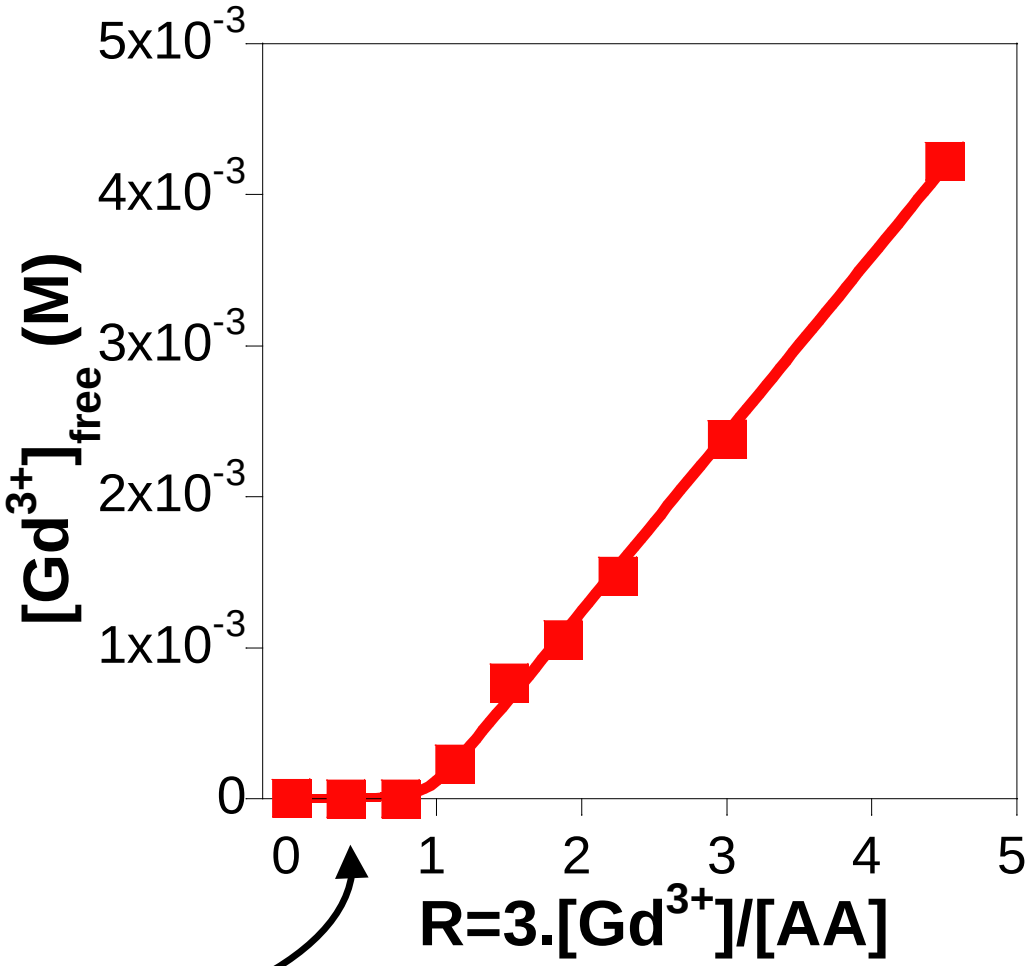
Gd Hybrid Poly-Ion Complexes

Static and dynamic light scattering



Gd Hybrid Poly-Ion Complexes

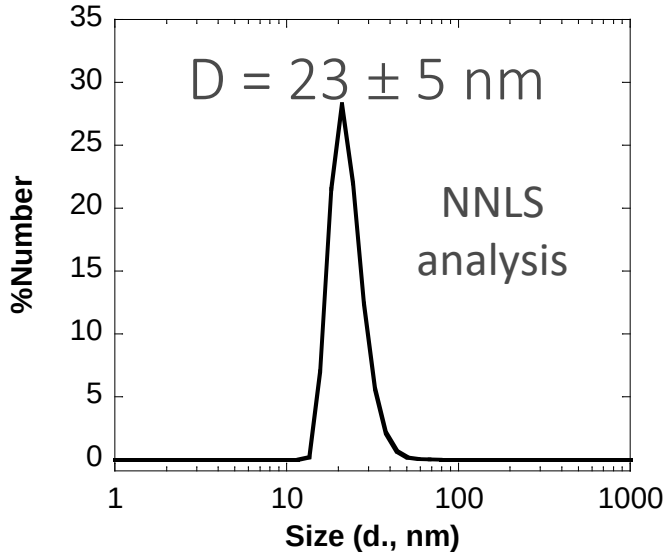
Titration by inductively coupled plasma atomic emission spectrometry (ICP-AES)



