

Functional coordination polymers at the nanoscale: old materials new tricks



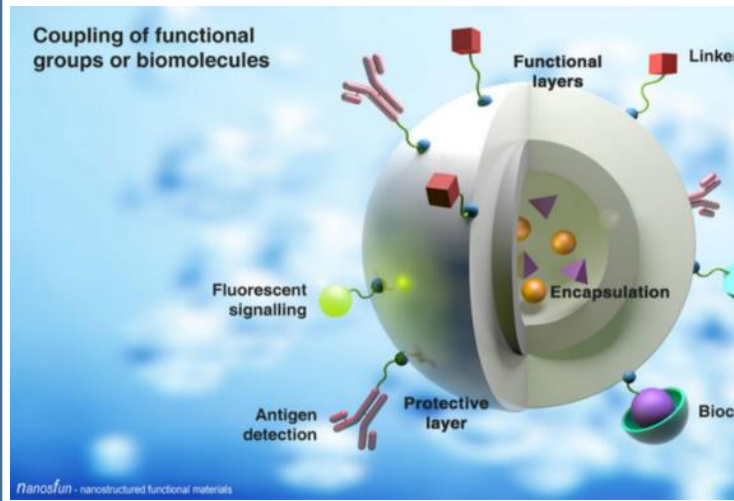
Daniel Ruiz-Molina

Institut Catala de Nanociencia i Nanotecnologia (ICN2-CSIC))

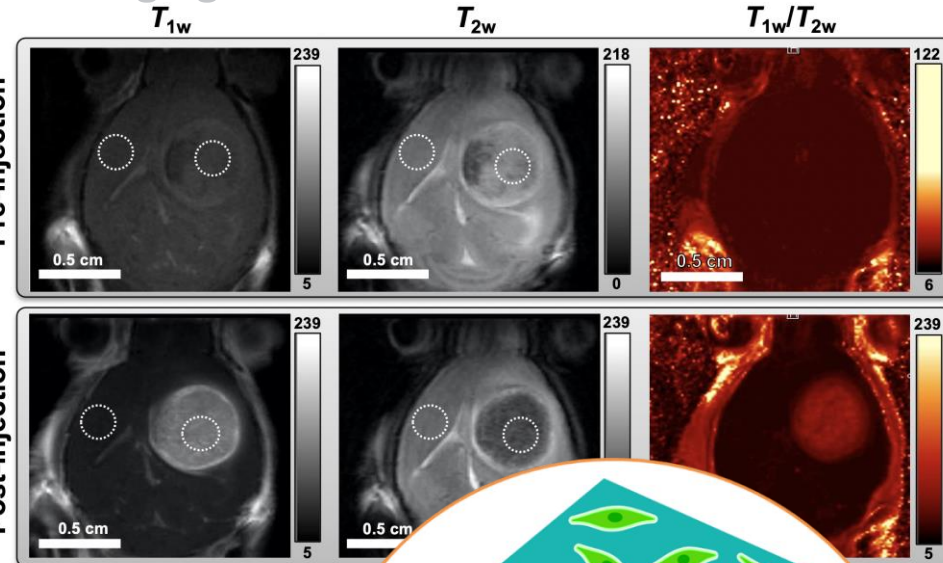
Where are we?



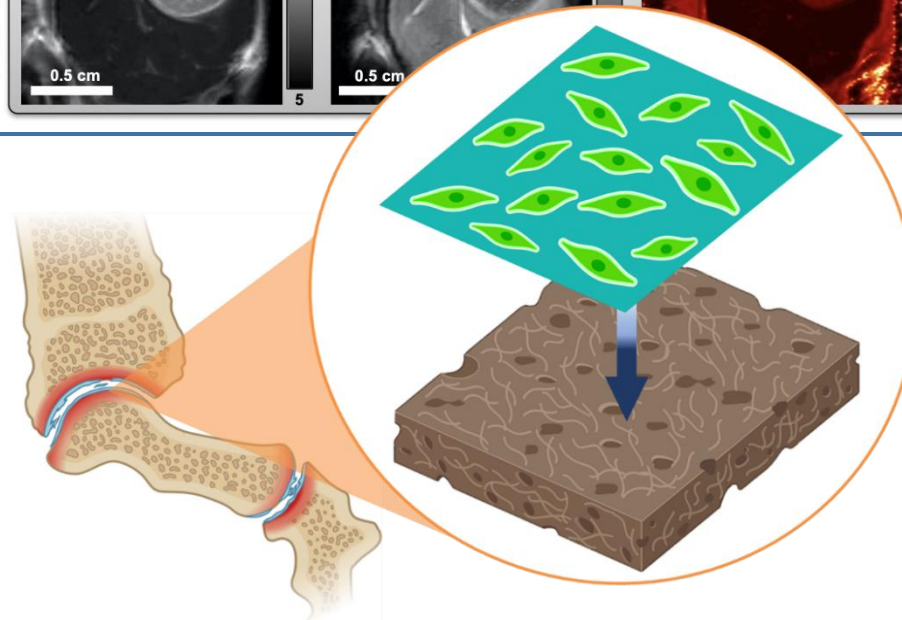
Drug delivery



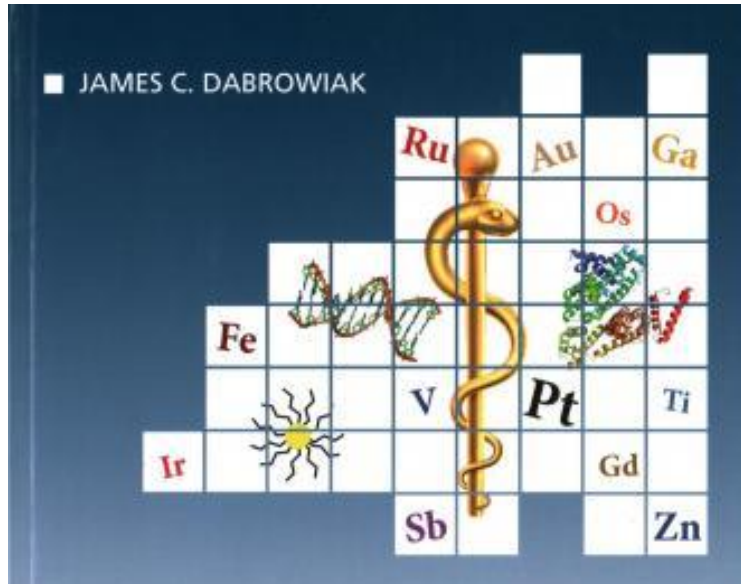
Imaging



Biodhesives



Tissue regeneration



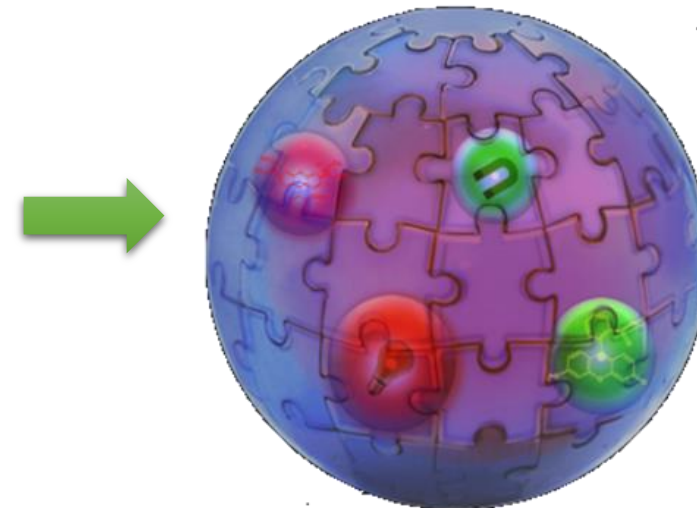
Metals can be used as **therapeutic** and **diagnostic** agents:

- Gadolinium(III), Iron(III), Manganese(II) for **MRI**
- Indium-111 and Copper-64 for **Positron emission tomography**
- Platinum(II) and Ru(II, III) to treat **cancer tumours**
- **Zinc(II)** to treat the herpes virus
- Etc...

Drawbacks of the treatment:

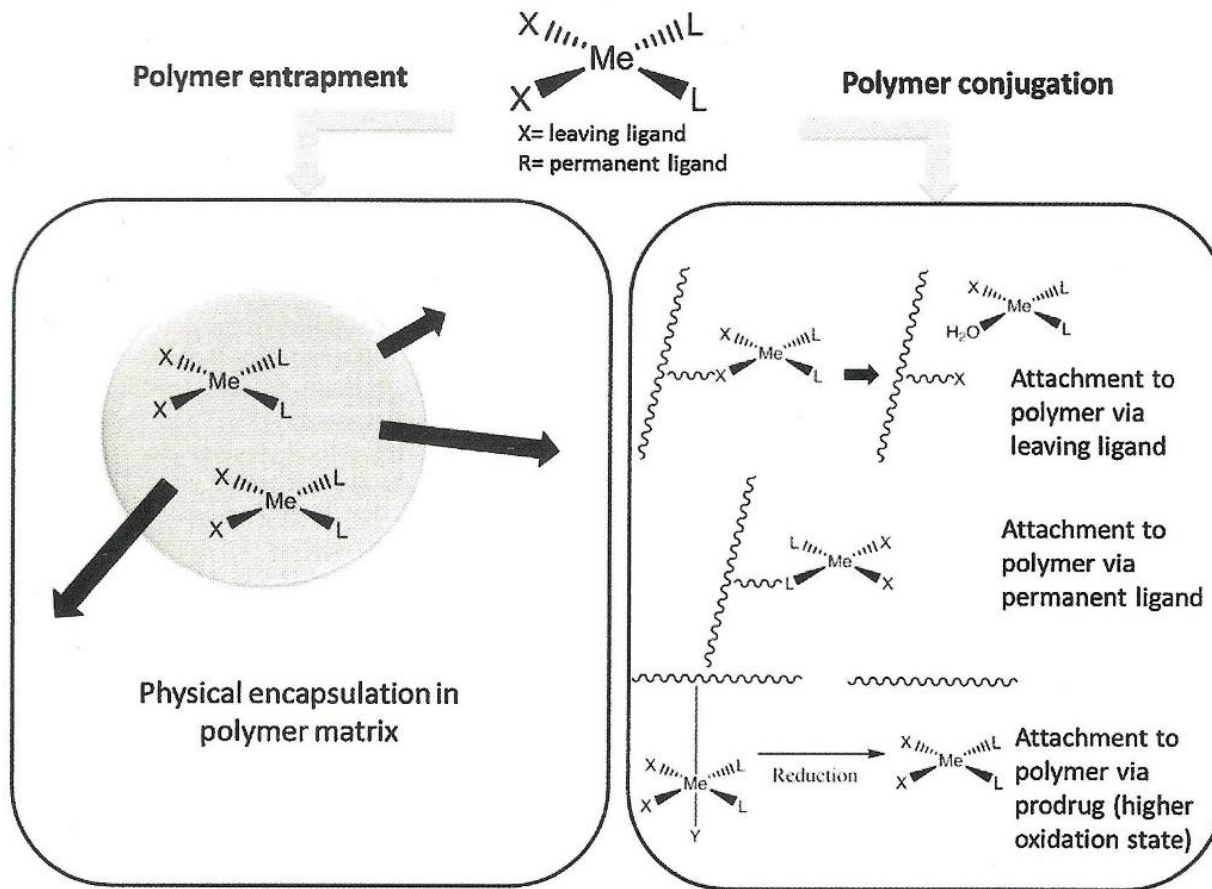
- **Side effects** caused by the systemic distribution
- Low hydrolytic **stability**
- **High reactivity** towards proteins and other biomolecules

Encapsulation!



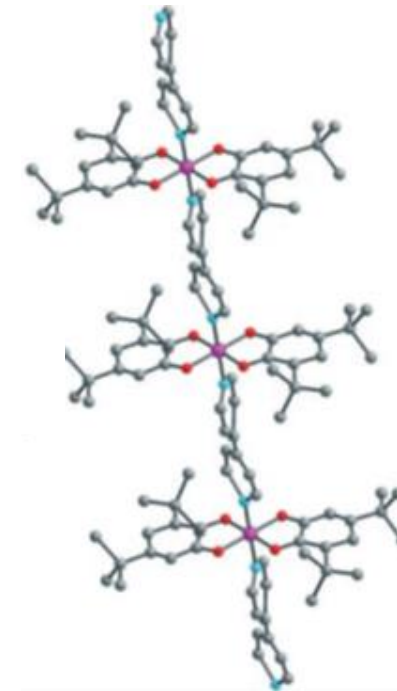
Nanocarriers

polymeric nanoparticles are one of the most widely used carriers

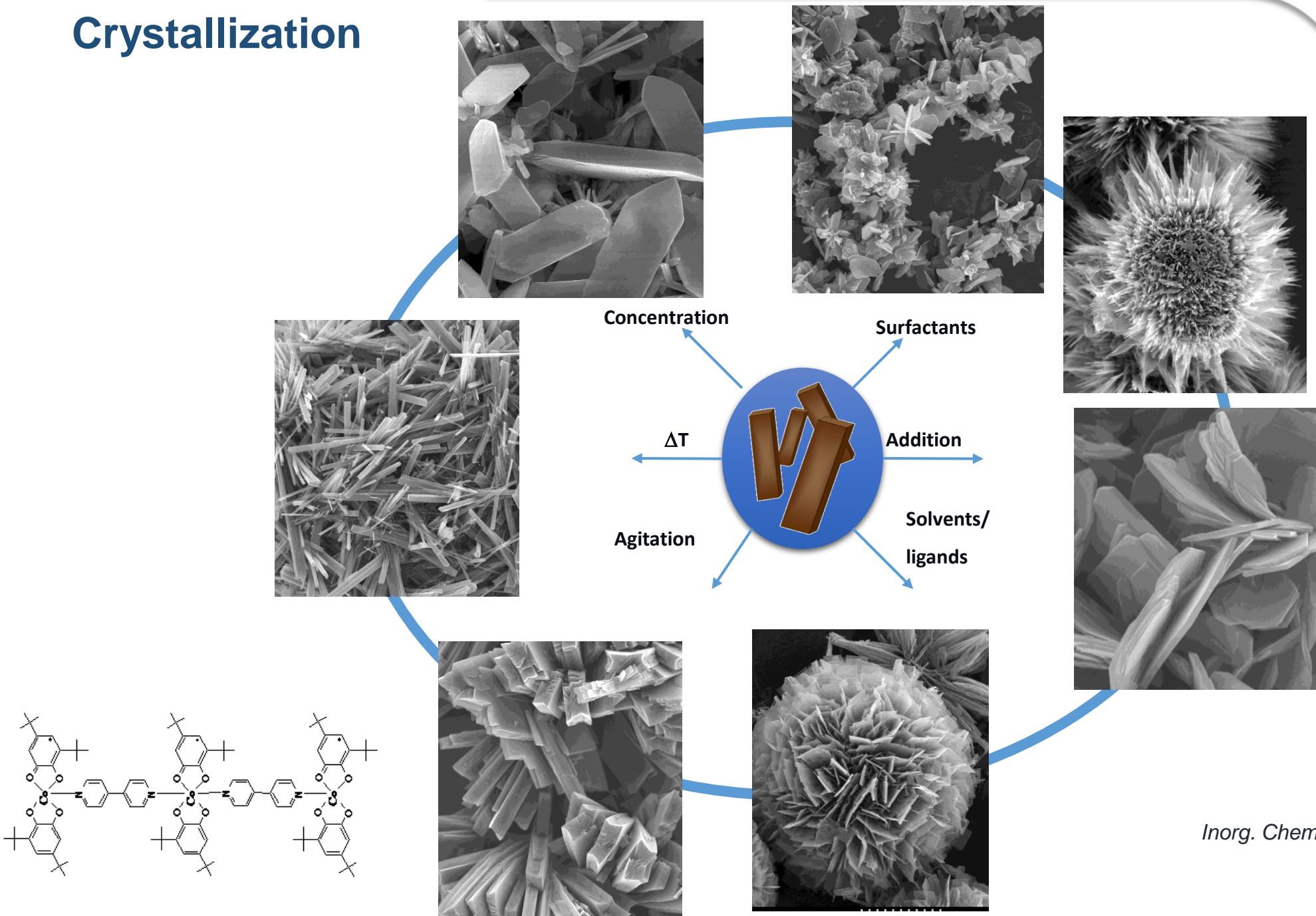


- ✓ Increase of the **encapsulation yield**
- ✓ Long lasting **release triggered**
- ✓ Excellent **biocompatibility and biodistribution**
- ✓ Chemical **flexibility**

