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# Development of silica nanoparticles for $^{1}$H MRI and Optical Imaging

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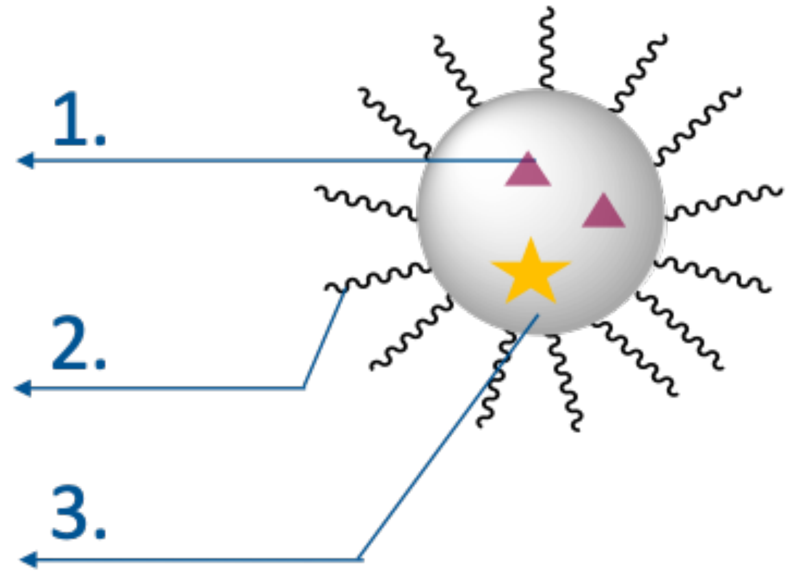
# Development of silica nanoparticles for $^{1}H$ MRI and Optical Imaging

## Graphical Abstract

**Paramagnetic complexes**
inside the $SiO_2$ matrix

**PEG chains**
(Stability, post function.)

**Fluorophore**




**[$SiO_2${Gd-HP-D03A ; ZW800}]-PEG**

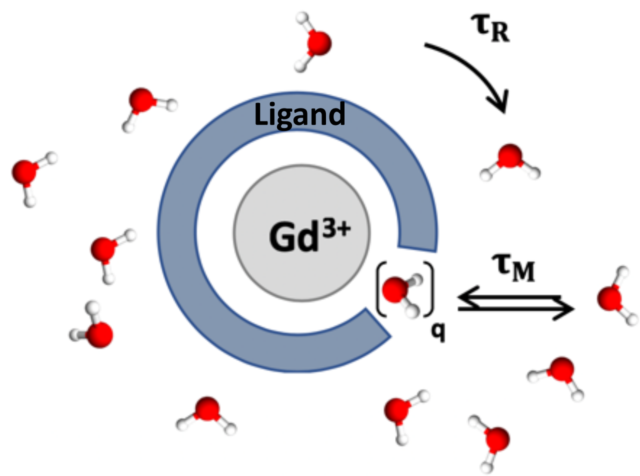
Among the numerous imaging techniques, magnetic resonance imaging (MRI) has become the most powerful tool for diagnosis owing to its high spatial resolution, unlimited tissue penetration, and nonionizing nature. Nevertheless, one can mention its lack of sensitivity, which constitutes a major drawback especially in the field of molecular imaging. The combination of MRI and optical imaging (OI), detecting the luminescence emitted by a tracer, offers the high spatial resolution of the former and the high sensitivity of the latter. In this context, this study focused on the improvement of the relaxation properties of a commercial gadolinium chelate, Gd-HP-DO3A, by a non-covalent confinement of the complex in a semi-permeable nanosystem. To induce the bimodality, a fluorescent compound, i.e. ZW800-1, has been co-encapsulated inside the nanoparticle in a one-pot process. Thanks to their exceptional properties (i.e. biocompatibility, chemical stability, low toxicity) silica nanoparticles ($SiO_2$ NPs) have been chosen as a matrix. Narrow size distribution $SiO_2$ NPs were obtained by a reverse microemulsion process ($D_H$: 80 nm). Relaxometric measurements of the synthesized nanoplatforms have proven its efficiency to decrease $T_{1,2}$ of water proton molecules. The fluorescent properties were kept after the encapsulation of the fluorophore. The final system was characterized by Dynamic Light Scattering (DLS), Nuclear Magnetic Resonance (NMR) spectroscopy, relaxometry measurements, UV-Vis and IR spectroscopies and Transmission electron microscopy (TEM).