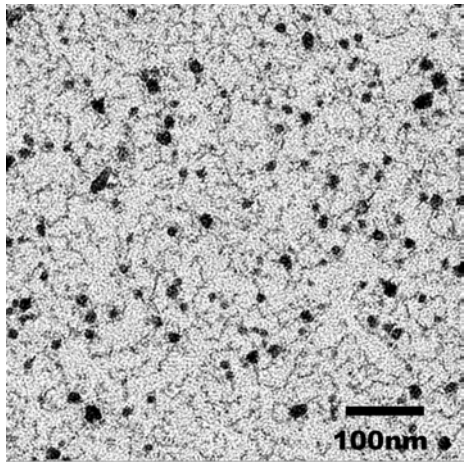
Less than 1 ‰

Gd Hybrid Poly-Ion Complexes

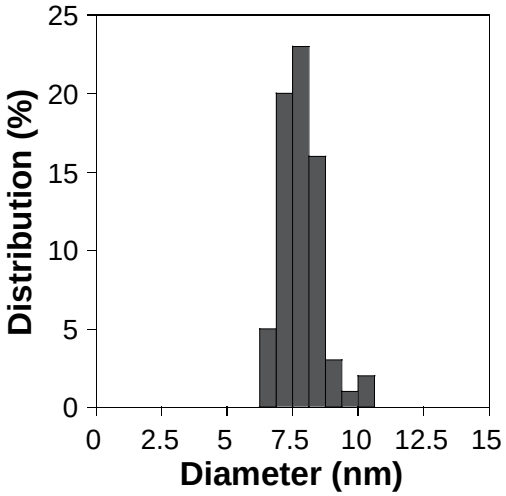
DLS



TEM

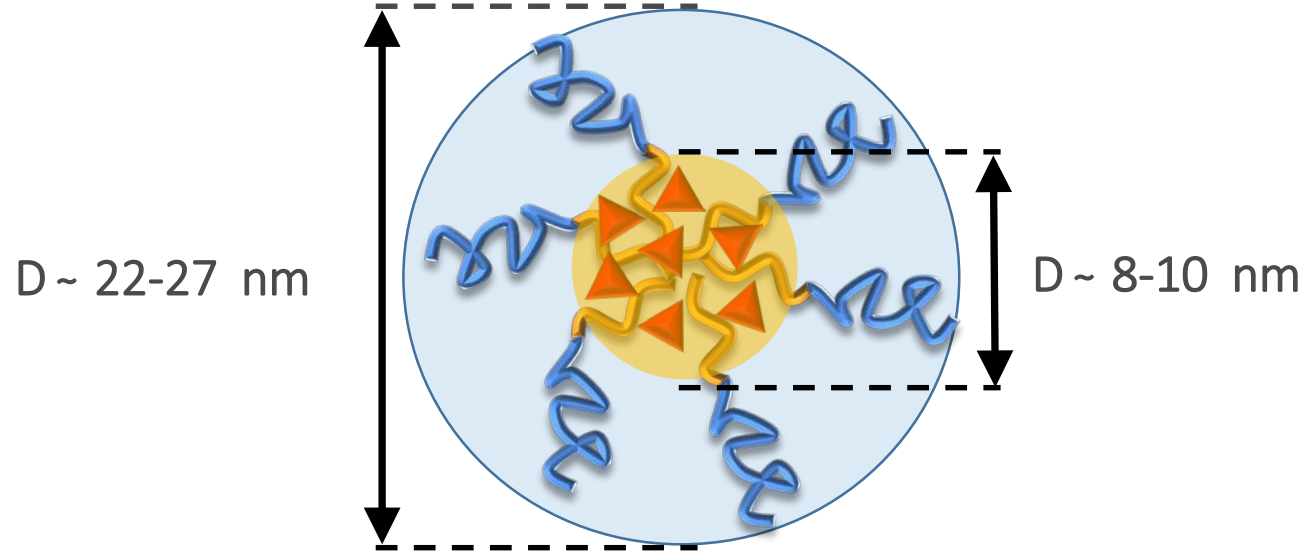


D = 8 ± 2 nm



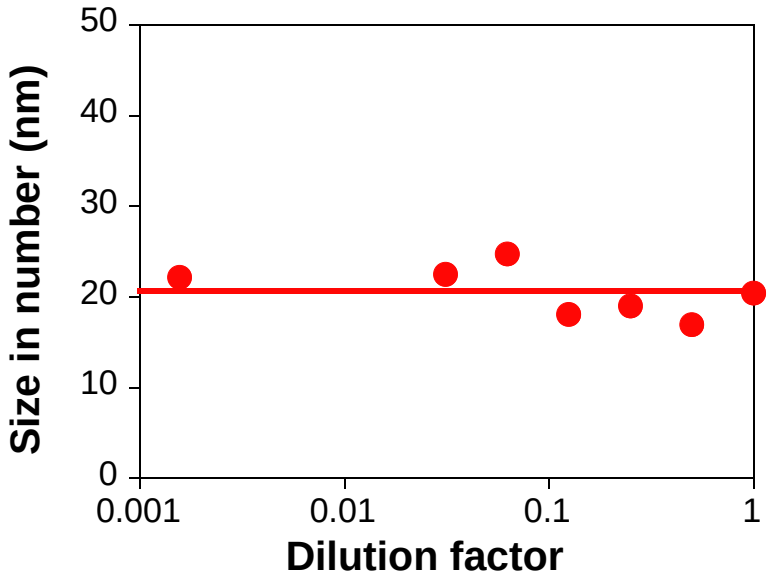
SAXS
Radius of gyration
(Guinier)