Coordination polymers



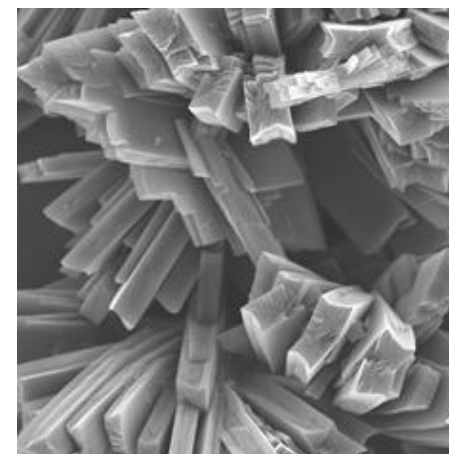
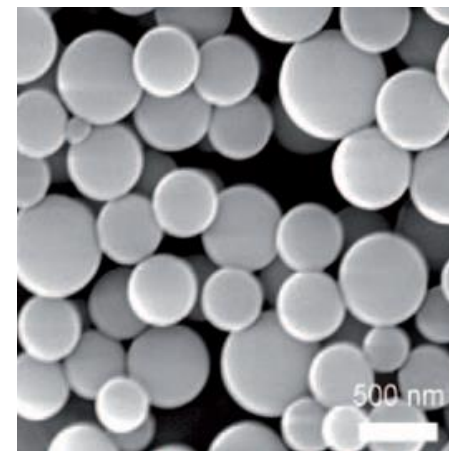
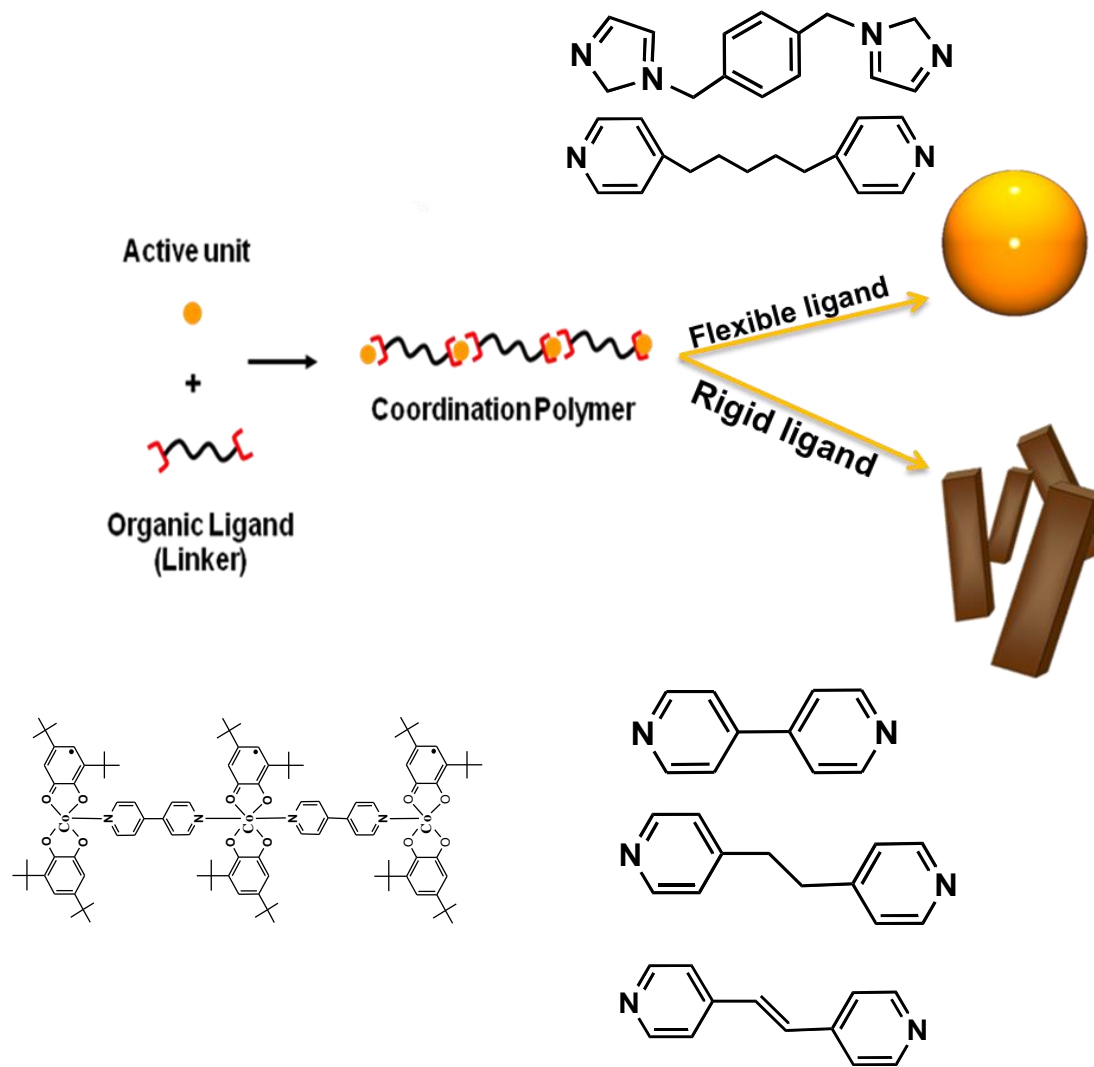
Crystallization



Inorg. Chem. **2014**, 53 (16), 8742-8748

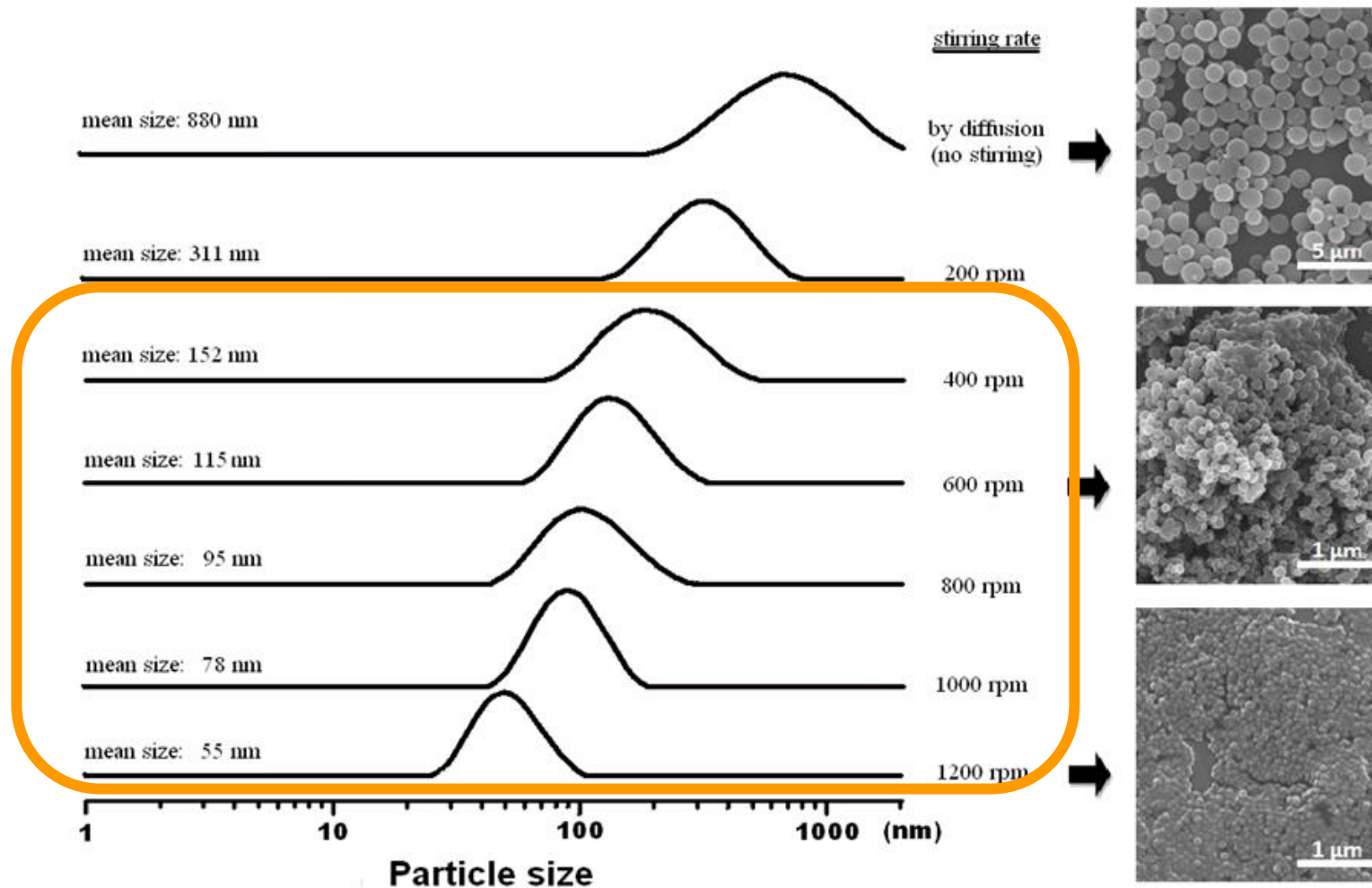
Synthesis

Flexible ligands and out-of-equilibrium conditions



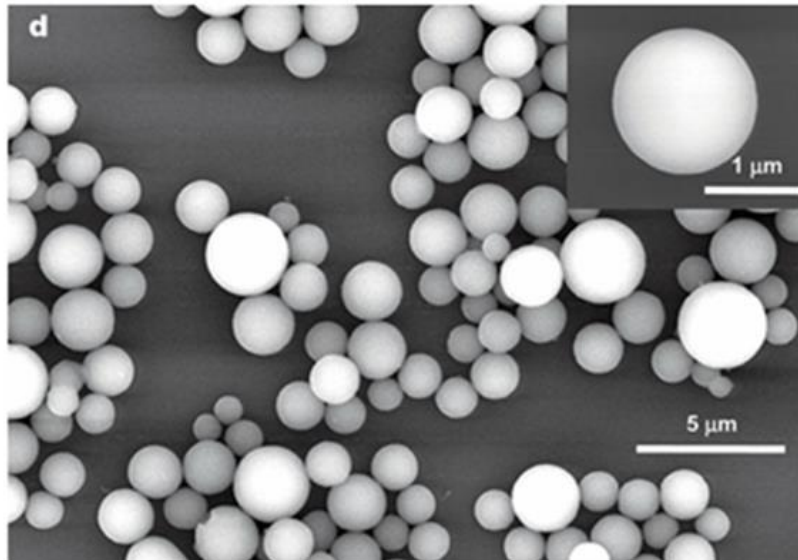
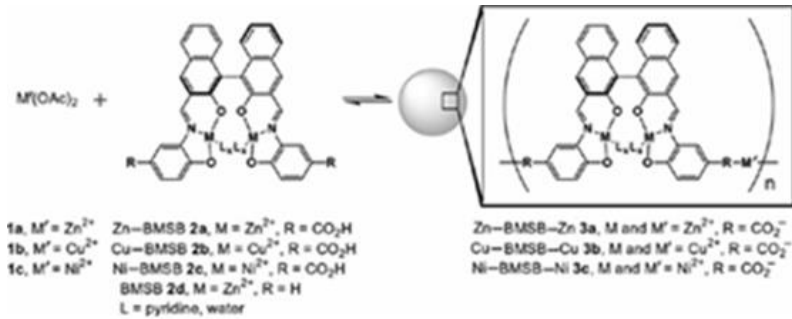
Size/stability control

Amorphous nanoparticles with controlled dimensions and stable colloidal suspensions



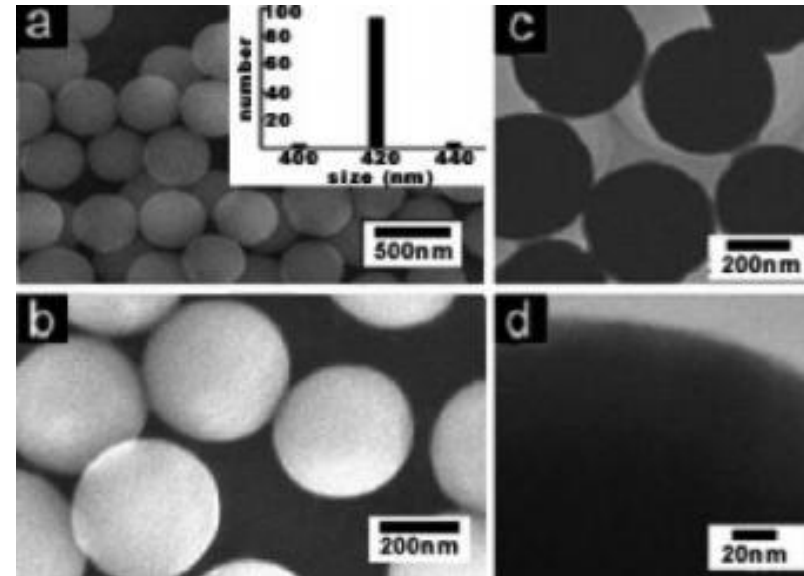
Precedents

A very successful strategy based on both coordination polymerization and precipitation in a poor solvent to produce crosslinked metal-organic spheres

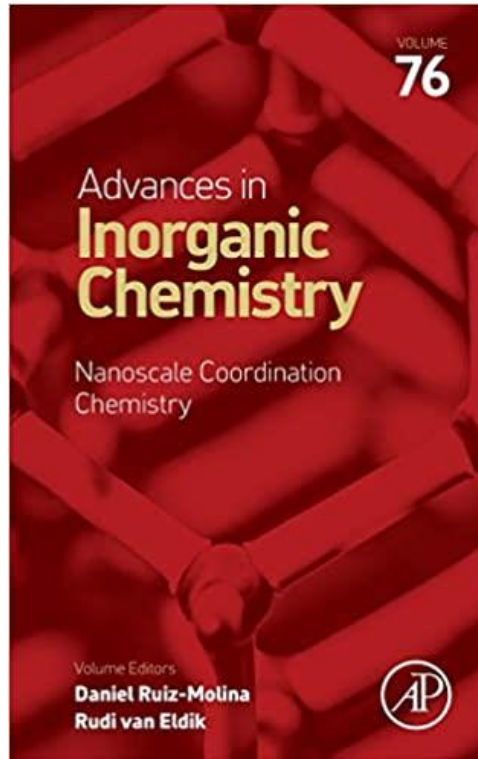


Mirkin et al., *Nature* **2005**, 438, 651

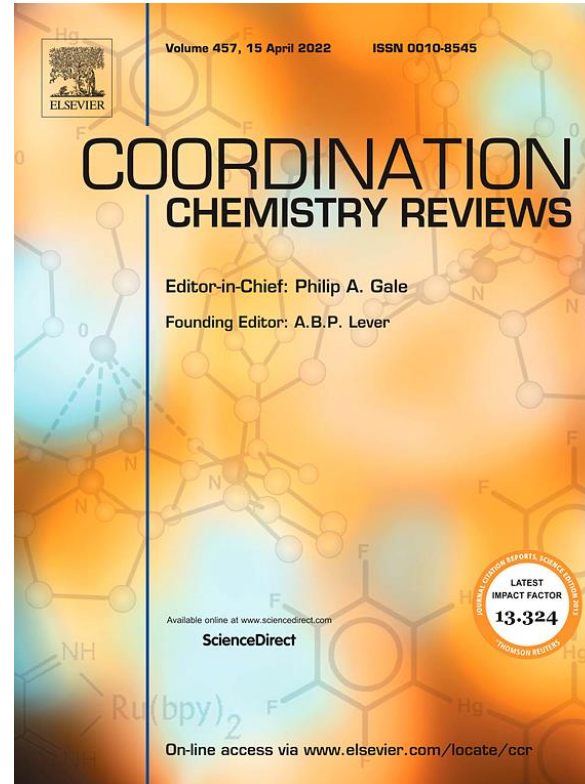
Coordination-Induced Formation of Submicrometer-Scale, Monodisperse, Spherical Colloids of **Organic-Inorganic Hybrid Materials** at Room Temperature



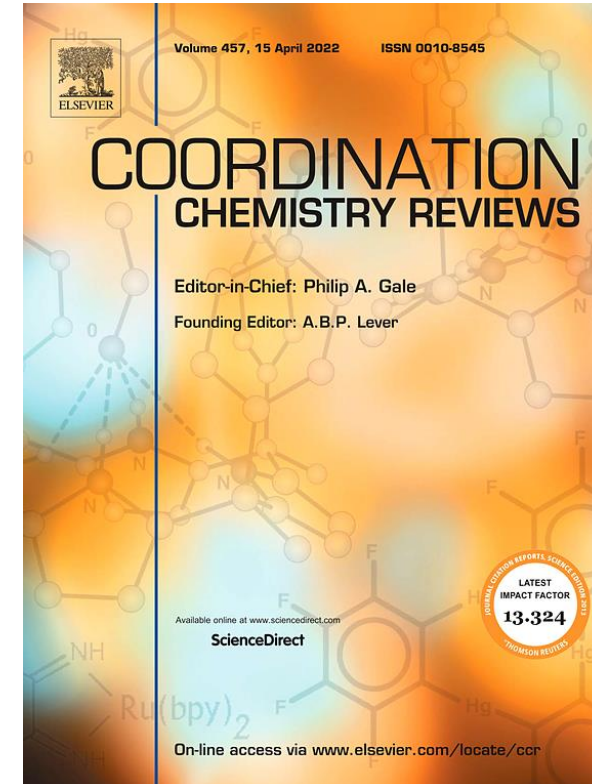
Wang et al. *J. Am. Chem. Soc.* **2005**, 127, 13102-13103