**Keywords:** Nanoparticles ; Silica nanoparticles; Contrast agents ; MRI ; OI; Diagnosis.

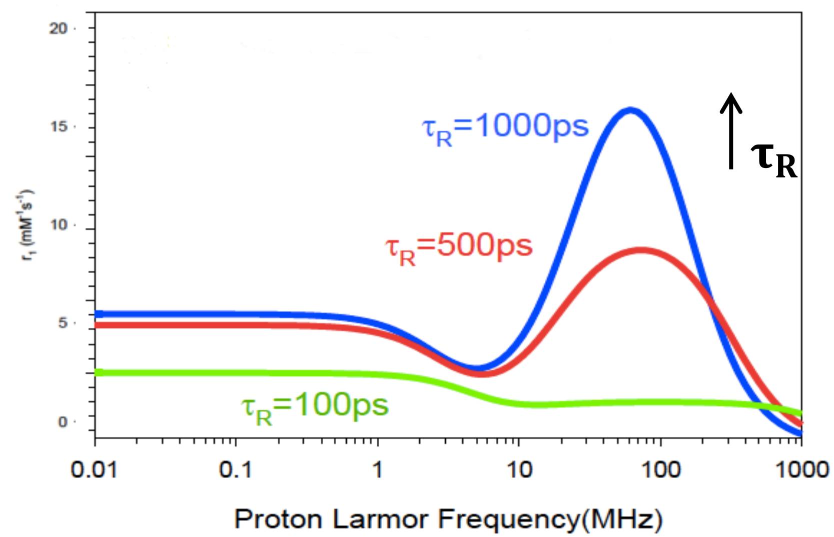
# Introduction

Drawback : Low sensitivity of MRI →Improvement by using paramagnetic Gd complexes.

Innersphere mechanism




→ Enhancement of longitudinal water relaxation by $\tau_R$ increases




With :
$\tau_R$ : rotational correlation time
$\tau_M$ : residence time of water molecules in the inner sphere
q : hydration number

Increasing of the MW → $\tau_R$ increases

→ MW modification by different structures

( dendrimer, nanoparticles, …)

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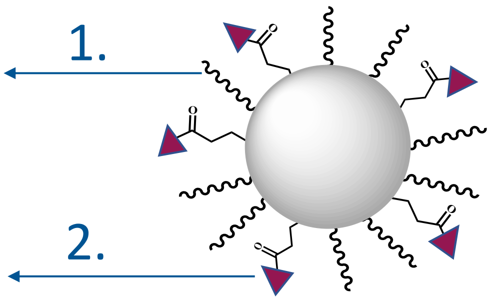
# Introduction