R_g ~ 5 nm

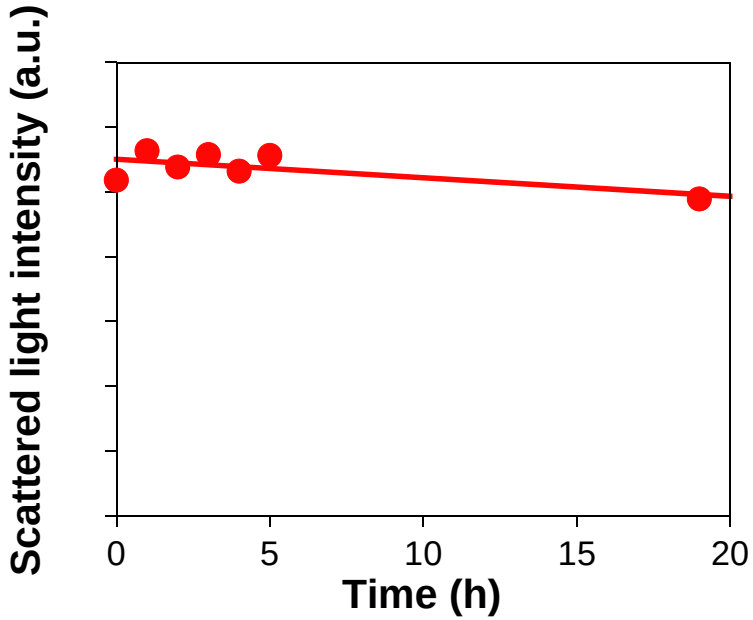


Gd Hybrid Poly-Ion Complexes

Dilution

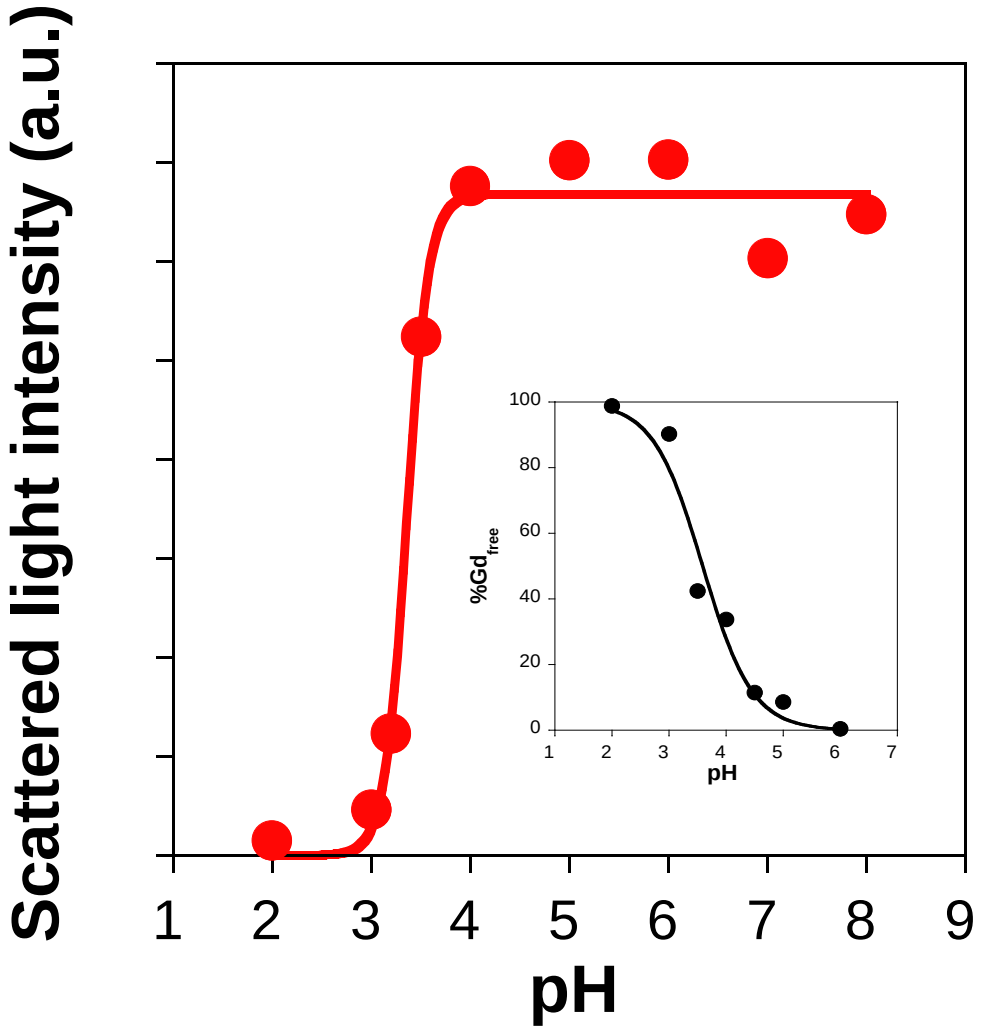


Dialysis
(against pure water)



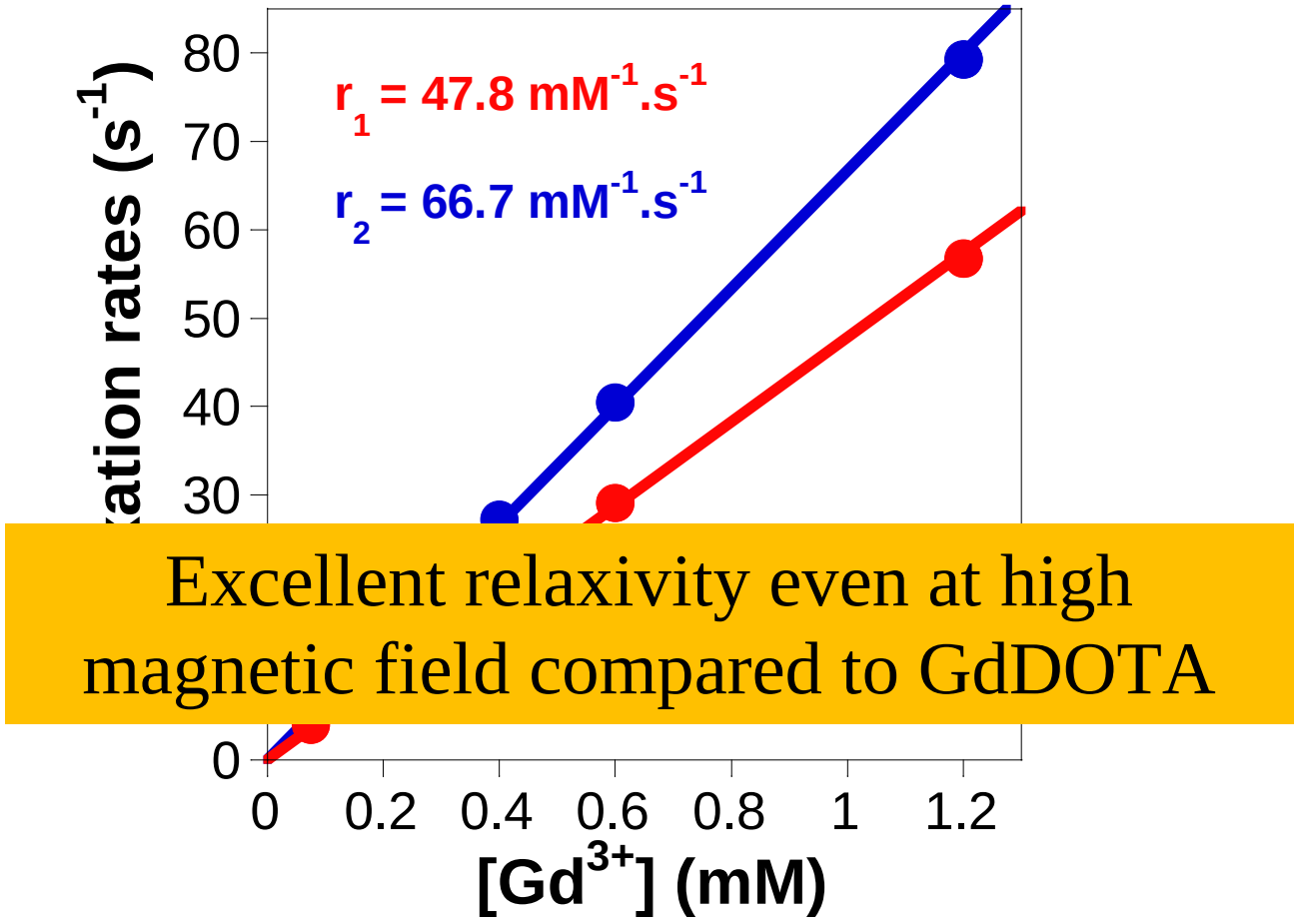
Gd^{3+}/PEO_{6k}-b-PAA_{3k} HPICs
(polymer concentration 0.1%wt; $[Gd^{3+}]=1.54.10^{-3}$ mol.L^{-1}; R=1)