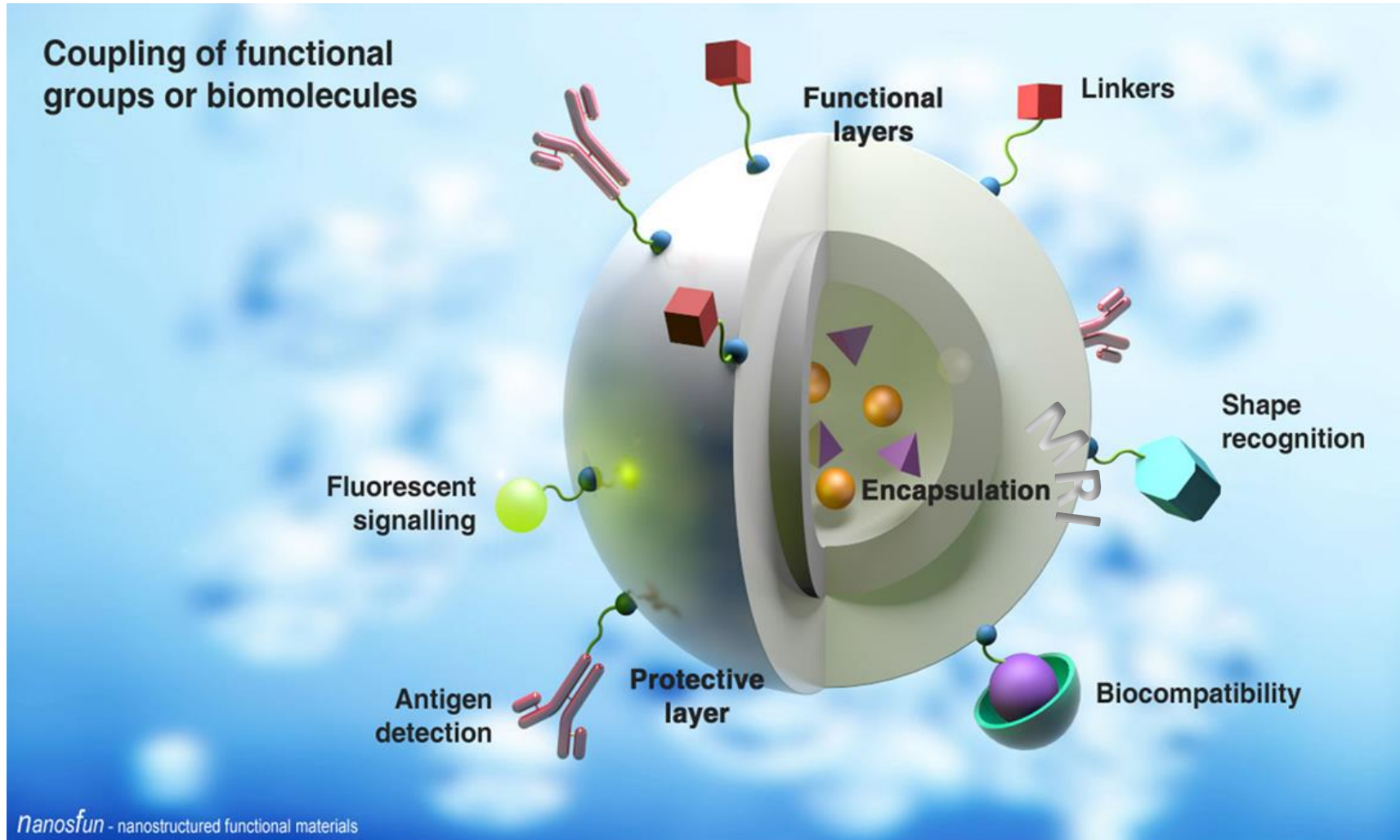
Publication Date: **July-2020**



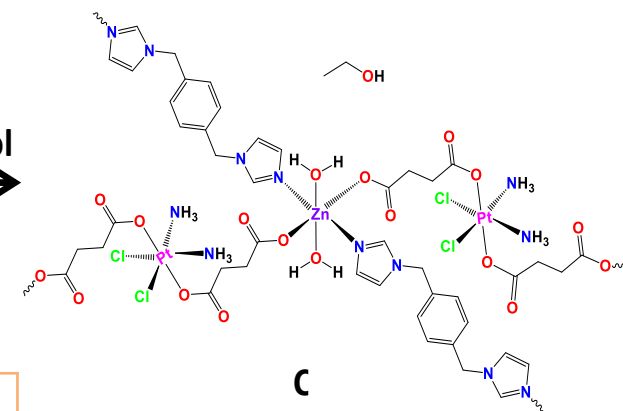
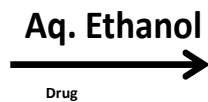
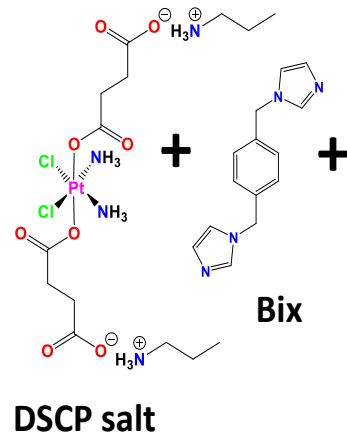
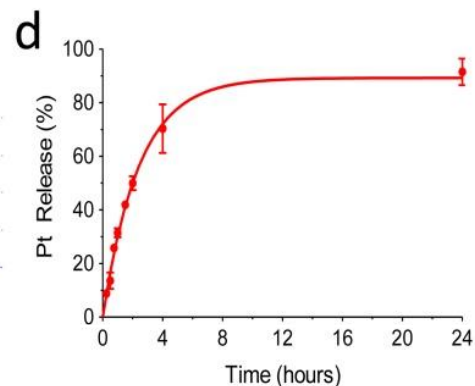
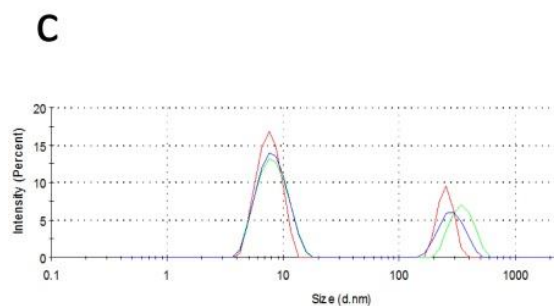
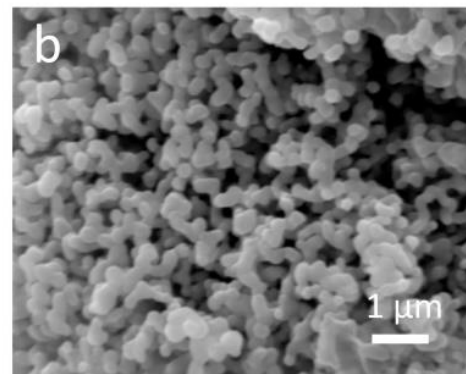
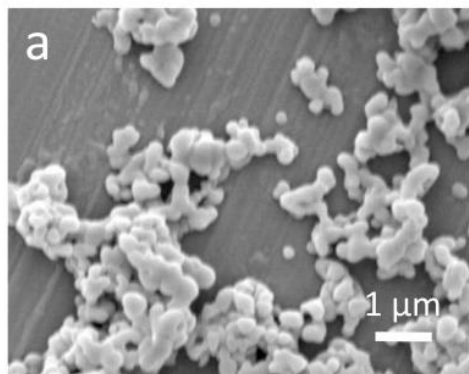
Coord. Chem. Rev. 2021, 441, 213977



Coord. Chem. Rev. 2021, 432, 213716



Pt(IV)-COOH



Pt (%) w/w	Zn (%) w/w
21.25	7.12

Cell line	24 h IC_{50} (μM) ¹		72 h IC_{50} (μM) ¹	
	Pt(IV) prodrug	Pt(IV)-NCPs	Pt(IV) prodrug	Pt(IV)-NCPs
HeLa	>1000	250 ± 35	431 ± 82	129 ± 27
MCF-7	>1000	249 ± 64	296 ± 31	59 ± 8
HePG2	>1000	316 ± 69	624 ± 174	199 ± 39
(BE)-M17	907 ± 20	218 ± 21	494 ± 66	133 ± 8

¹ Cell viability in the presence of the indicated compound and referred to Pt concentration. Data shown as $\text{IC}_{50} \pm \text{SE}$.

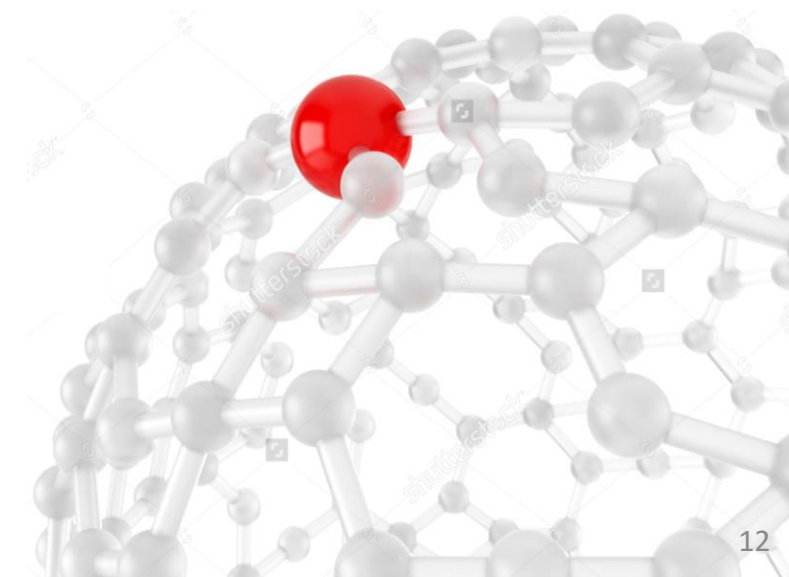


Table 3. Pt Uptake in different cell lines after 6 h treatment with Pt(IV) prodrug or Pt(IV)-NCPs at 75 μ M .

Cell line	fg Pt/cell	
	Pt(IV) prodrug	Pt(IV)-NCPs
HeLa	11.1 \pm 2.9	9.1 \pm 3.5
MCF-7	6.3 \pm 1.8	5.9 \pm 2.0
(BE)-M17	5.5 \pm 3.3	6.0 \pm 4.0

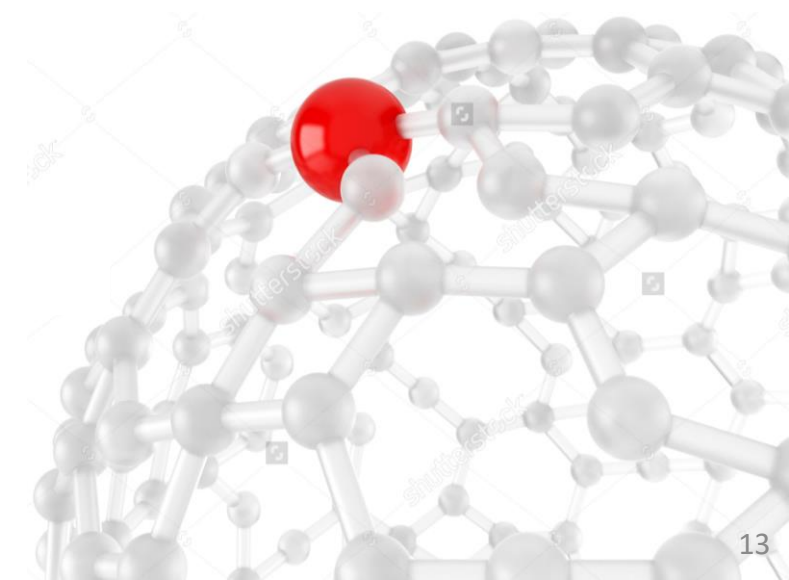
Data shown as mean \pm SD of three independent experiments performed in triplicate.

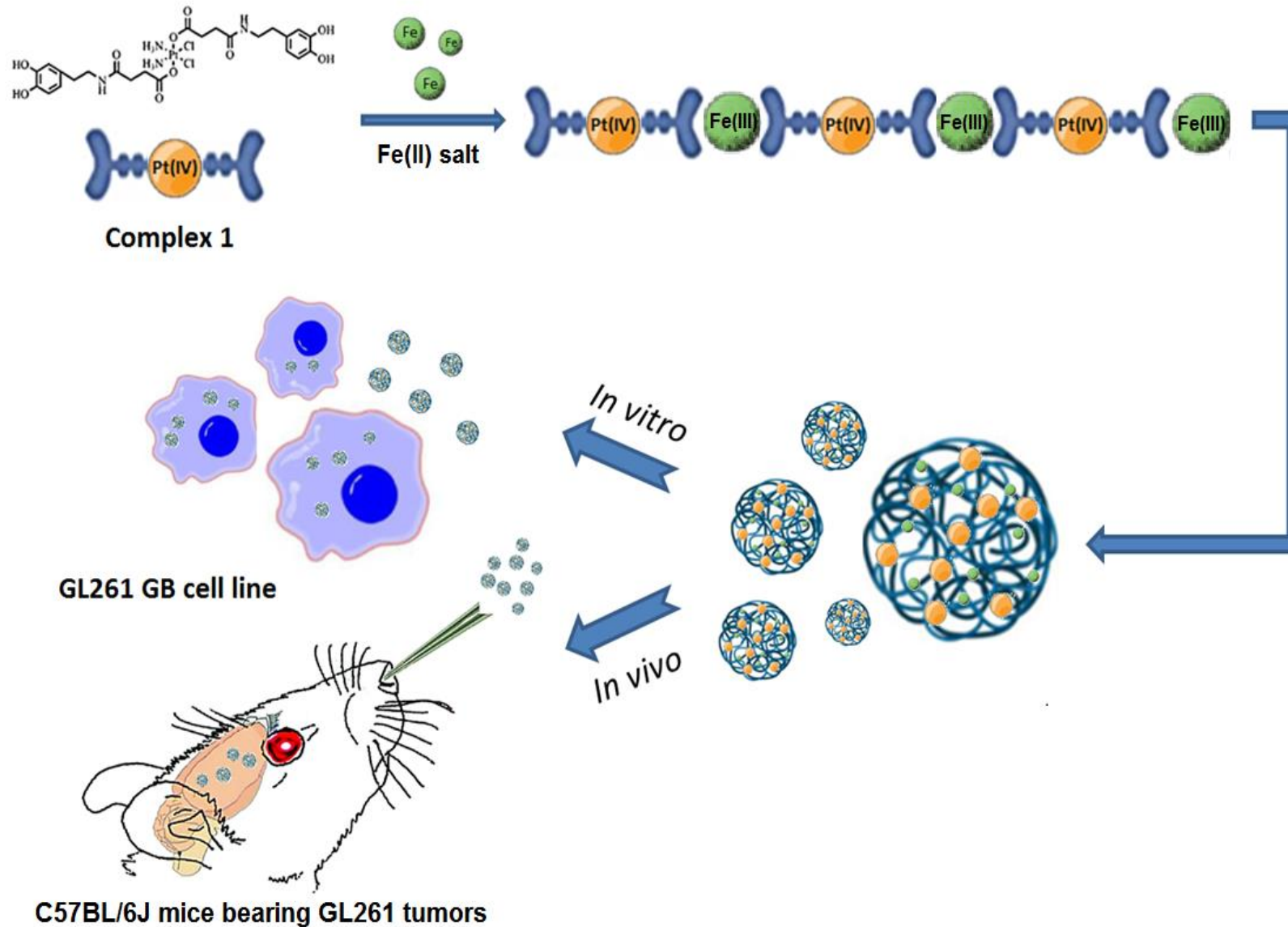
Collaboration with Dr. Julia Lorenzo, IBB-UAB

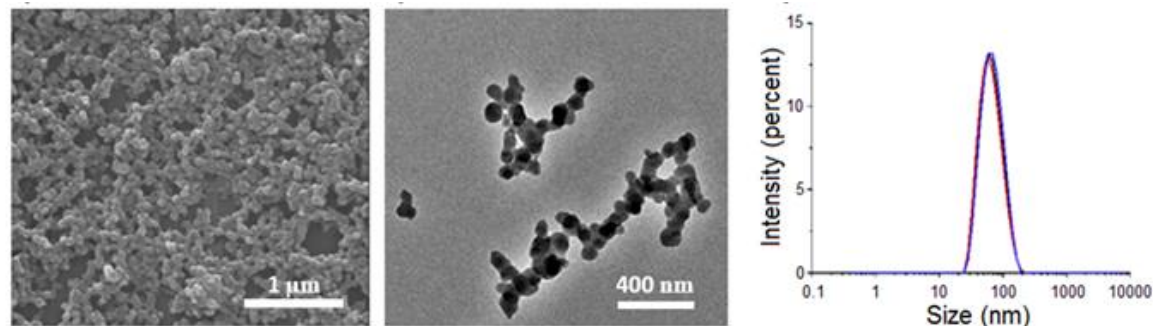
Table 4. Pt bound to DNA after 6 h treatment with Pt(IV) prodrug or Pt(IV)-NCPs at 150 μ M.

Cell line	fg Pt/ng DNA		
	Cisplatin -Pt(II)-	Pt(IV) prodrug	Pt(IV)-NCPs
HeLa	47.1 \pm 13.4	8.1 \pm 0.7	11.9 \pm 2.4
MCF-7	39.8 \pm 11.1	5.5 \pm 0.7	7.0 \pm 1.4
(BE)-M17	57.9 \pm 33.6	4.8 \pm 1.6	8.9 \pm 2.4

Data shown as mean \pm SD of three independent experiments performed in triplicate.