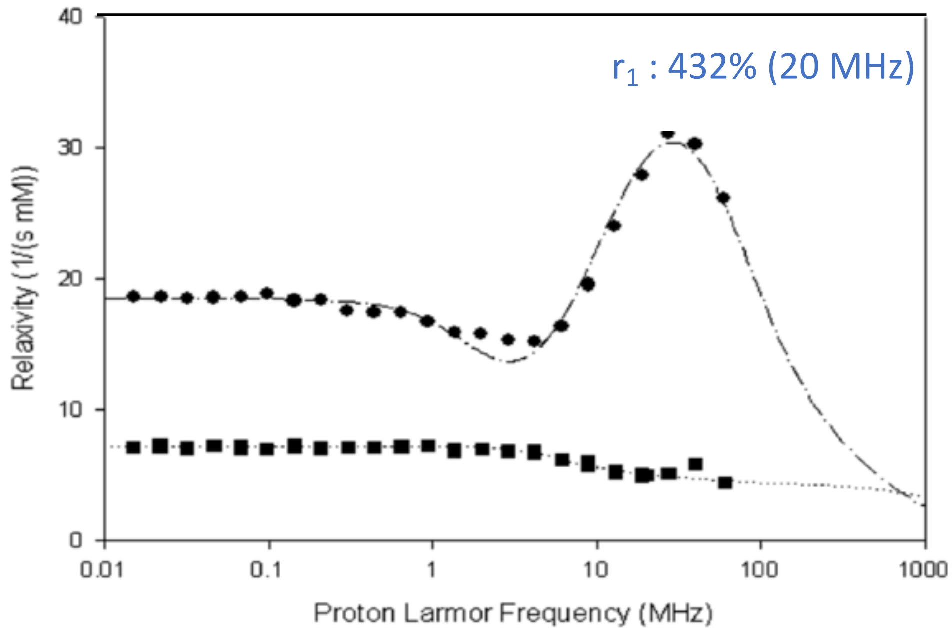
Previous researches[1] : Gd-complexes covalently bonded to pegylated silica nanoparticles ($SiO_2$ NPs)

**PEG chain**
(stability)

**Paramagnetic complexe**




Enhancement $r_1$ in high field




Full saturation of the nanoparticle surface
→ Grafting of biovectors on the surface

| Samples | $\tau_R$ [ns] |
|---|---|
| Gd-DTPA-$NH_2$ | 0.09 |
| [$SiO_2$]-NH-Gd-DTPA | 0.35 |

[1] E. Lipani *et al.*, *Langmuir*, 29, 3419-3427, 2013.

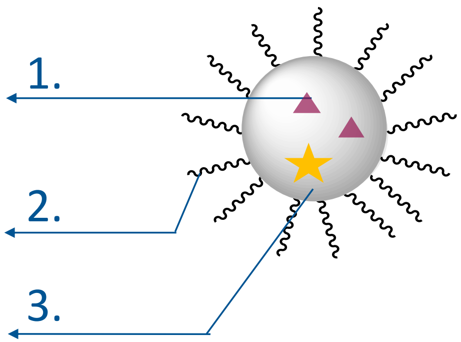
# Aim of the project

Target platform : Silica nanoparticles (biocompatibility, chemical stability, low toxicity)
Possibility of contrasts agents incorporation in the core during the synthesis

**Paramagnetic complexes** inside the $SiO_2$ matrix

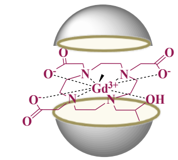
**PEG chains**
(Stability, post function.)

**Fluorophore**

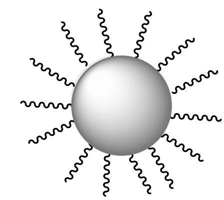



**[$SiO_2${Gd-HP-D03A ; ZW800}]-PEG**

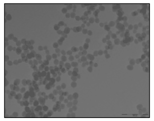
Synthesis of fluorescent/paramagnetic $SiO_2$ core



Surface modification by PEGylation



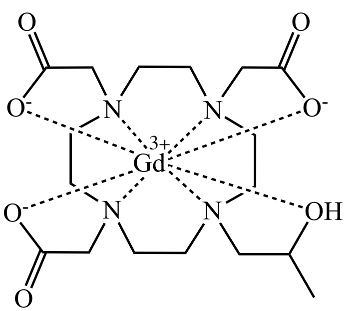
Characterization of the target platform



# Results and discussion

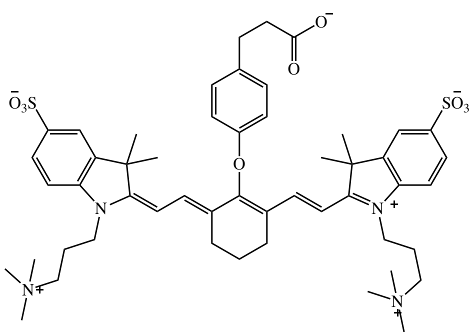
Target platform : Bimodal $SiO_2$ NPs for MRI and OI application