Gd Hybrid Poly-Ion Complexes



ICP-AES determination of the percentage of free Gd^{3+}. Solution of 0.1%wt PEO_{6k}-b-PAA_{3k} with R = 1, filtered with centrifugal filters after changes of pH

Gd Hybrid Poly-Ion Complexes



Excellent relaxivity even at high magnetic field compared to GdDOTA

Dialyzed Gd^{3+}/PEO_{6k}-b-PAA_{3k} with R=1,B_0= 1.7 T and T= 25°C

Gd Hybrid Poly-Ion Complexes

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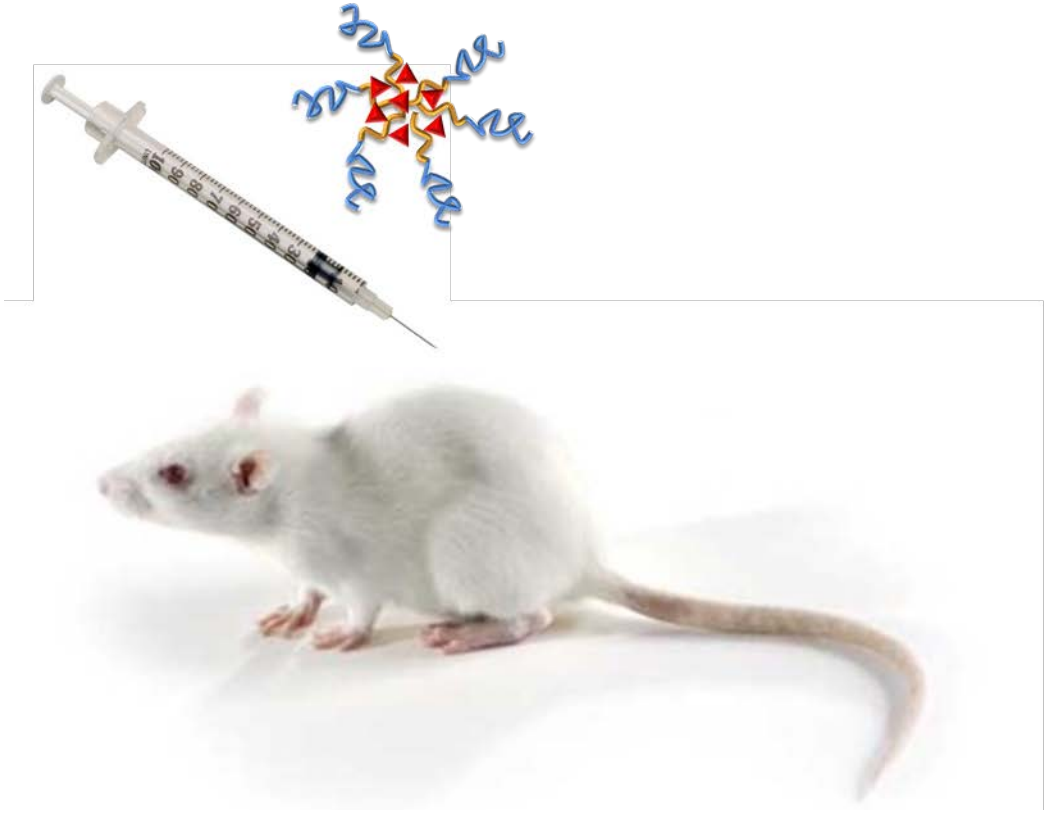
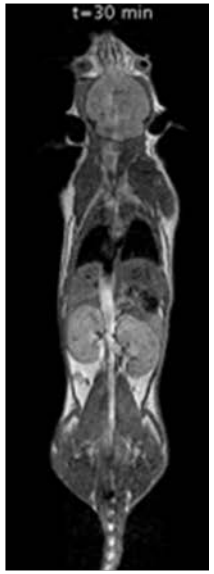
urence MARMUSE