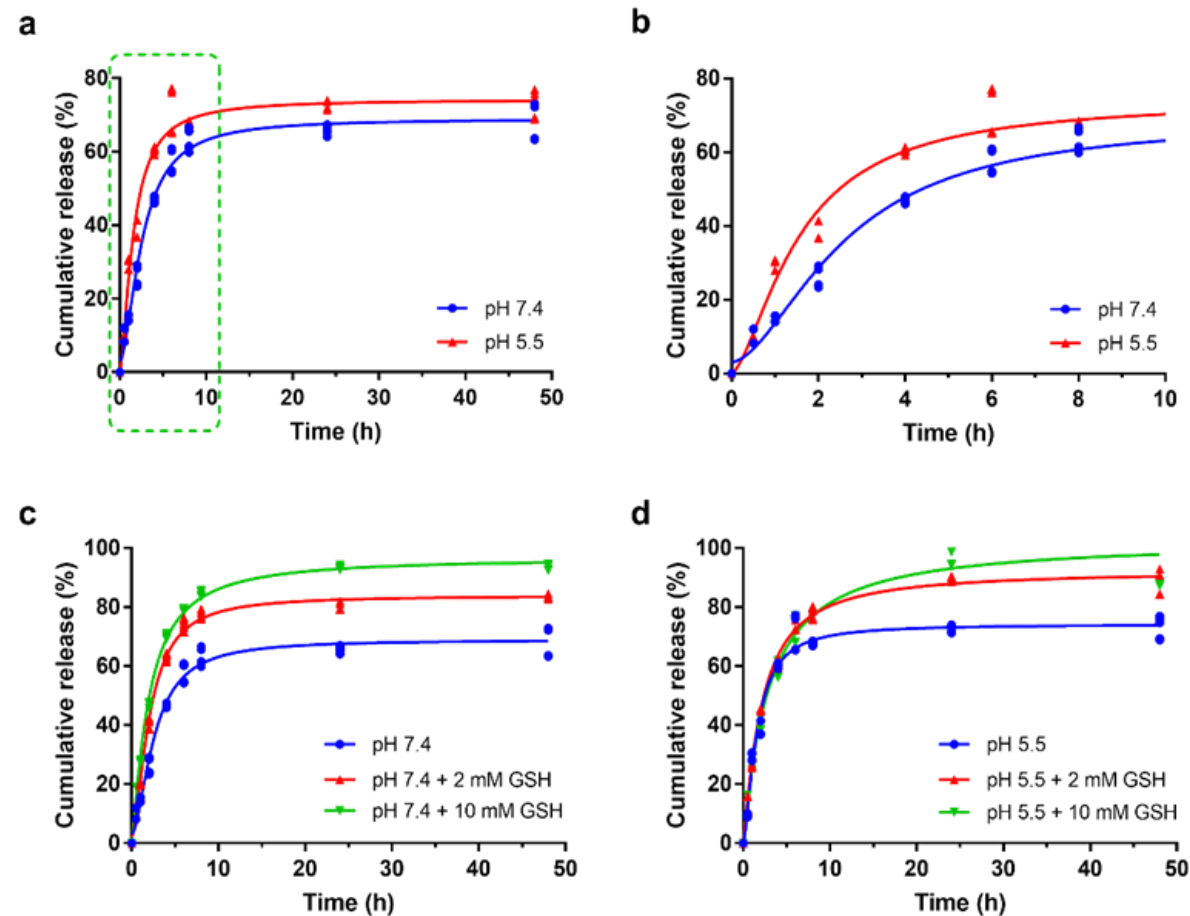






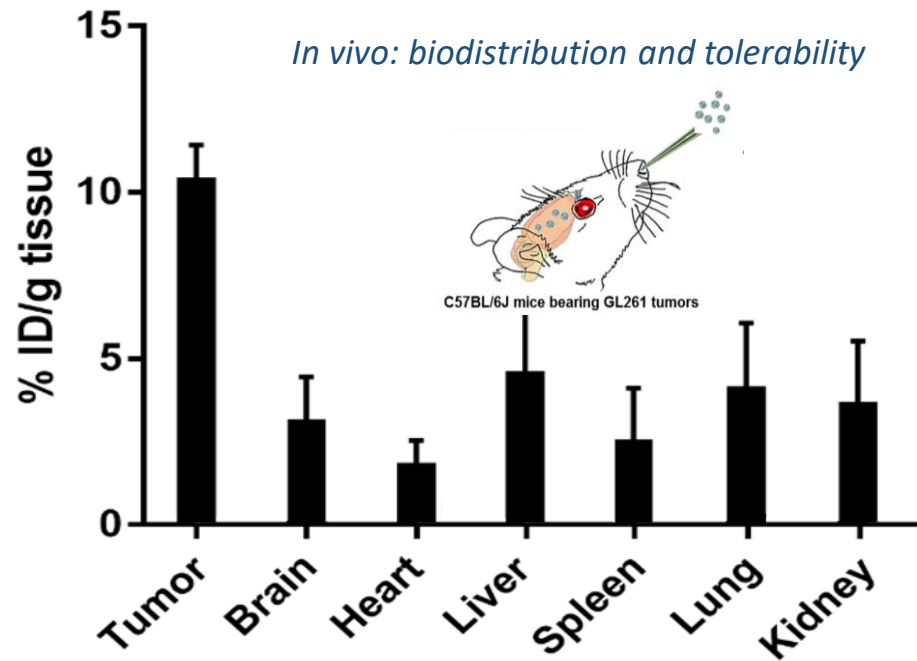
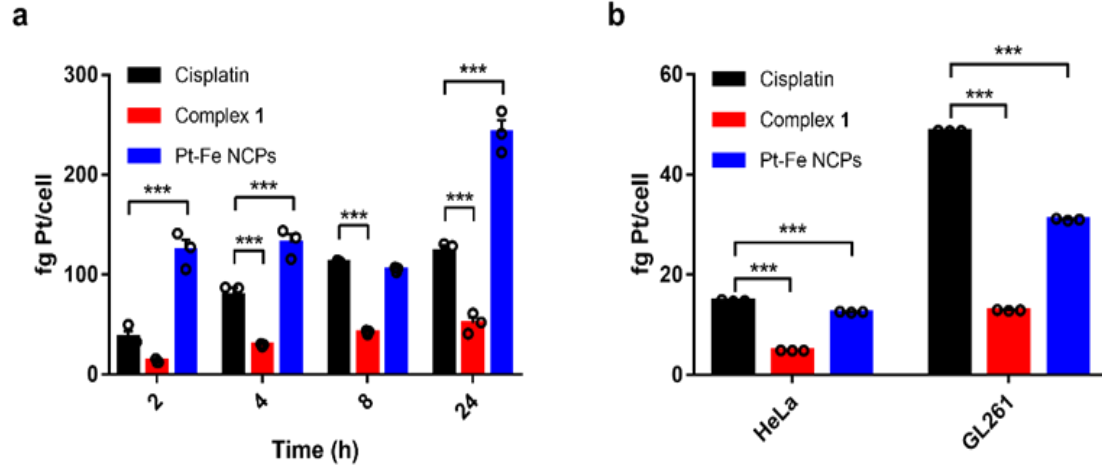
pH-sensitive!!!!

IC ₅₀ (μM) ^a	Cell line (24h)		Cell line (72h)	
Compound	HeLa	GL261	HeLa	GL261
Pt-Fe NCPs	31.45 ± 1.10	13.48 ± 0.90	2.56 ± 0.63	2.00 ± 0.18
Complex 1	29.94 ± 1.04	17.40 ± 1.08	1.85 ± 0.36	4.17 ± 0.12
Cisplatin	15.98 ± 1.04	5.61 ± 0.28	2.34 ± 0.30	2.16 ± 0.26

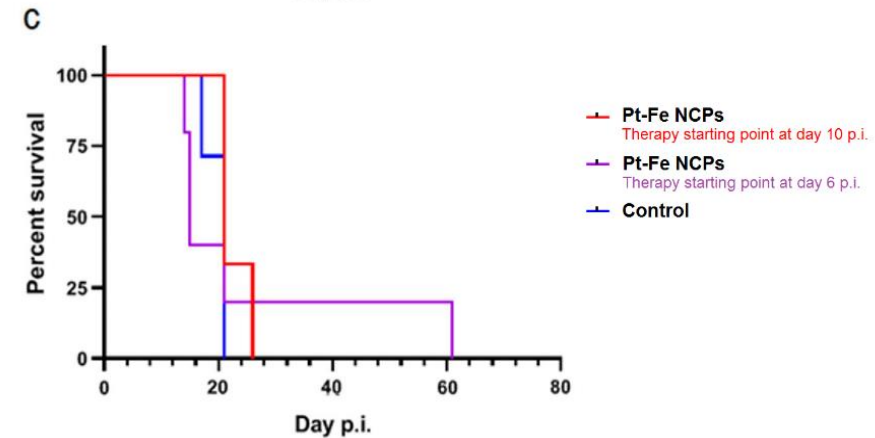
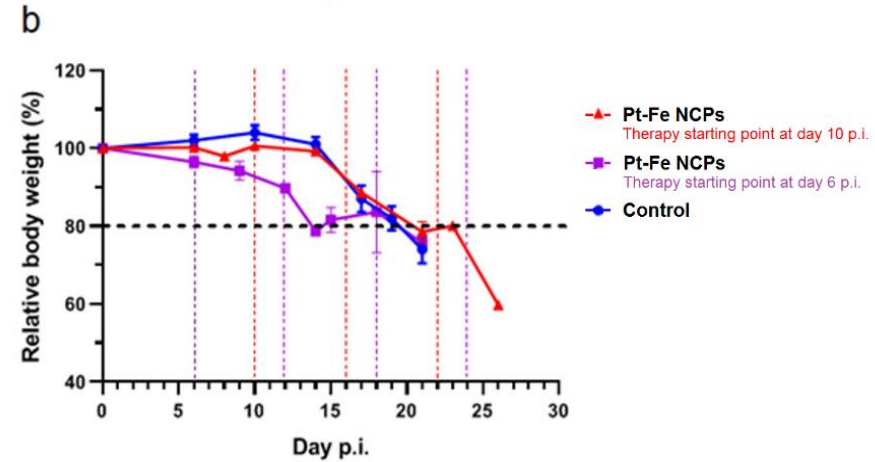
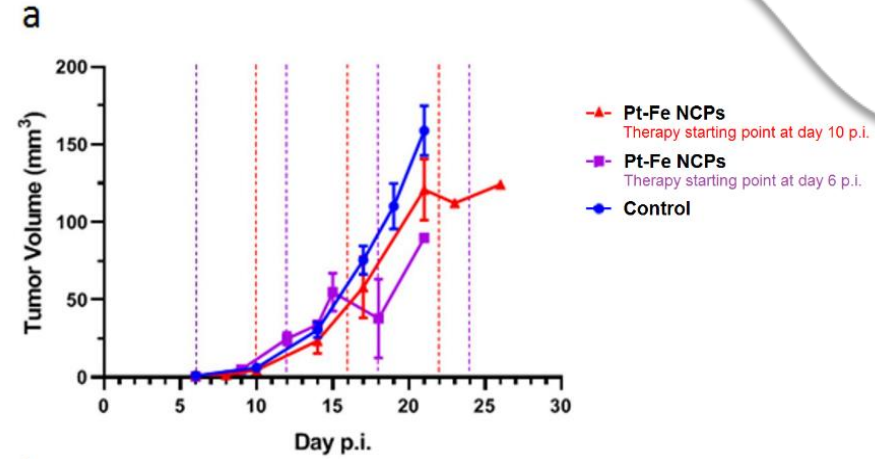


Submitted. 2022,

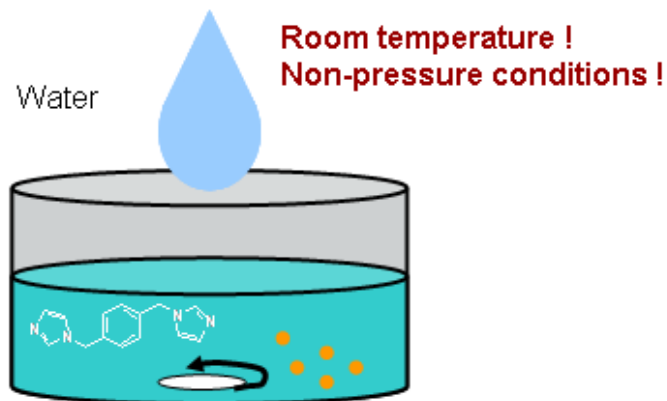
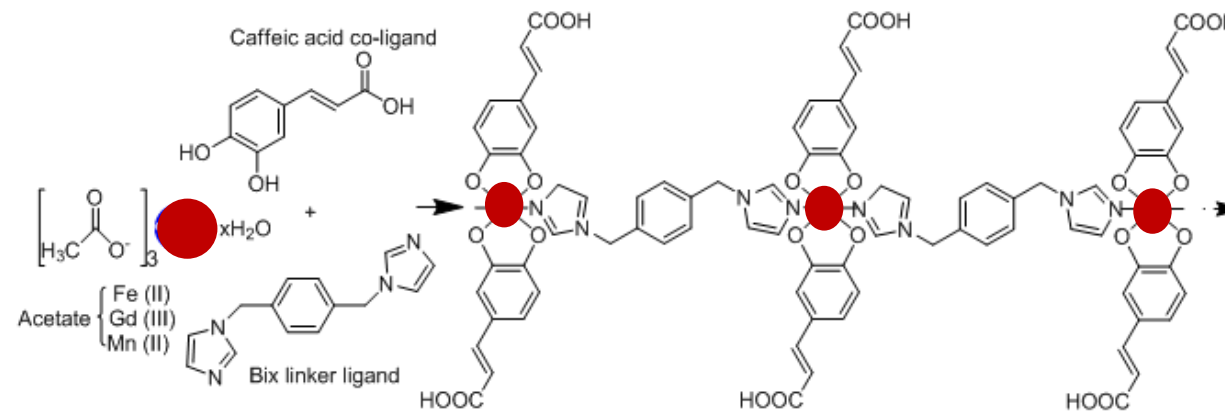
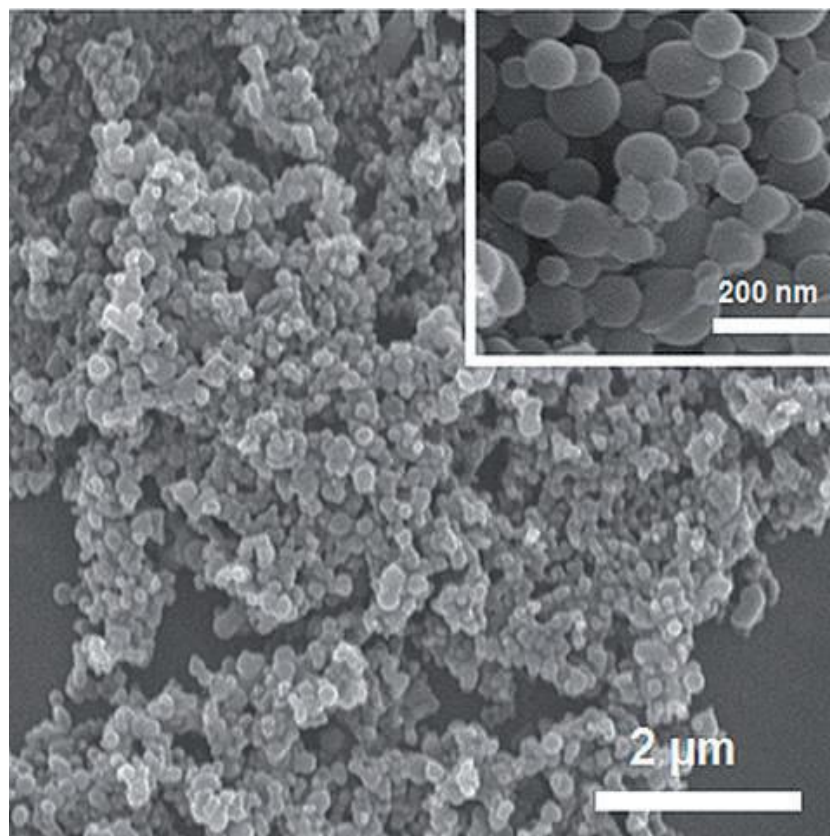
Pt(IV)-Catechol



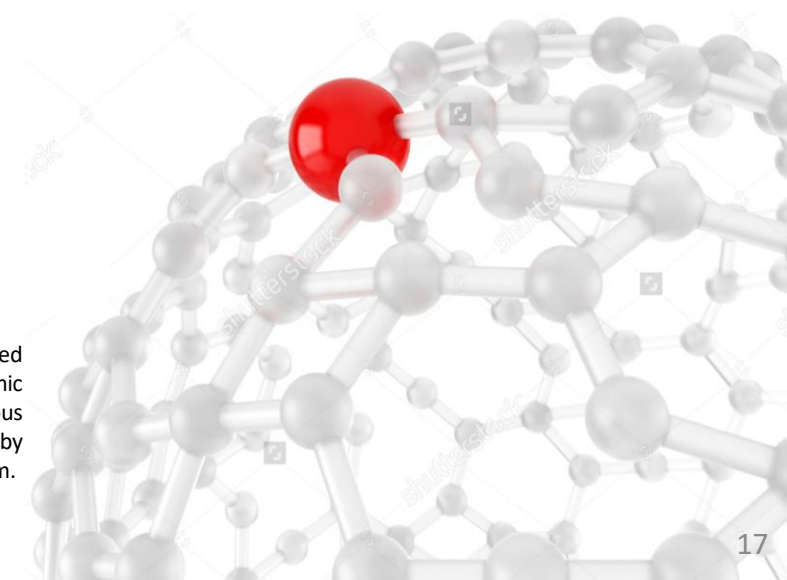
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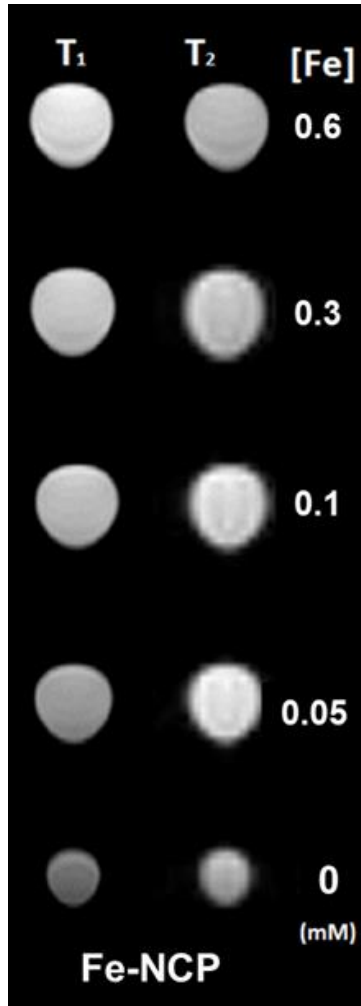
NCPs system	Size (nm) and ξ -potential (mV)				
	SEM	DLS (PBS)	ξ -Pot. (PBS)	DLS (PBS+BSA)	ξ -Pot. (PBS+BSA)
Fe-NCP	45 ± 5	97 ± 32	-31.2	56 ± 21	-19.1



In a typical experiment, an aqueous solution of $M(\text{CH}_3\text{COO})_2 \cdot x\text{H}_2\text{O}$ was added to an ethanolic solution combining two co-ligands: 3,4-dihydroxycinnamic acid (dhc), and 1,4-bis(imidazol-1-ylmethyl)benzene (bix). After vigorous stirring at room temperature, a precipitate that was then collected by centrifugation, washed several times with ethanol, and dried under vacuum.