## MRI



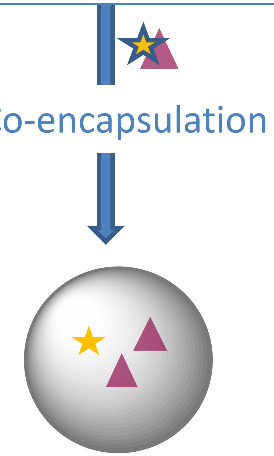
- **Gd-HP-DO3A =** ▲
  - ✓ Resolution

## OI



- **ZW800 =** ★
  - ✓ Sensitivity
  - ✓ High quantum yield
  - ✓ Therapeutic window
    - λ excitation: 772 nm
    - λ emission: 788 nm

**Reverse microemulsion**

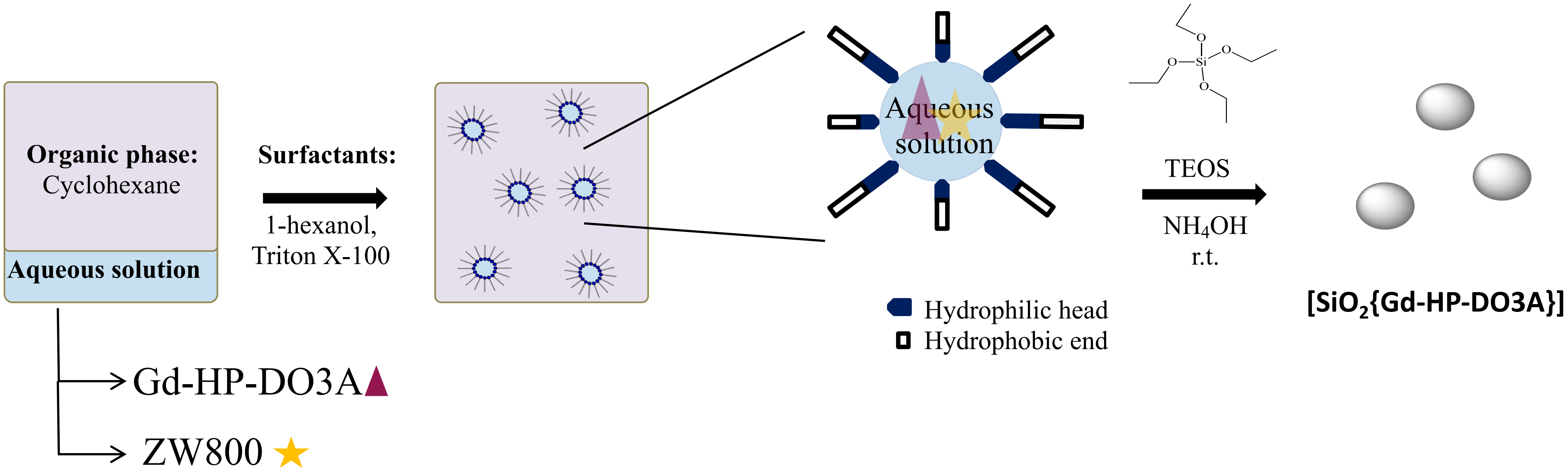



**[$SiO_2${Gd-HP-D03A;ZW800}]**

- Improvement of the relaxation process by a non-covalent confinement of Gd-complexes in a semi-permeable nanosystem
- Co-encapsulation of a fluorophore and a paramagnetic agent → **bimodality application**