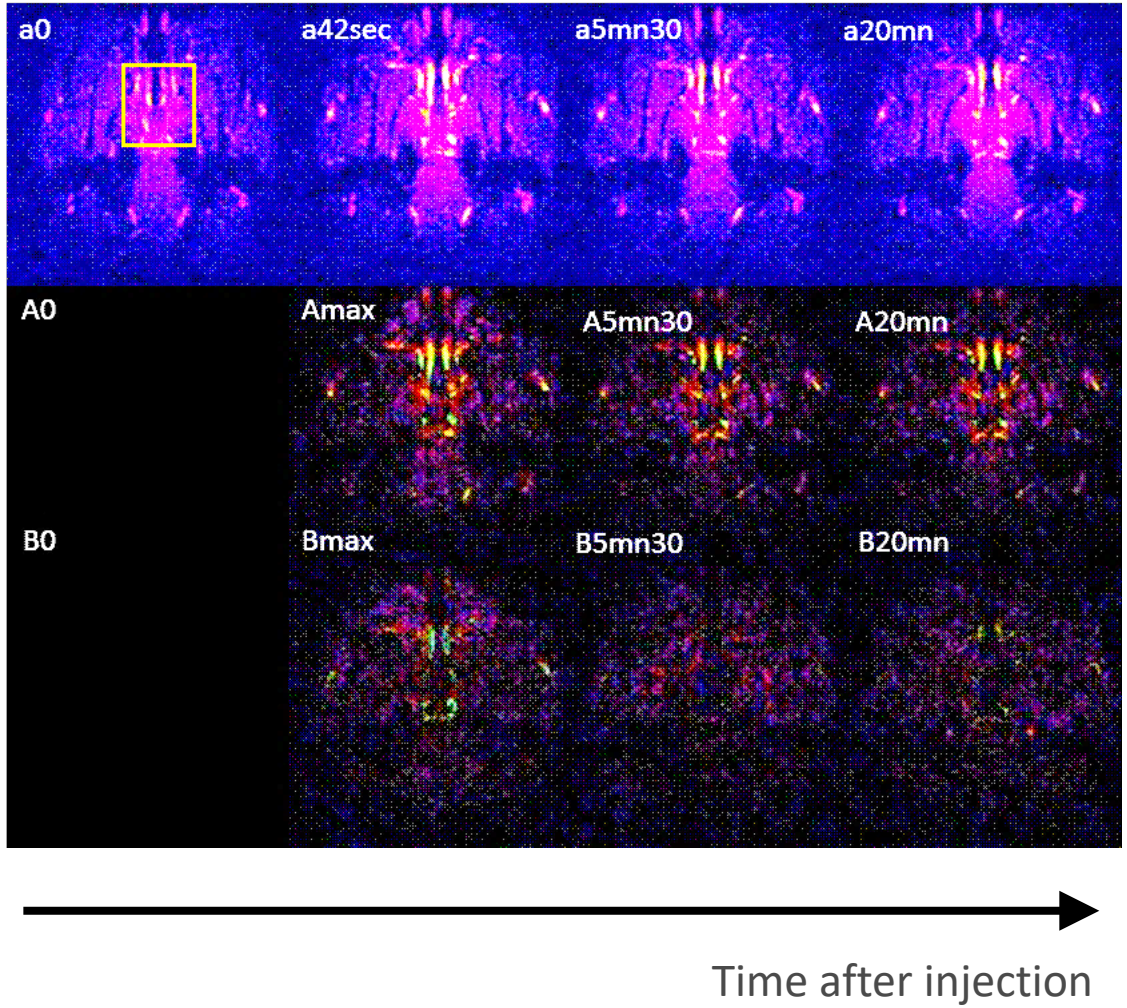
Protocols used for in vivo experiments approved by the local animal ethics committees (UCBL, Lyon, France). Acquisition performed on 190 g to 240 g female wistar rats under gaseous anesthesia.

Gd Hybrid Poly-Ion Complexes

Brain angiography images versus time

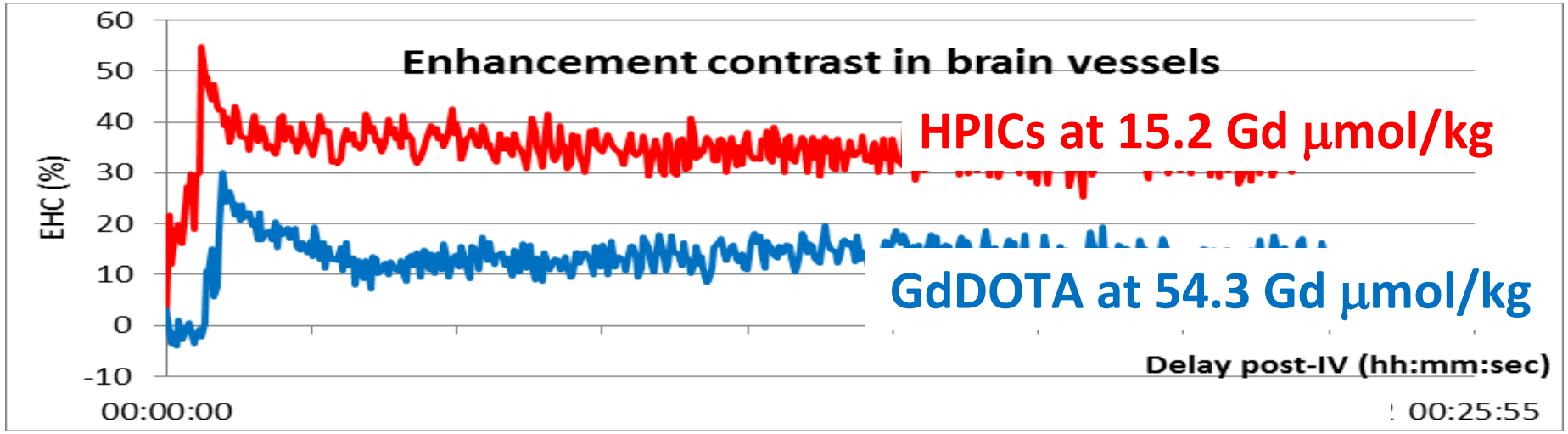
HPICs
at 15.2 Gd µmol/kg
(substraction of the pre-injection image)

GdDOTA
at 21.8 Gd µmol/kg
(substraction of the pre-injection image)



C. Frangville et al. *Nano Lett.* **2016**, 16, 4069

Gd Hybrid Poly-Ion Complexes



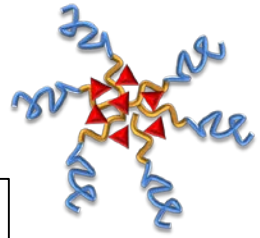
Higher intensity and more persistent enhancement than GdDOTA

EHC vs time curves generated from same dynamic acquisition centered on Willis polygone (i.e. brain angiography) and acquired in rats