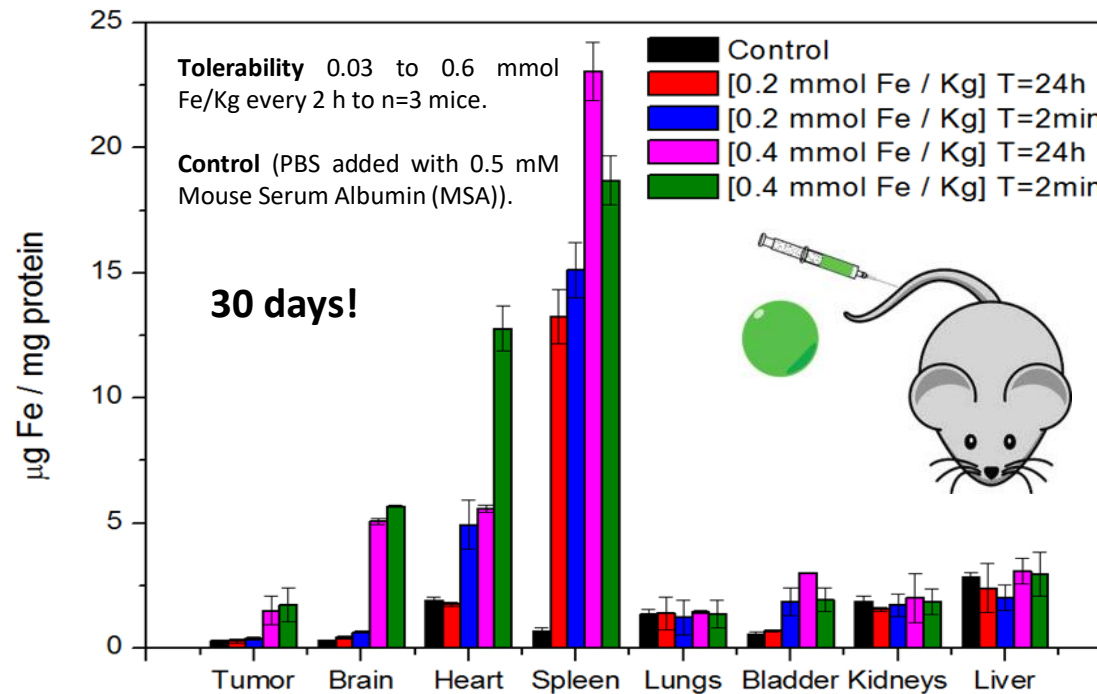
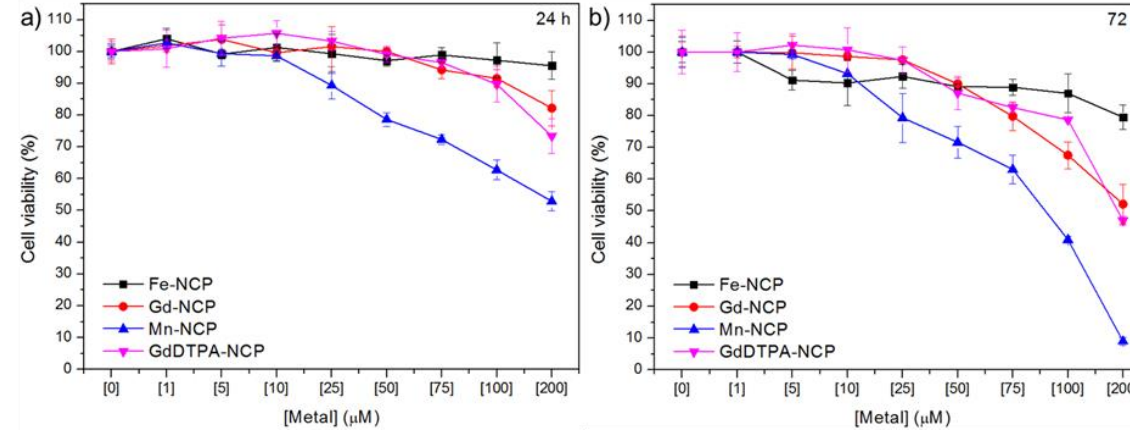


Agarose 1% solution

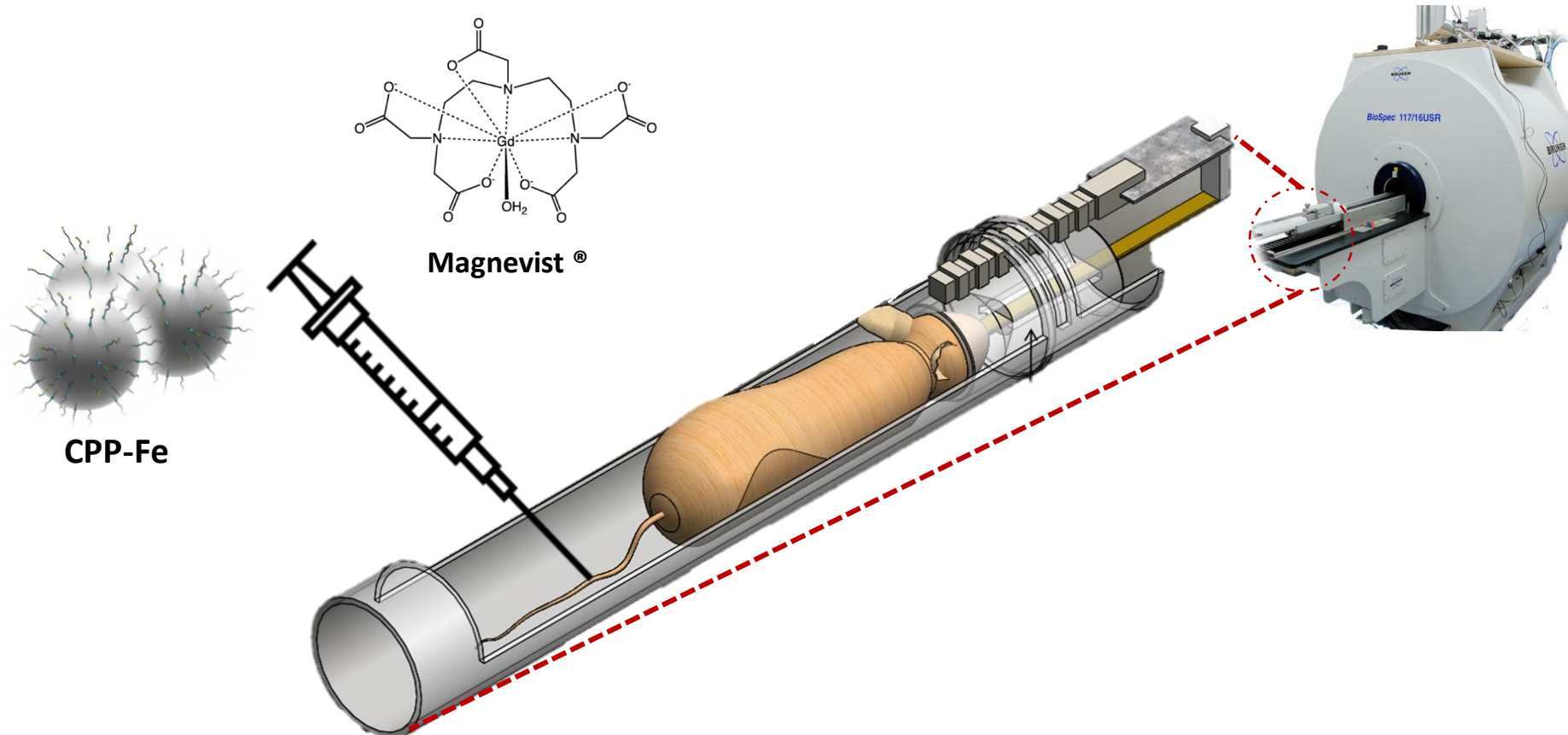


: **Better T1 contrast and dual T1/T2 contrast agent**

IN VITRO: HeLa cell viability at **24 h** (a) and **72 h** (b).

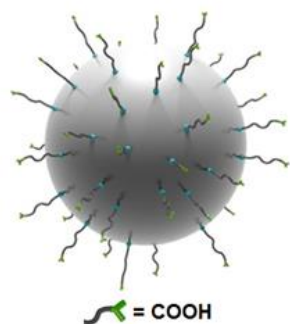


- **Target:** Mice with tumor GL261 (BBB broken)
- **Weighted** T1 and T2 images
- **Comparative study** with commercial contrast agent: Gadopentetic acid (Magnevist[®] based on Gadolinium)



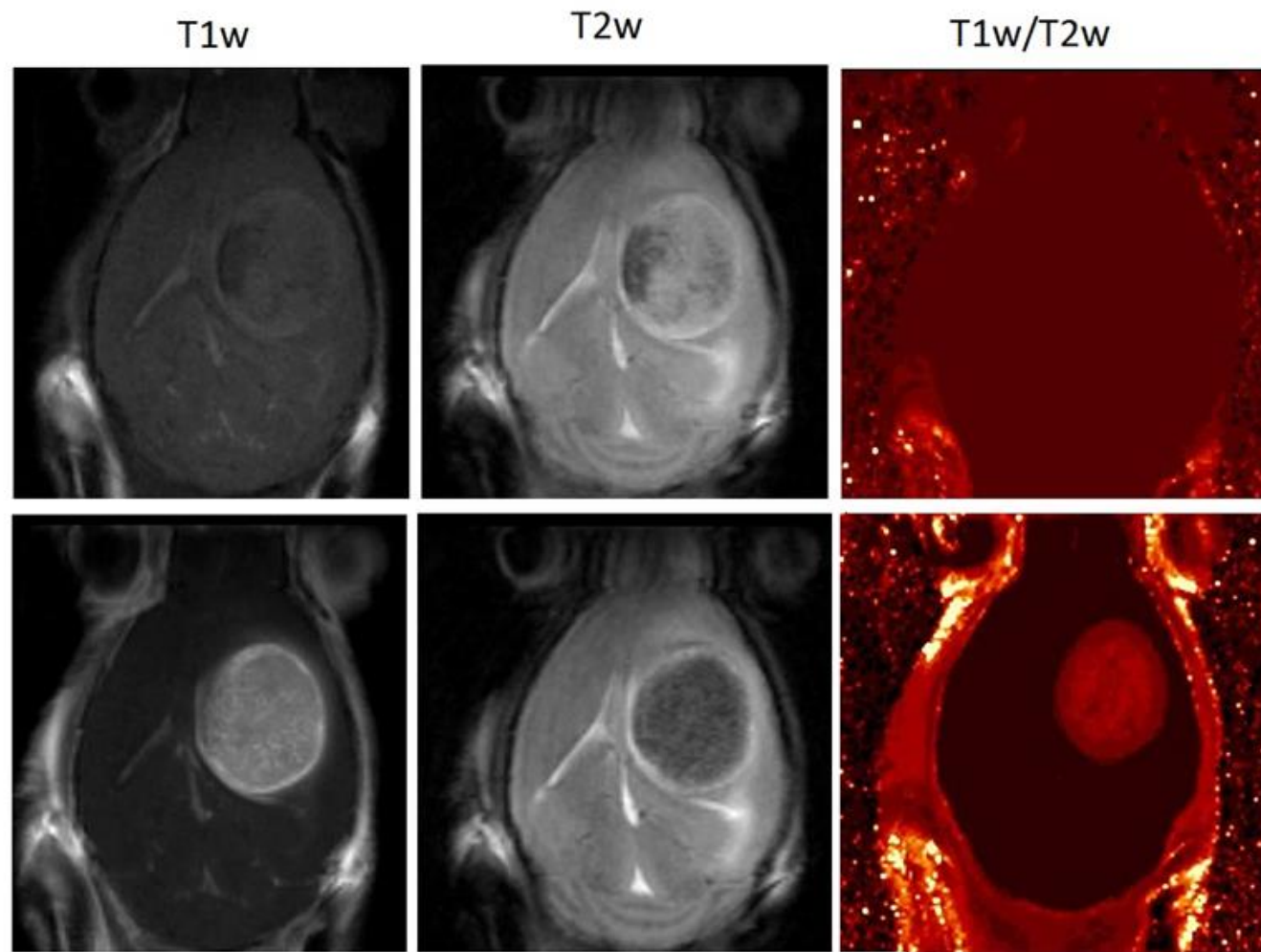
Three T1w and three T2w images were acquired before the CA injection

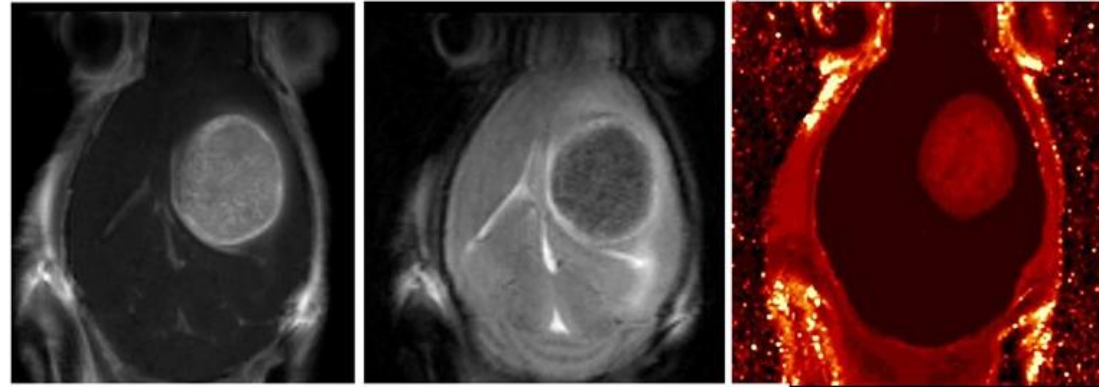
Pre-injection



T1 max after injection

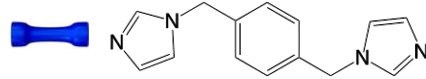
Alternated T1w – T2w images were acquired continuously during 30 minutes after CA administration, resulting in a total of 15 frames for T1w and 15 frames for T2w images.



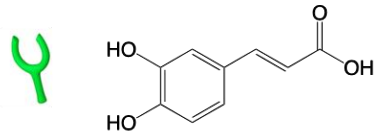


- ✓ **Greater accumulation** T1 maximum at 9.4 ± 1.1 min and T2 minimum at 5.3 ± 1.1 min. (6.1 ± 1.1 min. and 2.6 ± 1.1 min for Magnevist) due to the EPR effect.
- ✓ **Enhanced RCE:** T1w relative contrast enhancement (RCE) ($317.4 \pm 9.4\%$) was notably superior to those observed with Magnevist ($250.9 \pm 3.1\%$). Notable T2w signal (26%) decrease (no signal decrease was observed for Magnevist)
- ✓ **Simultaneous exploration:** T1 and T2 RCE at a reasonably short time frame in the preclinical glioblastoma model (between 3.95 and 10.72 min after administration for maximum T1/T2 effect), allowing to obtain both data types in the same exploration

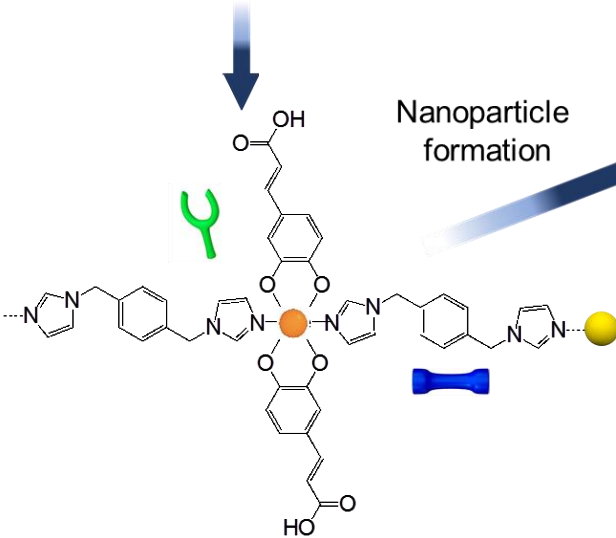
Imidazole ligand (L1)



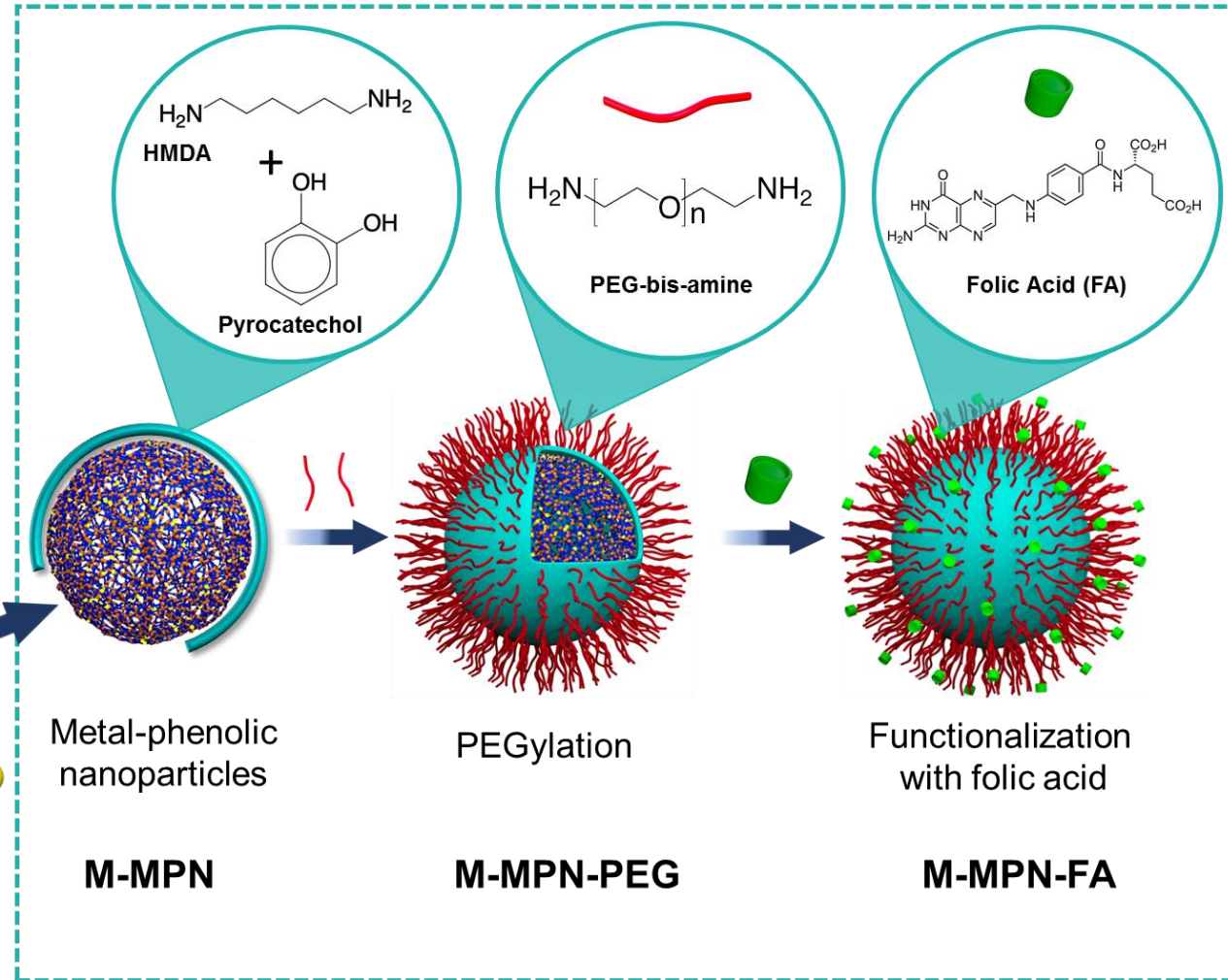
Catechol ligand (L2)