# Results and discussion

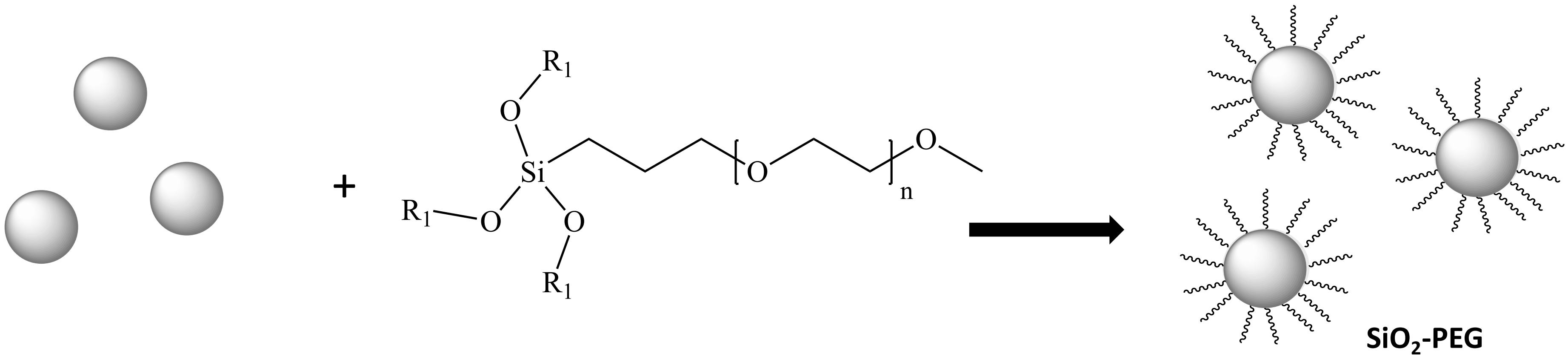
Synthetic route: Water in oil microemulsion (reverse microemulsion)




- Room conditions:
  1. Encapsulation of hydrosoluble molecules
  2. Surface modification

# Results and discussion

Optimization of the coating : surface modification by PEGylation




Coating agent:

Full saturation with biocompatible Si-PEG chains :

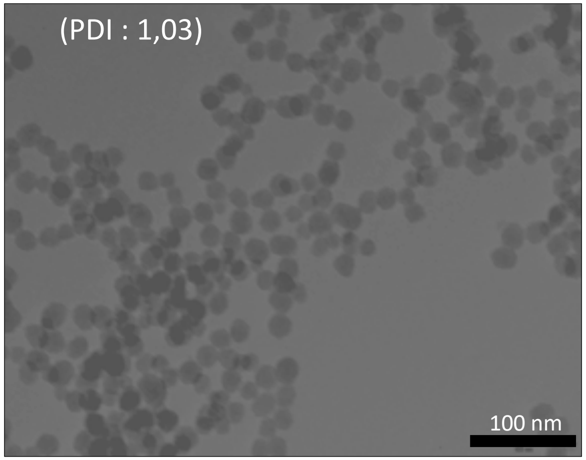
- Si-$PEG_{11}$: 591-719 g/mol.
- Si-$PEG_{44}$: 2175 g/mol.)

- Precipitation of the NPs:
  Acetone
- Purification steps:
  Washing with EtOH through several cycles of centrifugation
- Redisperion in $H_2O$, sonication