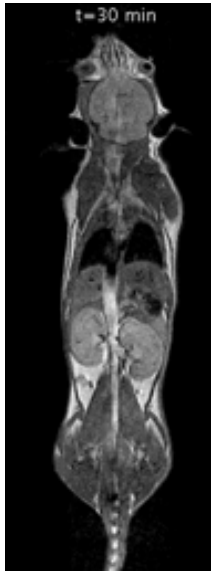
Conclusion

Gd HPICs easy to form and surpr… st…

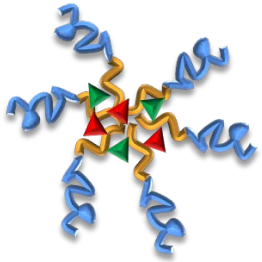
Mixture of metal ions



Very good relaxivity properties and in vivo results



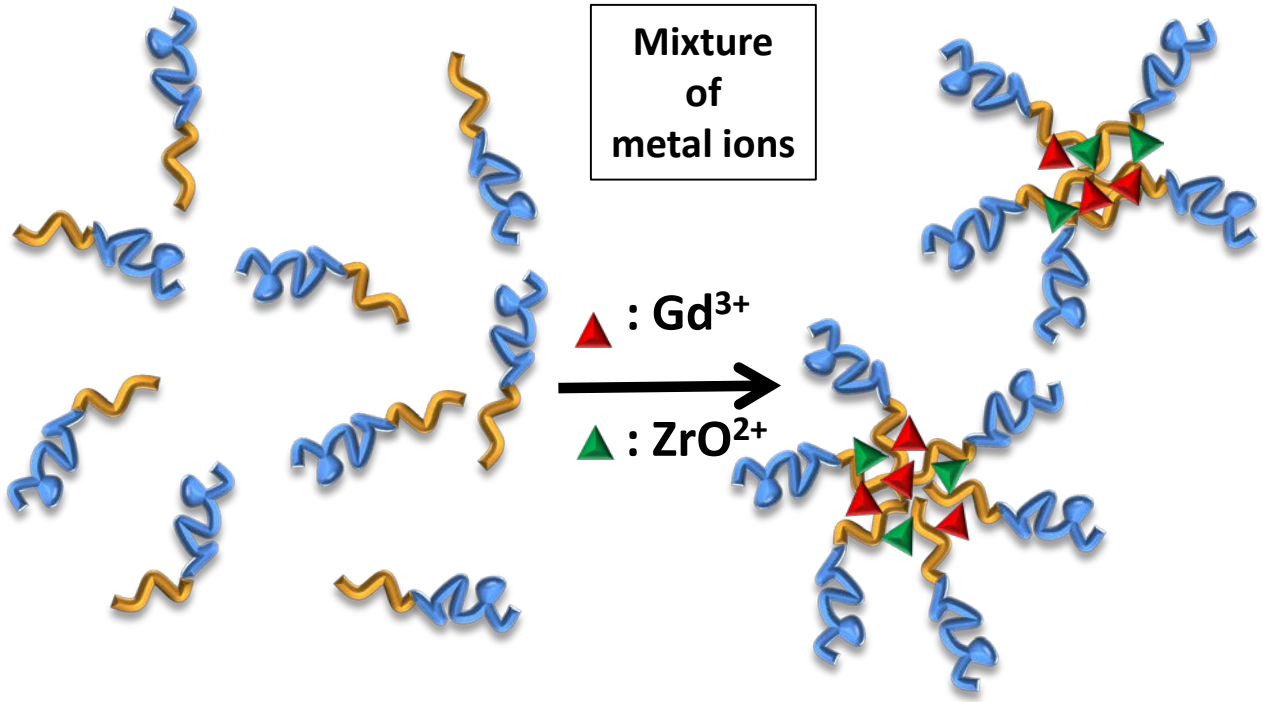
Easy modulation of the stability and properties

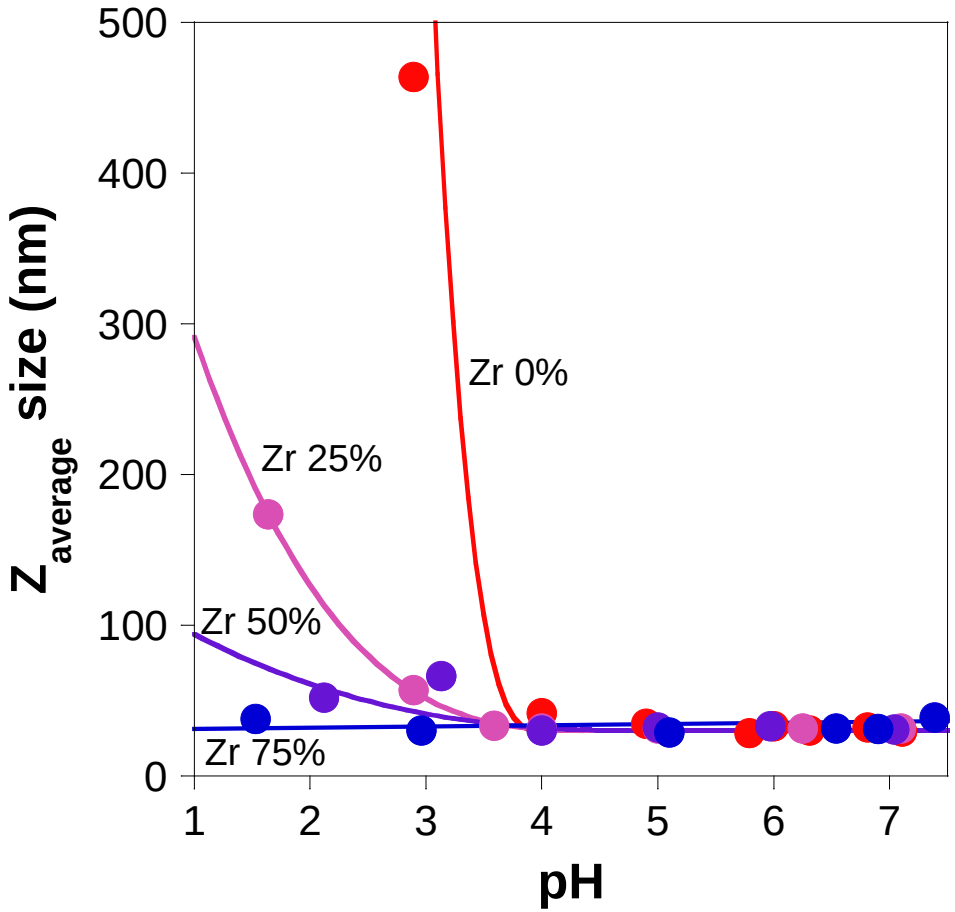


Easy functionali-zation of nano-hybrid

How to improve the stability of HPICs ?