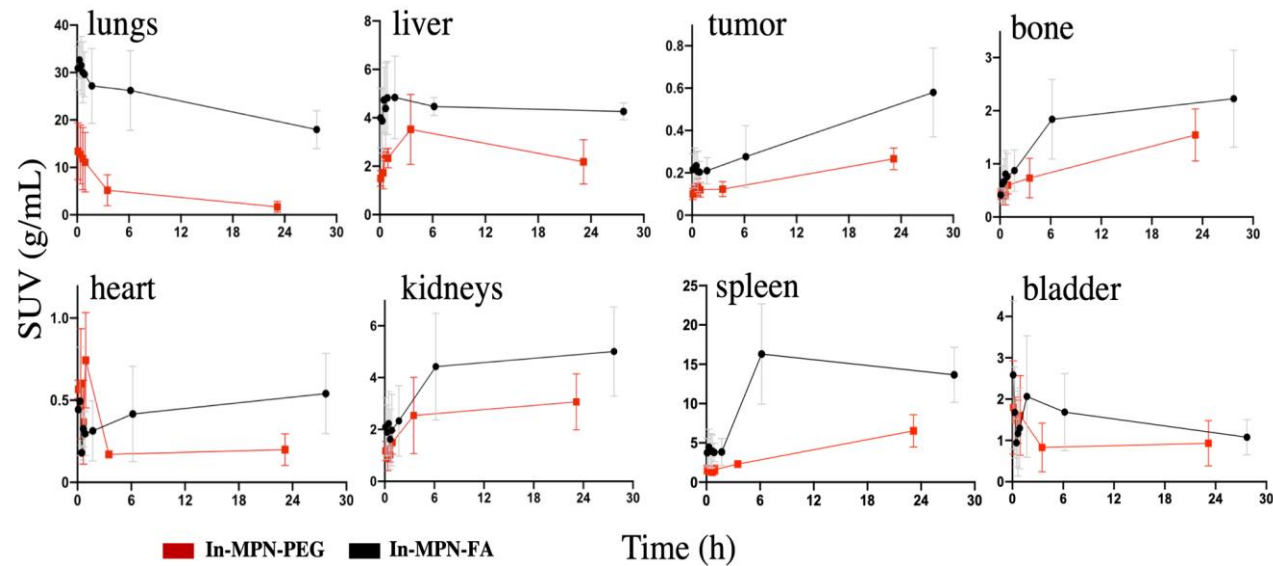
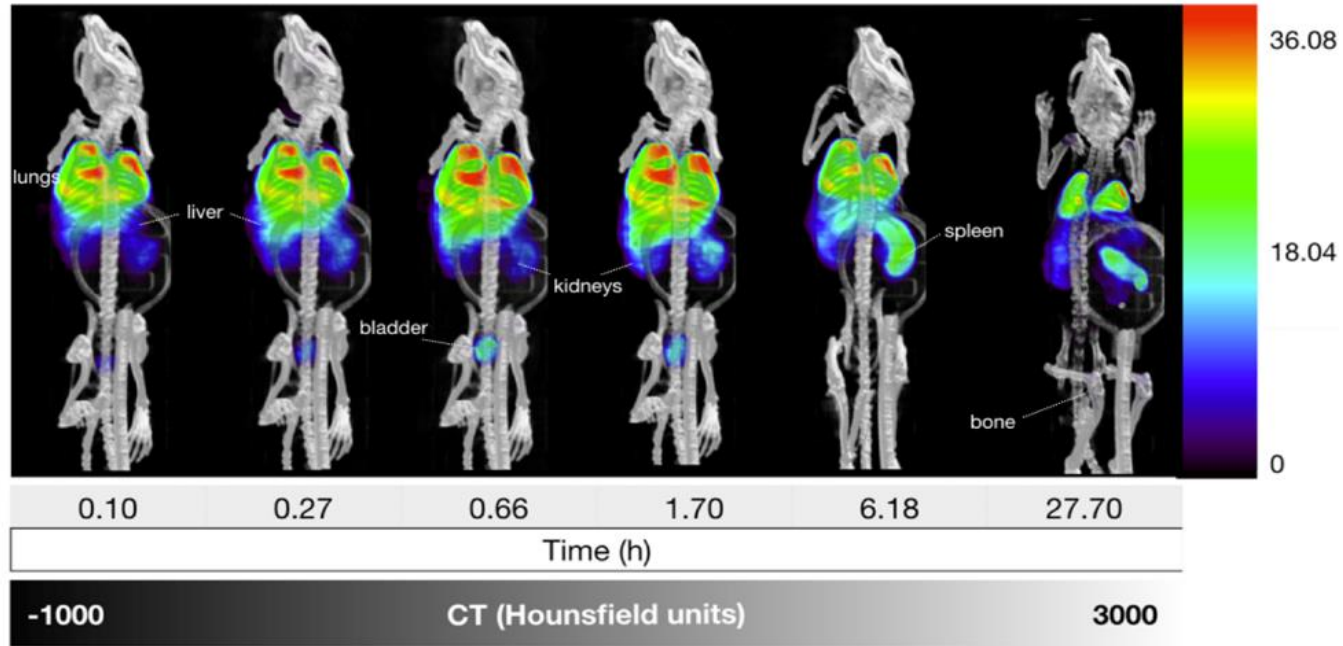


- Metal (M) In^{3+} Cu^{2+}
- Radioactive (M) $^{111}\text{In}^{3+}$ $^{64}\text{Cu}^{2+}$



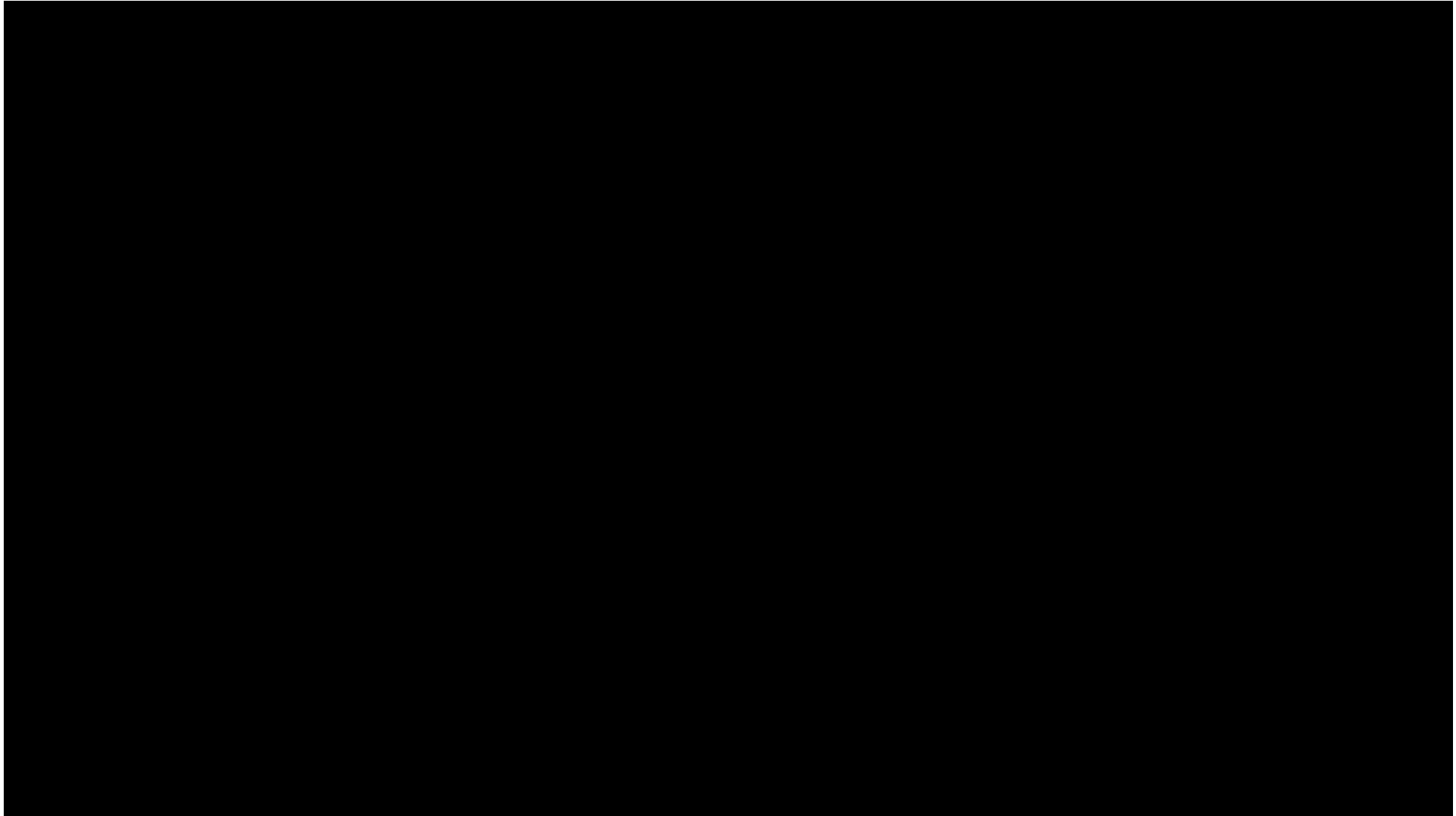
Nanoparticle formation





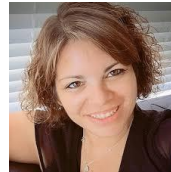
✓ *Greater accumulation.*

✓ *Retention Biodistribution:*





Prof. Urs Hafeli



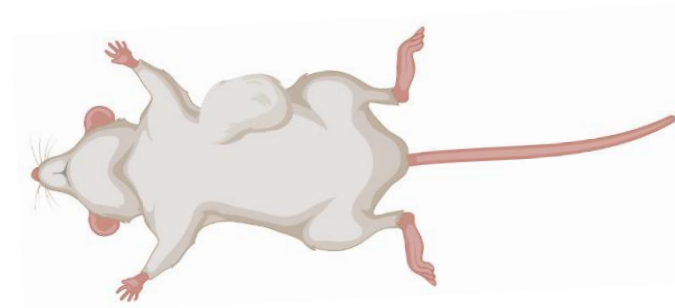
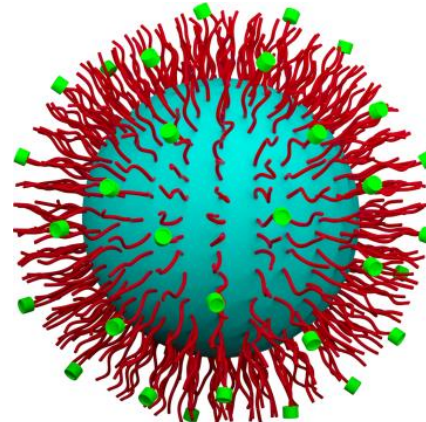
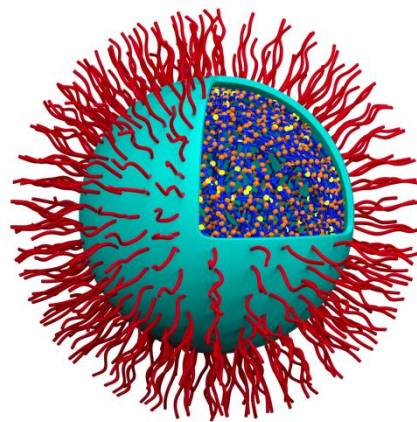
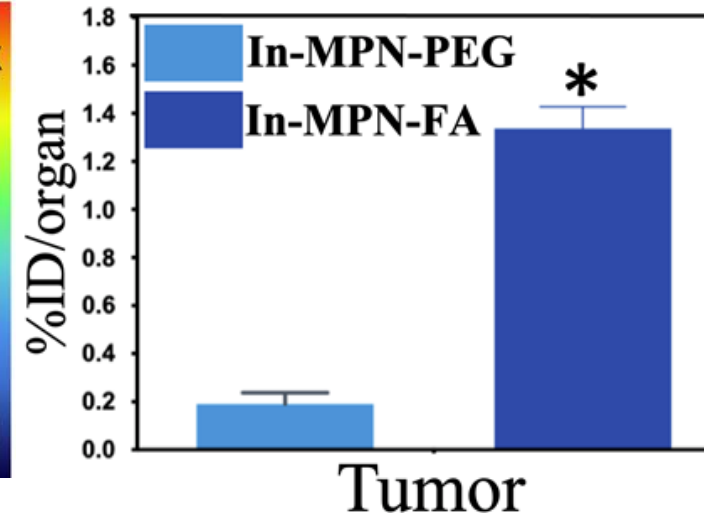
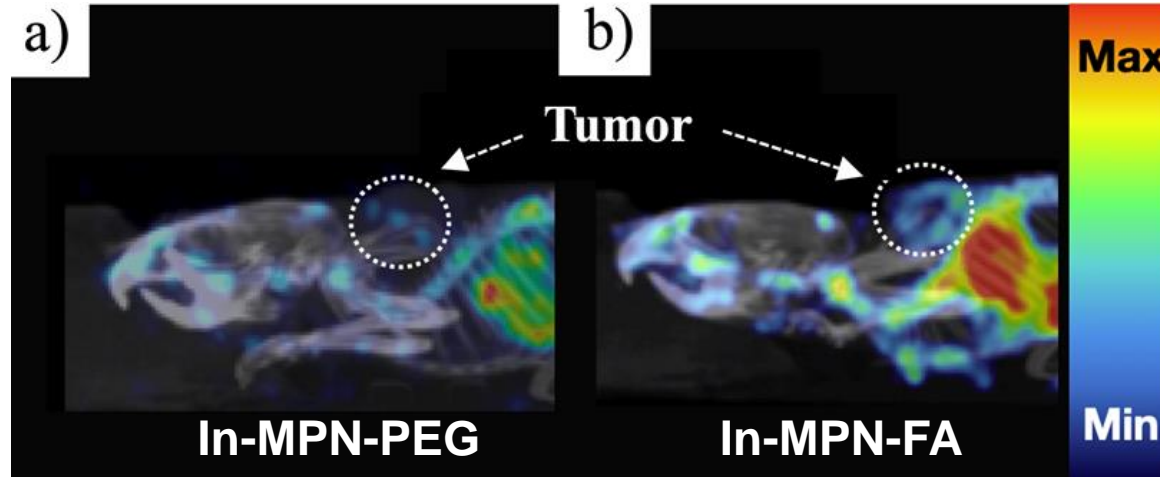
Dr. Cristina Rodriguez



THE UNIVERSITY OF BRITISH COLUMBIA



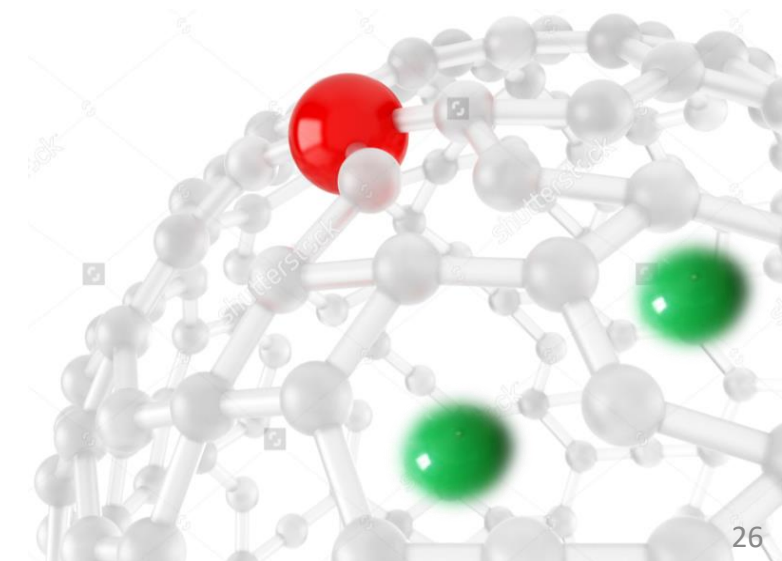
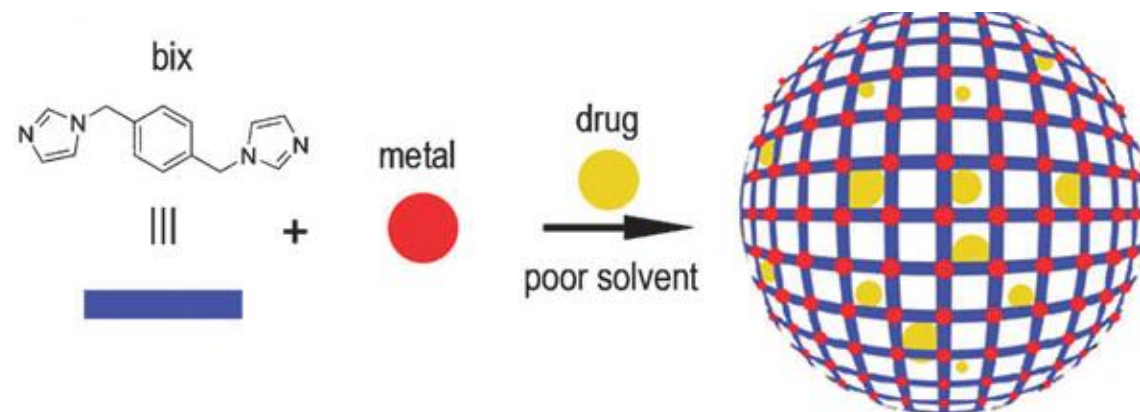
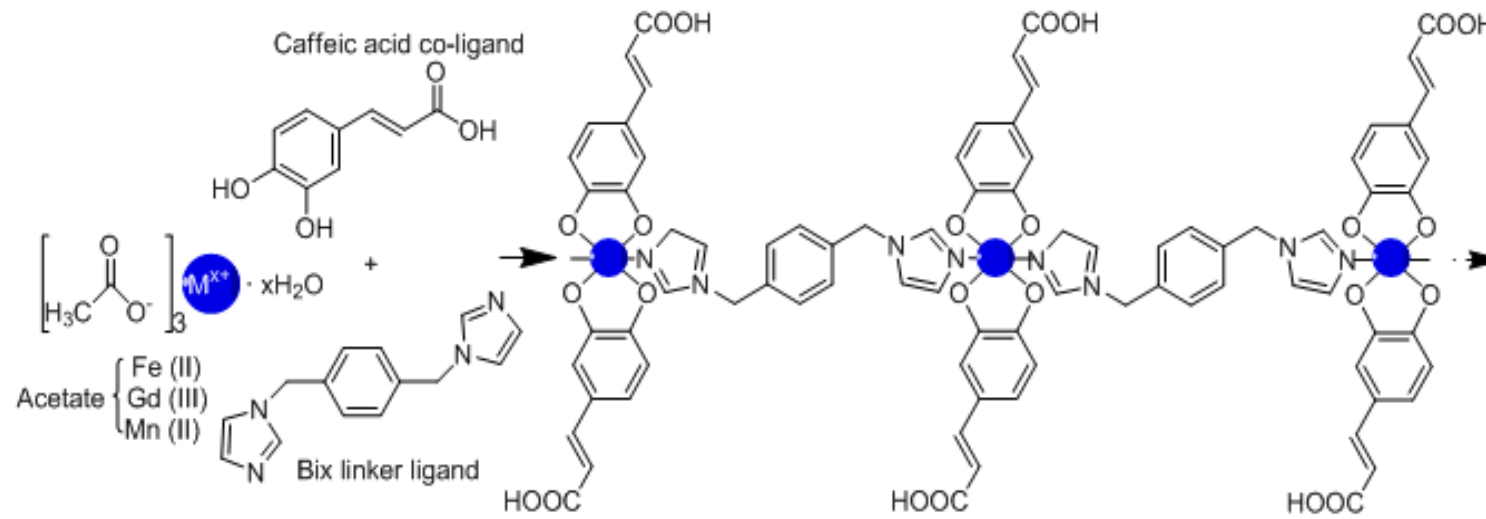
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ACS Appl. Mat. Interf. 2021, 13 (9), 10705

Theranostics

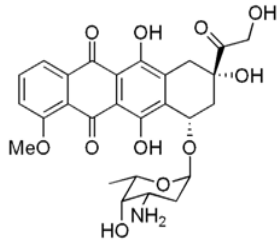
encapsulation of CPT antitumoral applications.