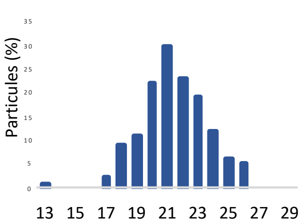
# Results and discussion

## Size charaterization:

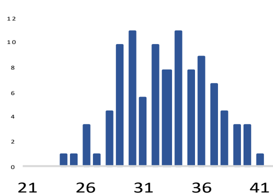
### Transmission Electron Microscopy



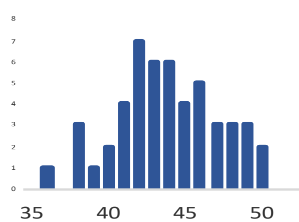

Spherical morphology




$[SiO_2]$: 20,93 ± 2,17 nm

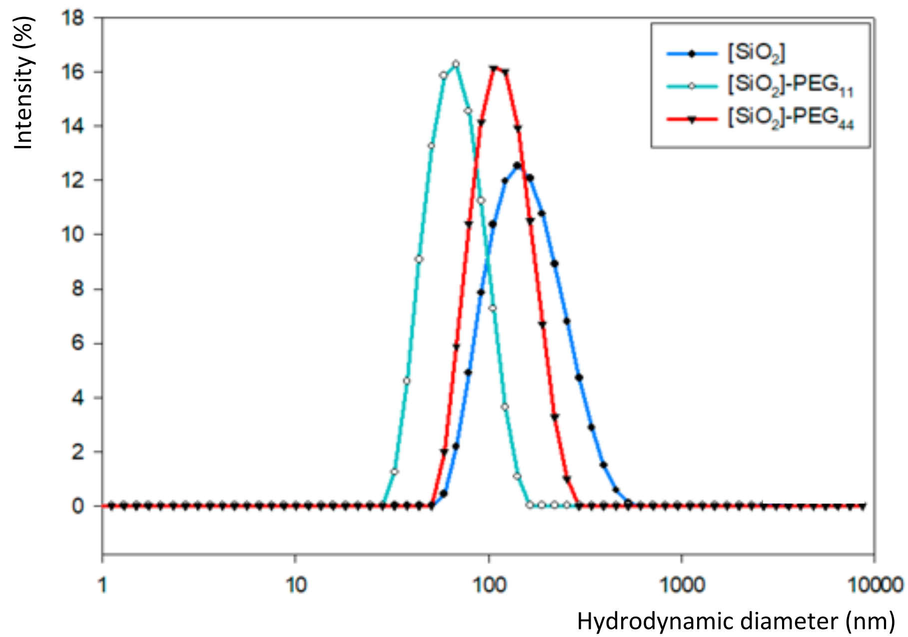



$[SiO_2]$-$PEG_{11}$: 34,31 ± 3,98 nm




$[SiO_2]$-$PEG_{44}$: 42,04 ± 4,44 nm

### Photon Correlation Spectroscopy




After PEGylation:

- Narrow size distributions
- Stable NPs in aqueous media

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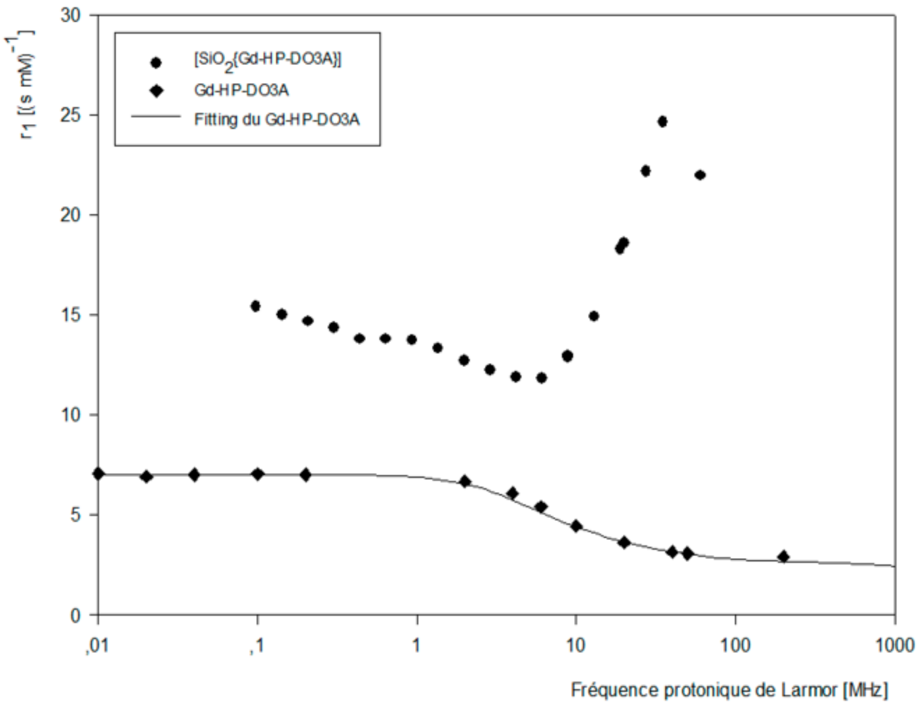
# Results and discussion