First strategy :

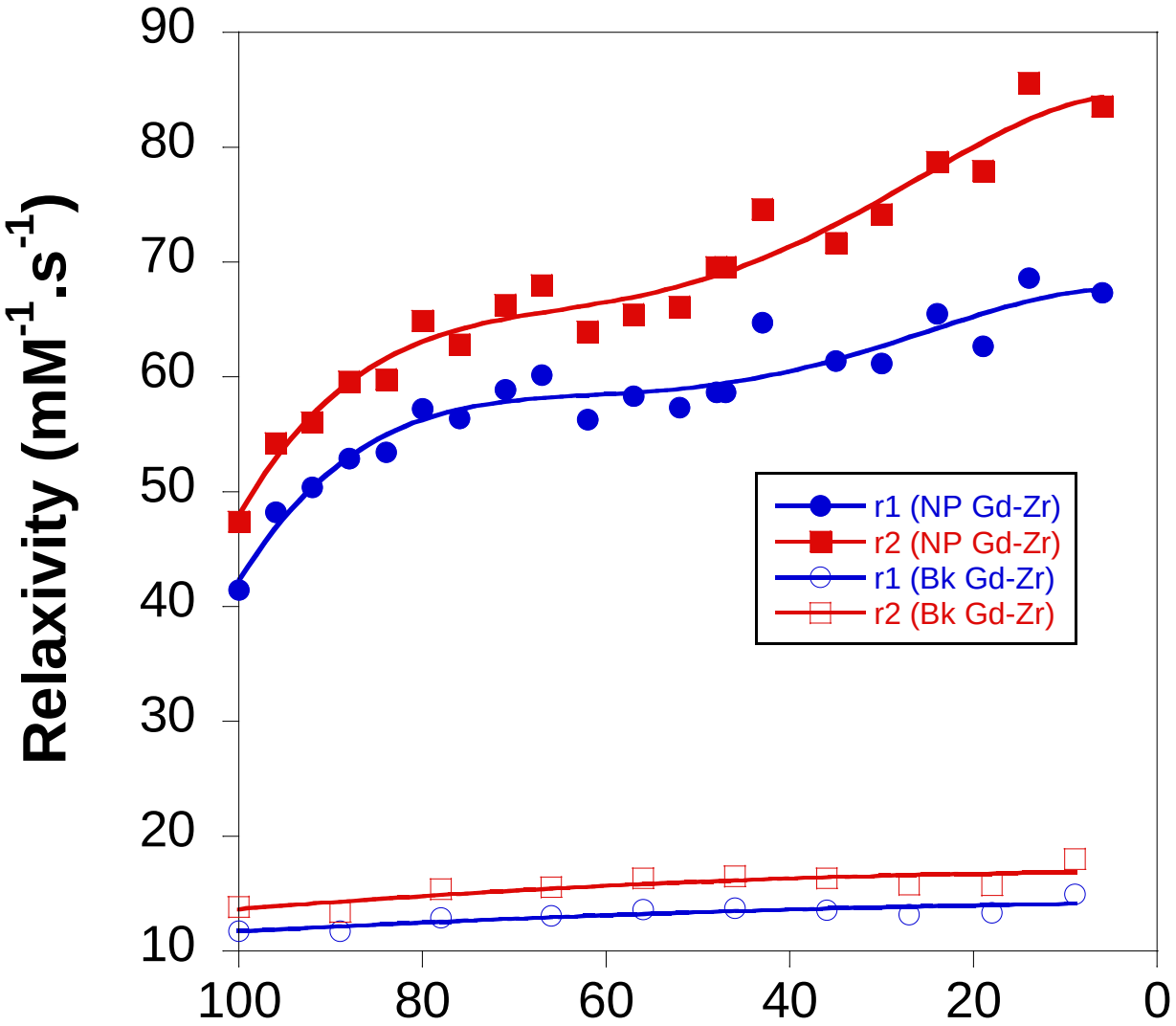




Polymer concentration 0.1 wt%

J.-D. Marty, C. Frangville, C. Mingotaud, D.R. Talham. FR Patent n°1560635. **2015**

How to improve the stability of HPICs ?