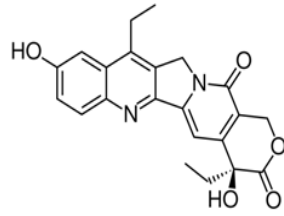
Drug release

Different families of fluorescent drugs

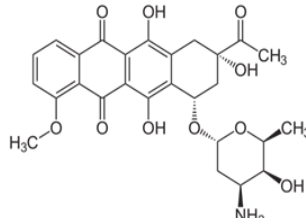
Camptothecin (CPT)



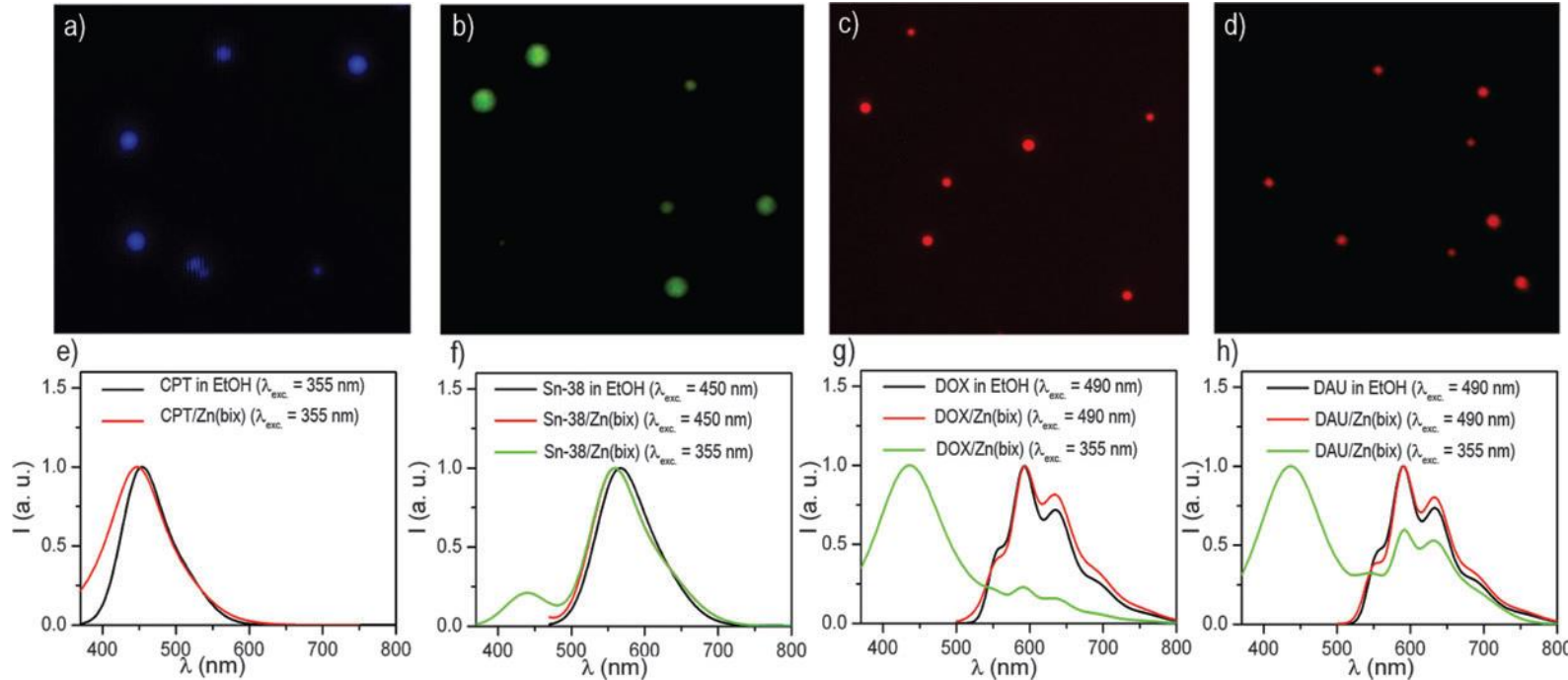
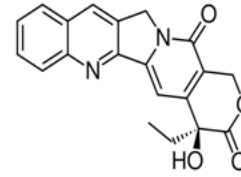
Hidroxicamptotecin (SN-38)



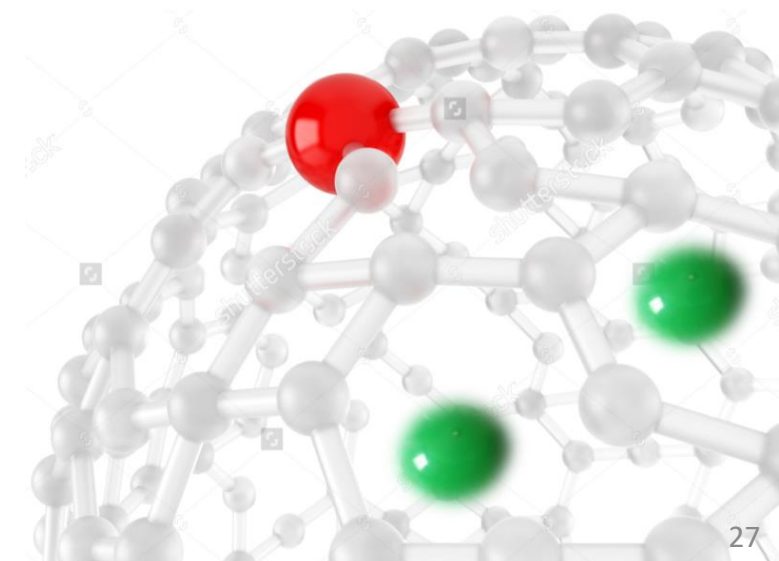
Doxorubicin (DOX)



Daunorubicin (DAU)

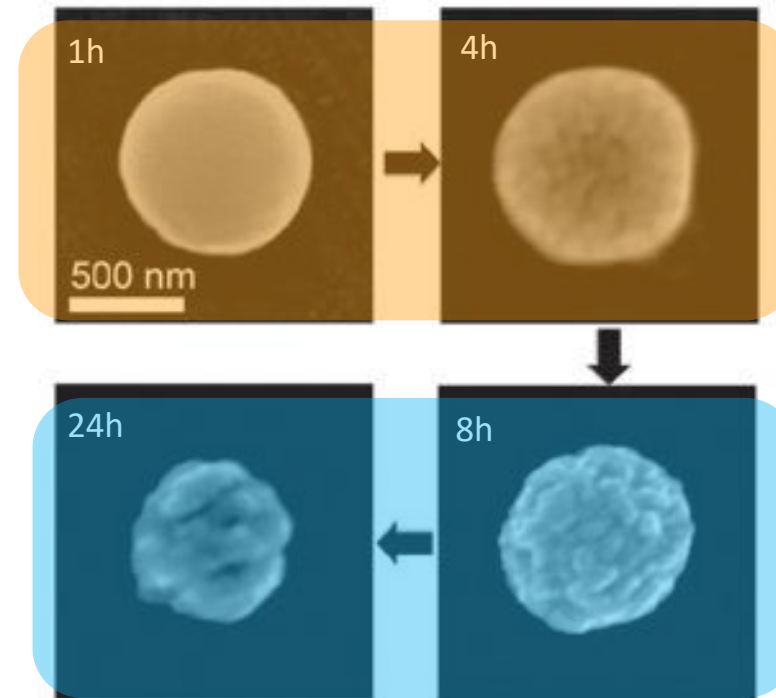
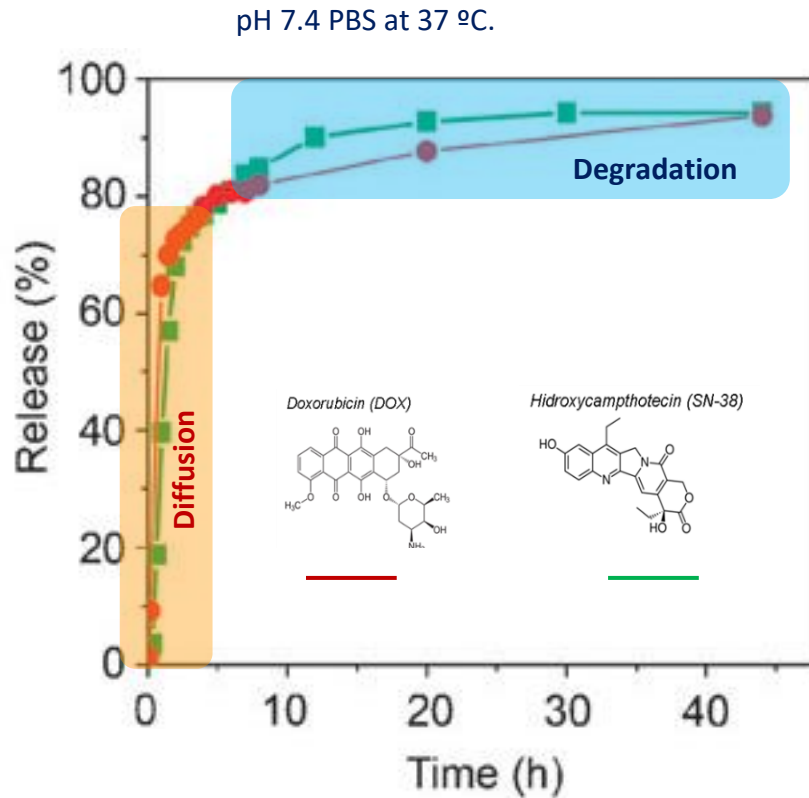


Encapsulation yields 10-20%



Release process

In vitro release profile of DOX and SN-38 from DOX/Zn(bix) and SN-38/Zn(bix) spheres incubated in pH 7.2 PBS at 37 °C.

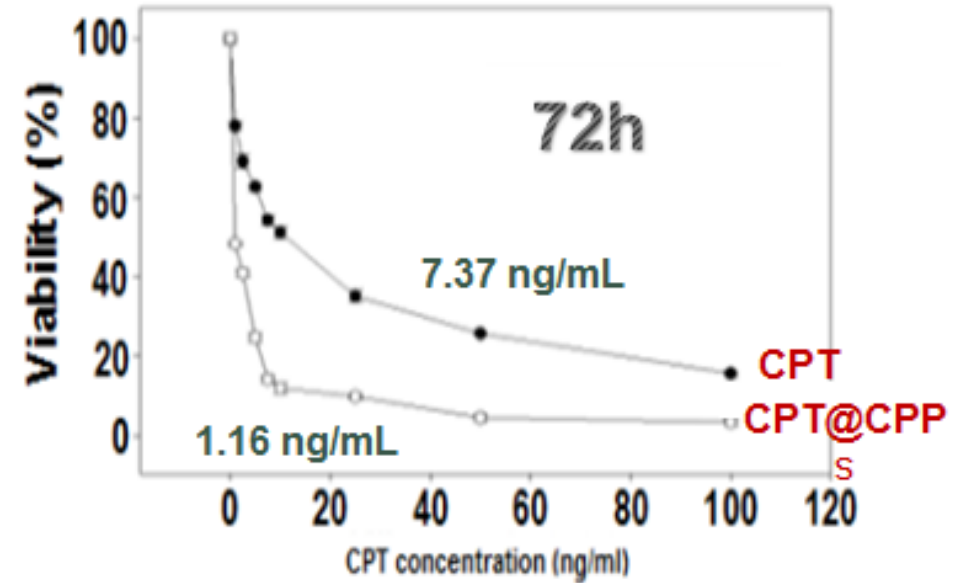
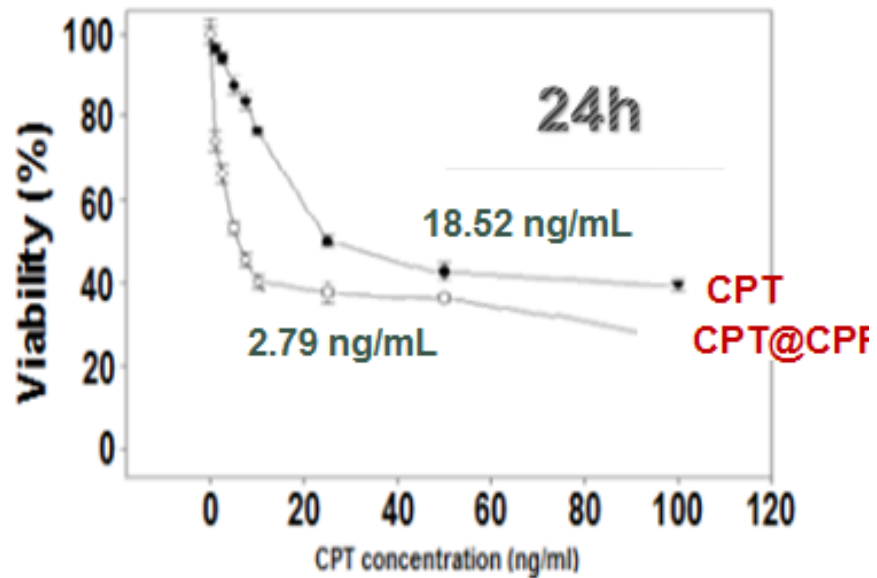


Chem. Commun., 2010, 46, 4737 - 4739

Citotoxicity CPT@CPP0-Fe

half maximal inhibitory concentration (IC50)

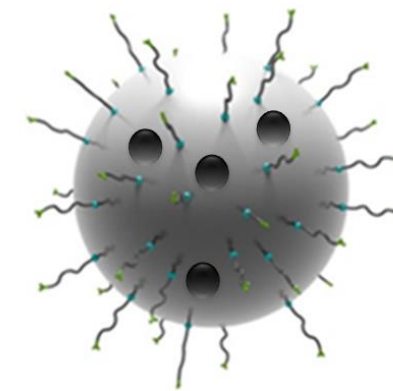
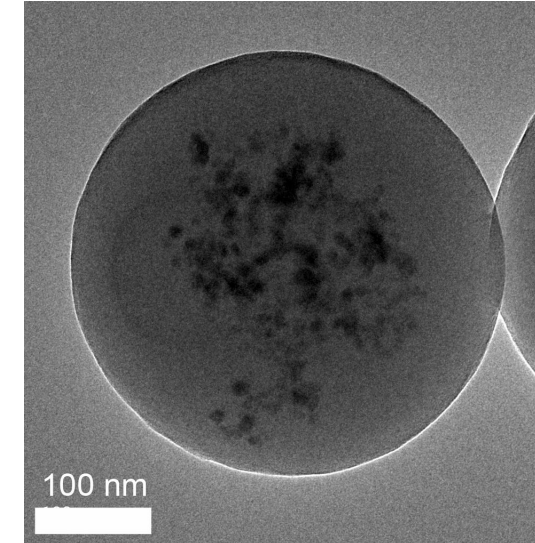
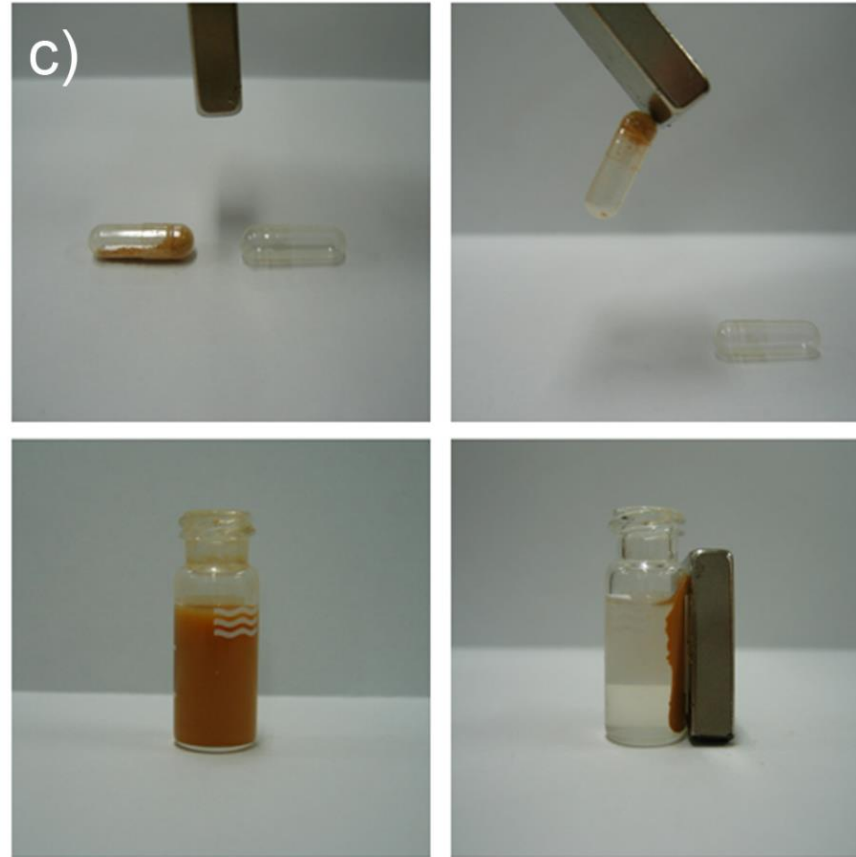
Seven-fold drug efficacy increase!