## Magnetic propreties : stability, relaxivity characterization




| Samples | 20 MHz $[s^{-1}mM^{-1}]$ | 60 MHz $[s^{-1}mM^{-1}]$ |
|---|---|---|
| | $r_1$ (37°C) | $r_1$ (37°C) |
| Gd-HP-DO3A | 3.7 | 2.9 |
| $[SiO_2\{Gd\text{-}HP\text{-}DO3A\}]$ | 18.3 | 24.7 |

→ $r_1$ increases

- Nonporous $[SiO_2\{Gd\text{-}HP\text{-}DO3A\}]$
- Gd-HP-DO3A

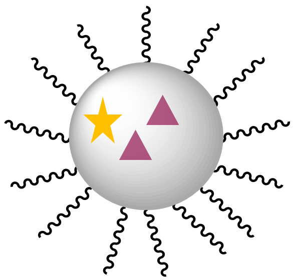
**$r_1$: 494% (20 MHz)**

**Enhancement of $r_1$ at clinical fields**

Increasing of the MW → **slow rotation**

# Results and discussion

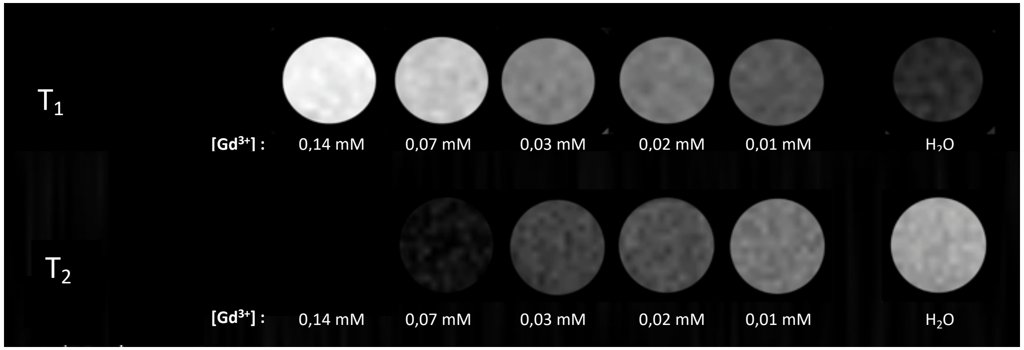
## Preliminary *in vitro* imaging :



$[SiO_2\{$Gd-HP-D03A;ZW800$\}]$-PEG

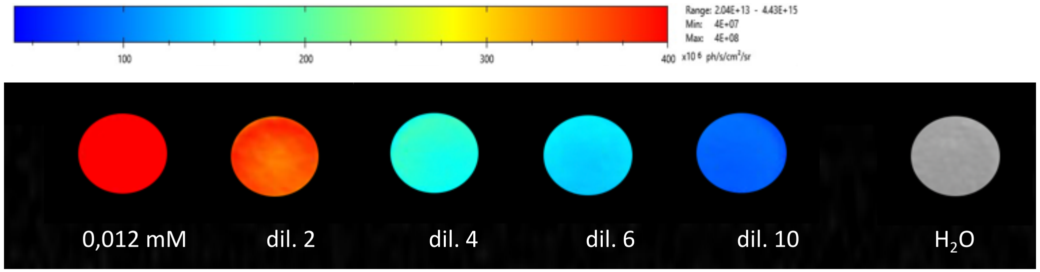
MRI (1T):

$[Gd^{3+}]$ ←




OI by FLI:

[ZW800-1] ←




λ Excitation: 737 nm
λ Emission: 797 nm

# Conclusions

| Synthesis of fluorescent/paramagnetic $SiO_2$ core | Surface modification by PEGylation | In vitro imaging |
|---|---|---|

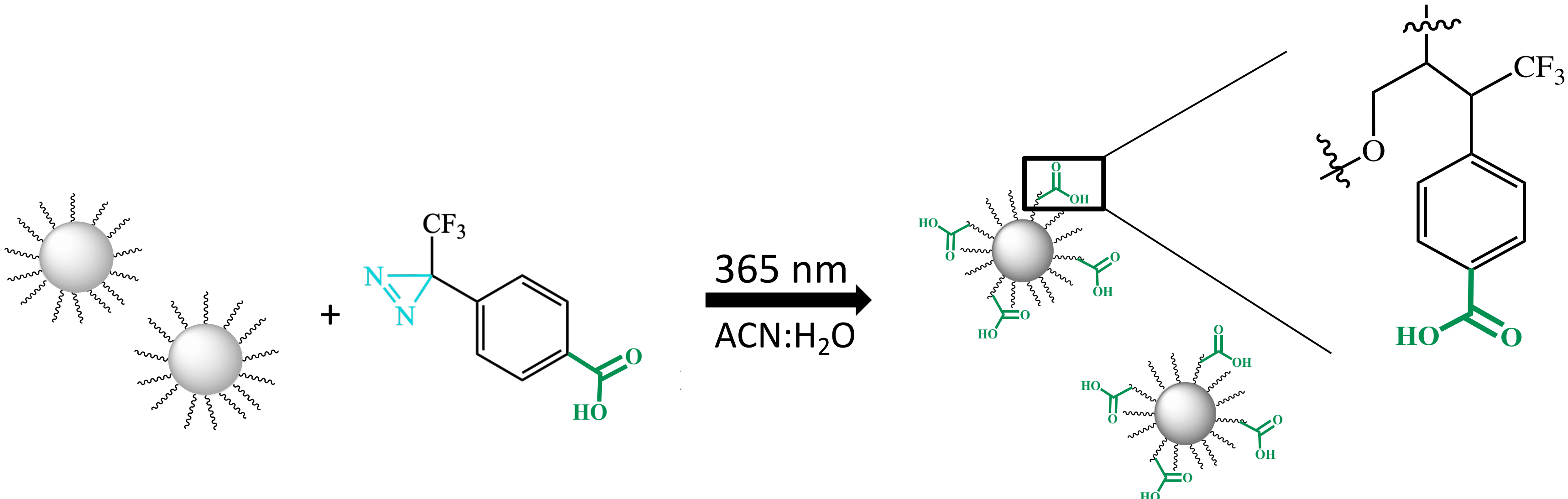
- Synthesis by water in oil microemulsion
- Co-encapsulation of a fluorophore (ZW800) and a pramagnetic agent (Gd-HP-DO3A).

- Surface modification by silanol-PEG chains to ensure the stability

- Efficient relaxation process

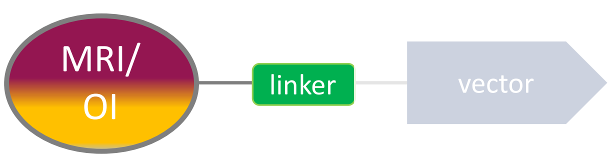
# Perspectives

*hv*-chemistry :




$SiO_2$-$PEG_{44}$ UV-sensitive linker $SiO_2$-$PEG_{44}$-linker

Introduction of the linkers **on the top of the coating agent** → Less sterically hindered of –COOH functions




***Post*-derivatisable plateform for MRI and OI**

→ Possibility of grafting biovectors on the surface

# Acknowledgments

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LE FONDS EUROPÉEN DE DÉVELOPPEMENT RÉGIONAL
ET LA WALLONIE INVESTISSENT DANS VOTRE AVENIR