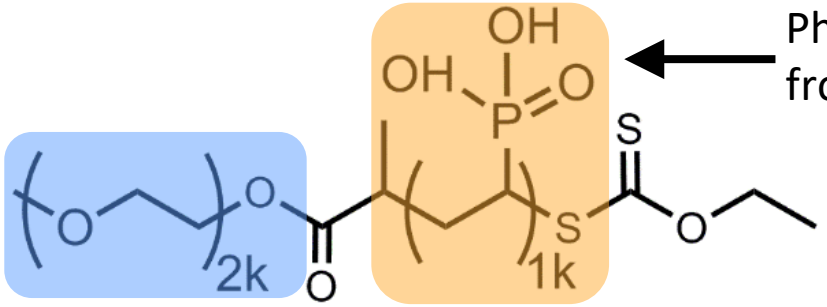


B_0= 1.7 T and T= 25°C

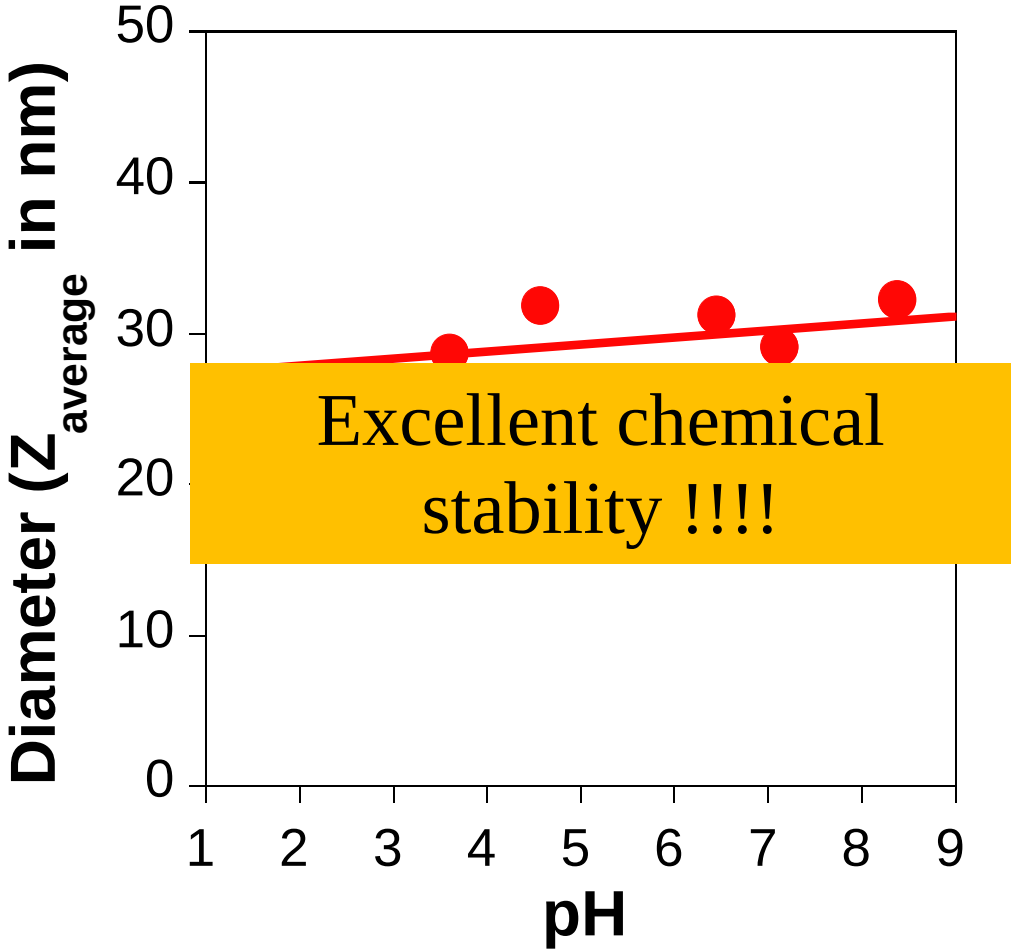
How to improve the stability of HPICs ?

Second strategy :

PEO_{2k}-$PVPA_{1k}$



Phosphonate groups
from vinyl phosphonic acid



Excellent chemical stability !!!!

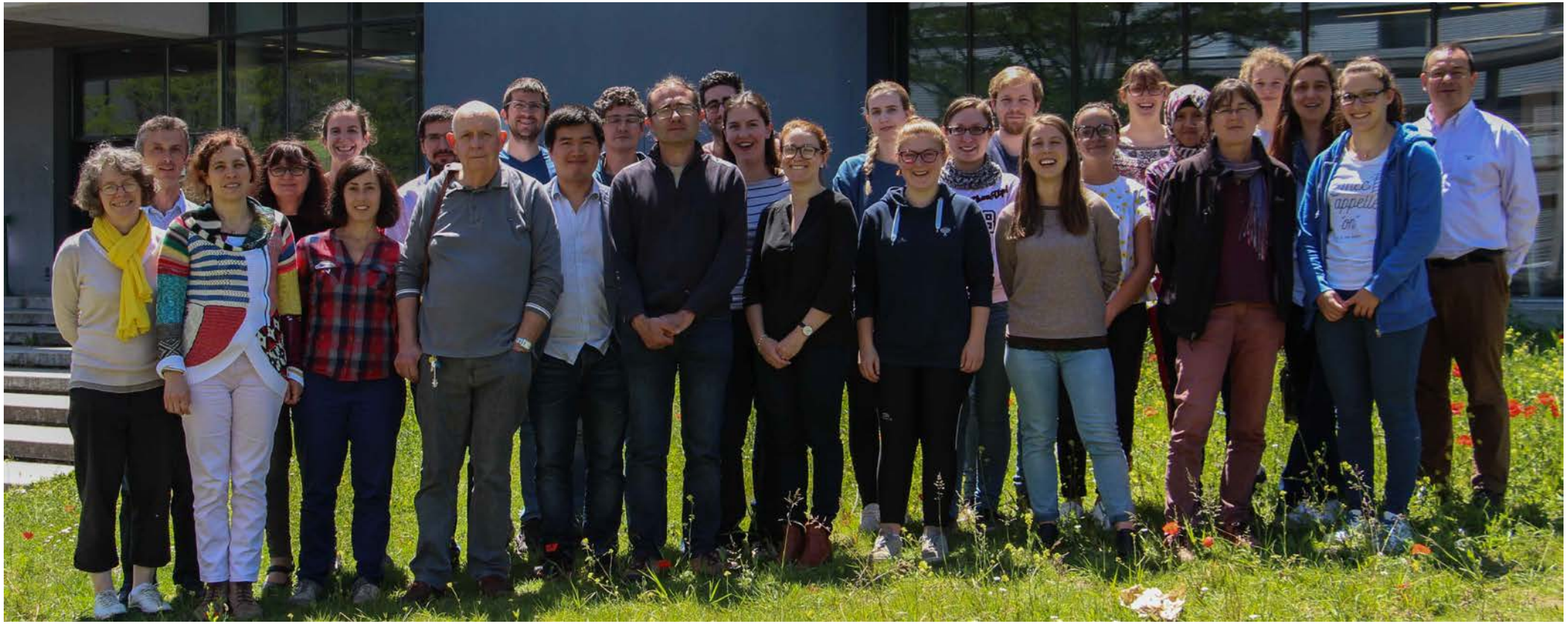
r_1 = 10 $mM^{-1}s^{-1}$ and r_2 = 43 $mM^{-1}s^{-1}$ at 7 T

IMRCP

Pr Mathias DESTARAC
Dr Simon HARRISSON

Acknowledgments

The IDeAS team



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Claire BILLOTEY
Laurence MARMUSE

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Pierre de Fermat

Nathalie PINKERTON
Stéphane CHASSAING

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Thank you for your attention!

RÉGION MIDI-PYRÉNÉES

PROJET FINANCÉ PAR L'ANR - PROJECT FUNDED BY THE ANR

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