mammary humane adenocarcinoma: MCF7 cells

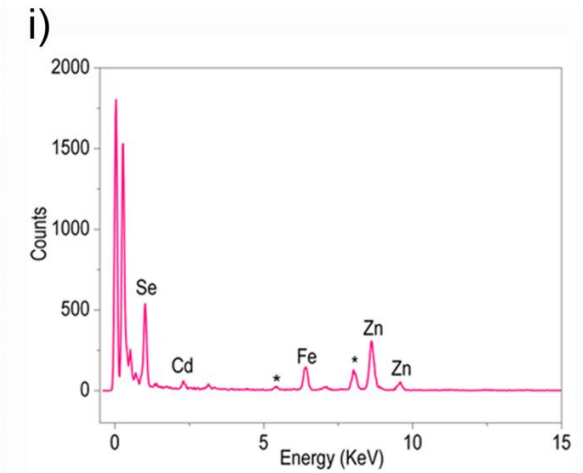
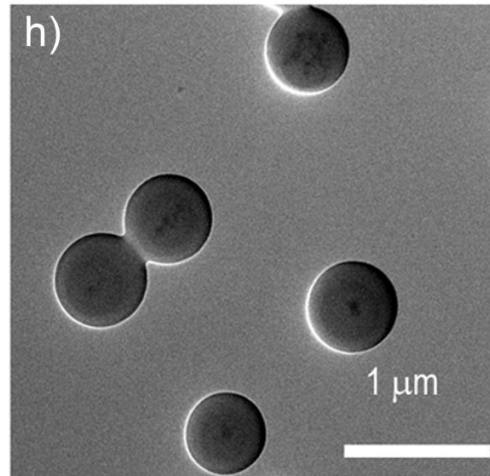
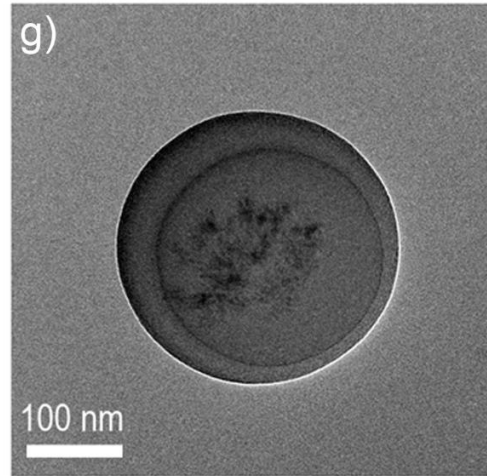
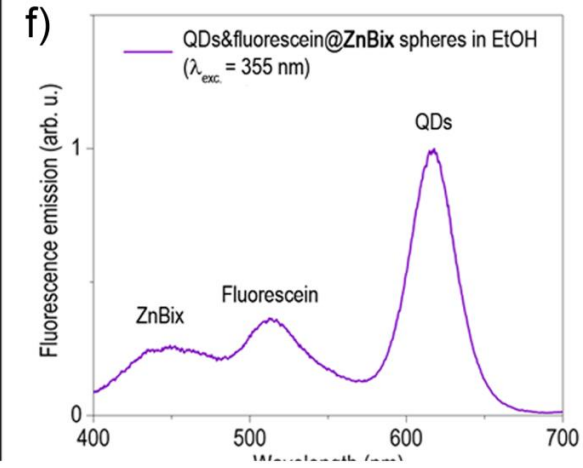
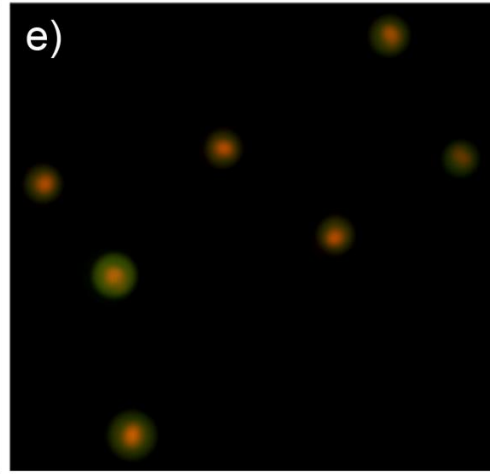
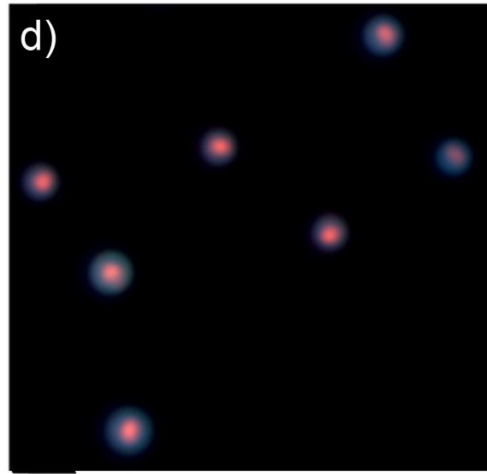
Encapsulation

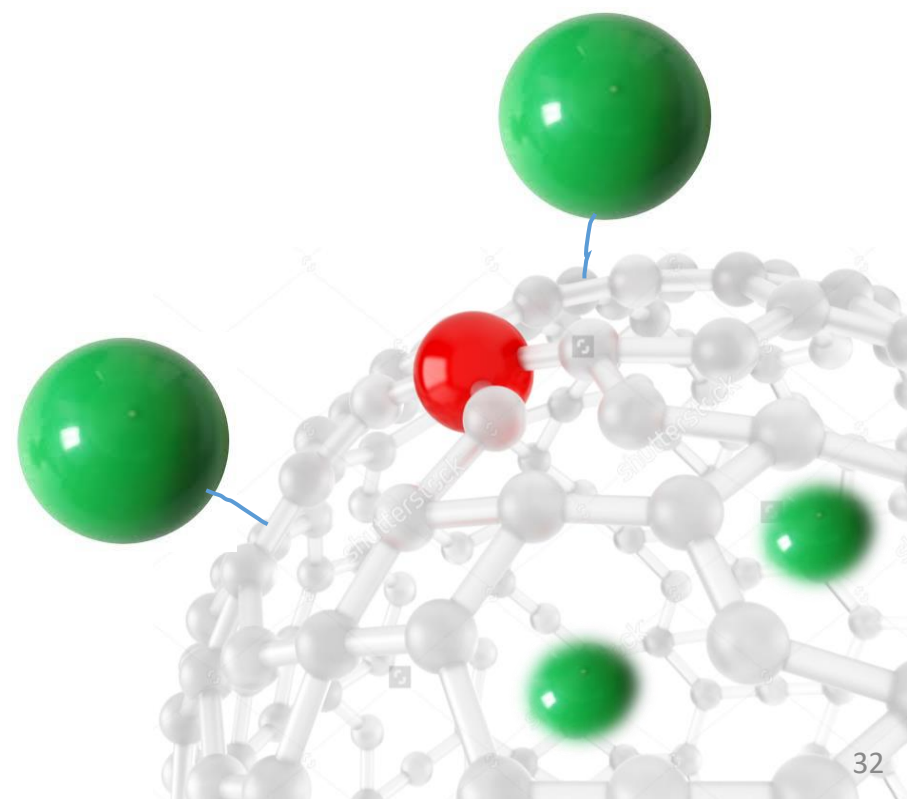
hybrid SPION@CPPs



Addition of an aqueous solution of $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ to an ethanolic solution of bix (in a 1:1 molecular ratio) with vigorous stirring at room temperature. After 5 minutes, ethanol was added to the reaction mixture to stabilize the particles. $\text{Zn}(\text{bix})$ spheres were then purified by centrifugation and washed several times with ethanol, and finally redispersed in ethanol.

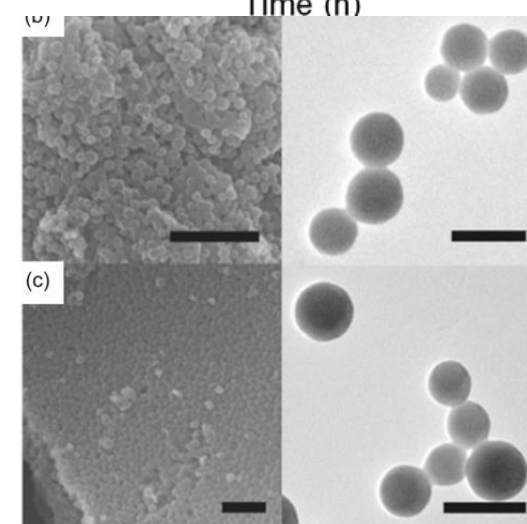
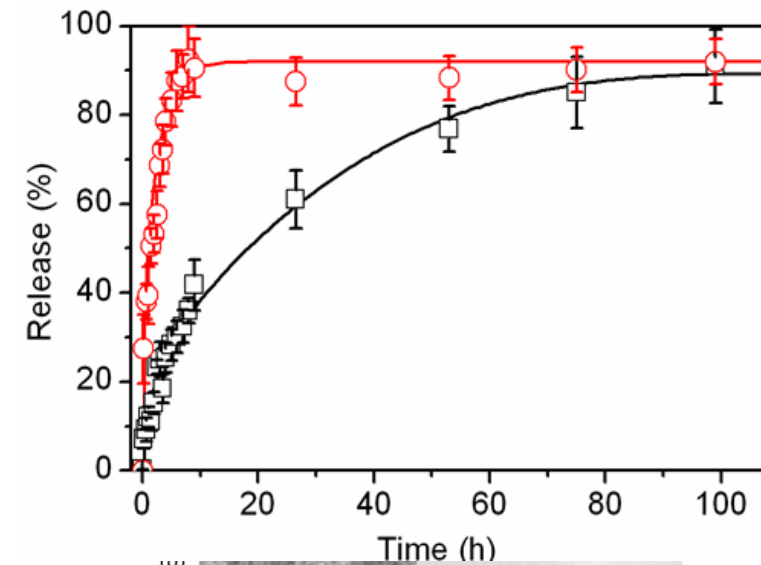
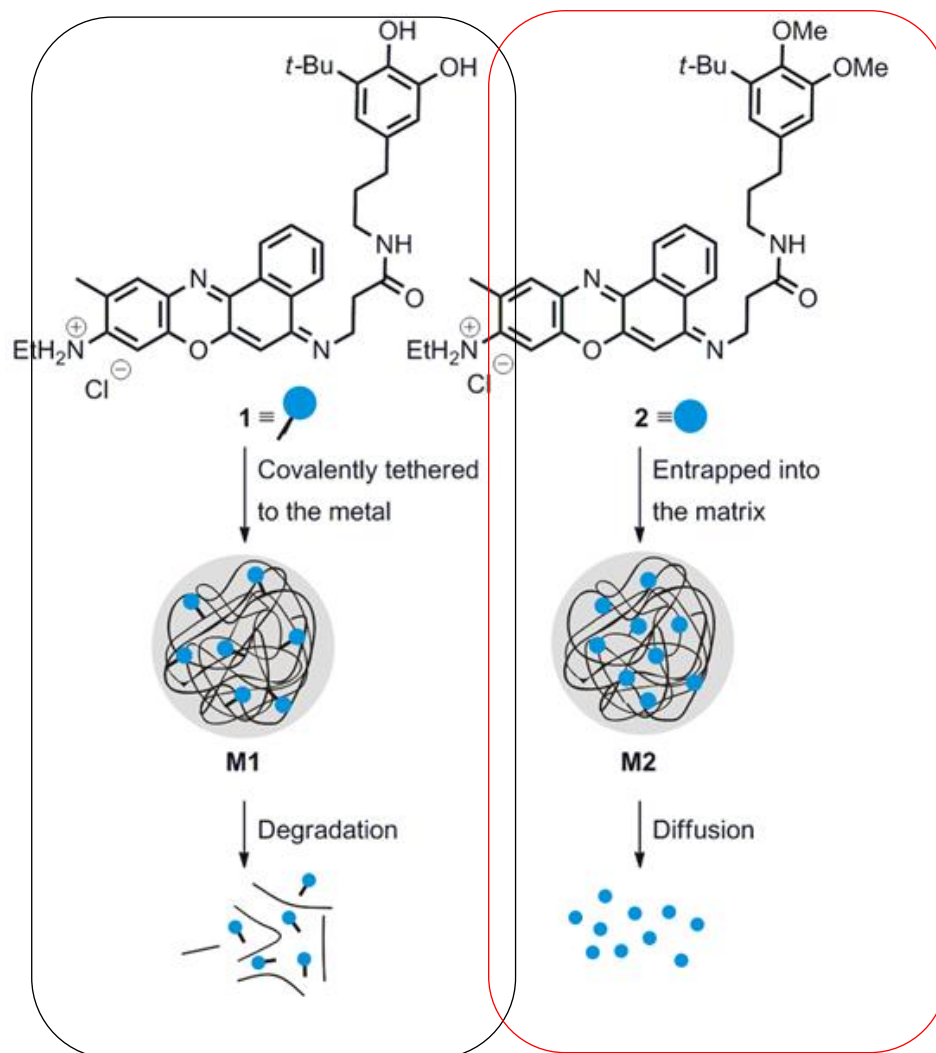
Angew. Chem. Int. Ed. , 2009, 48, 2325





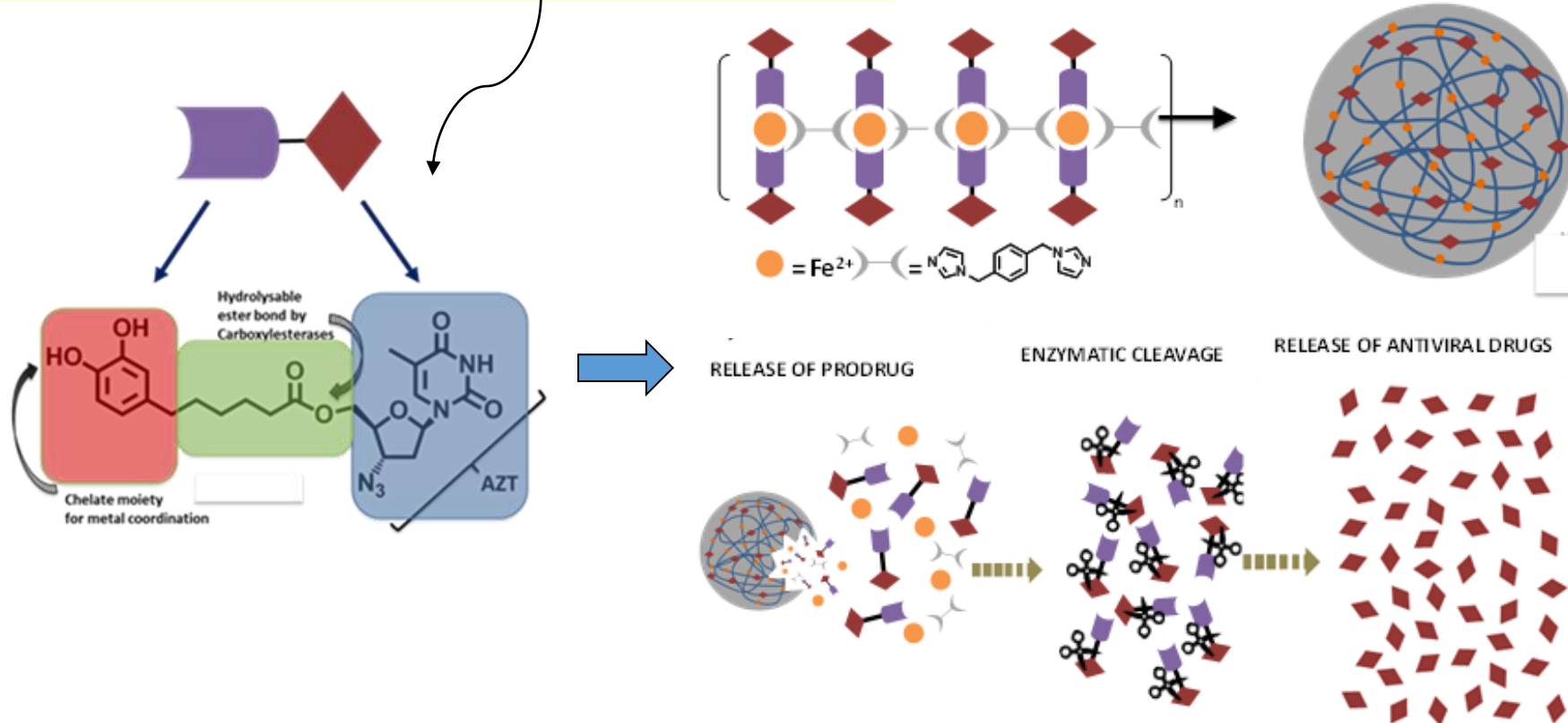
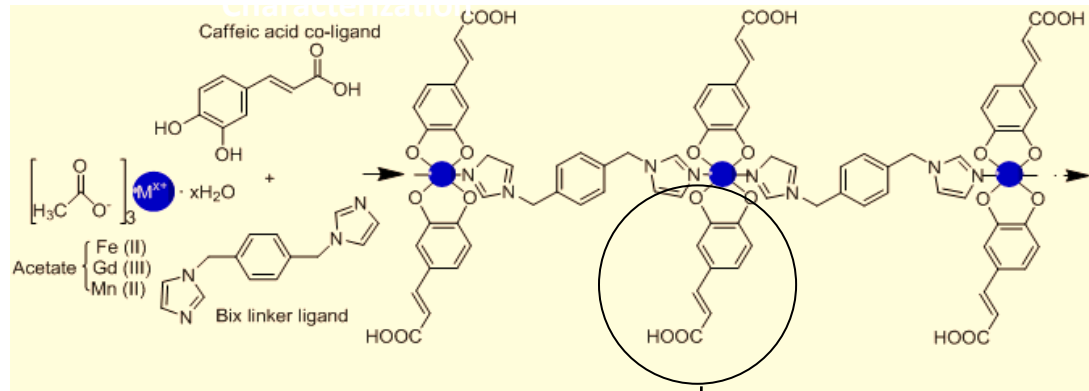
Tuneable release

prodrug ligands

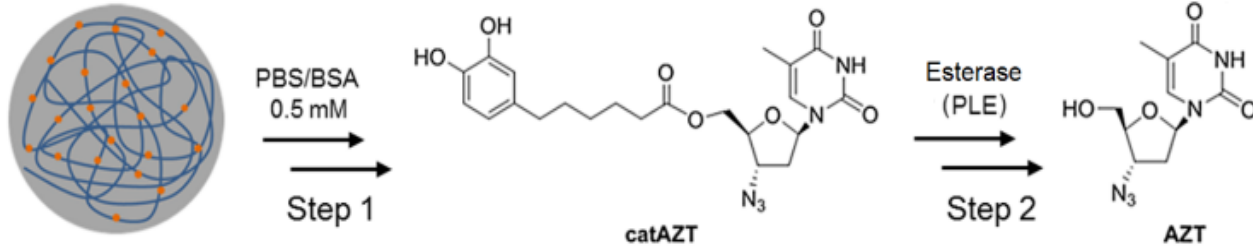


Chem. Eur. J., 2013, 19, 17508–17516.

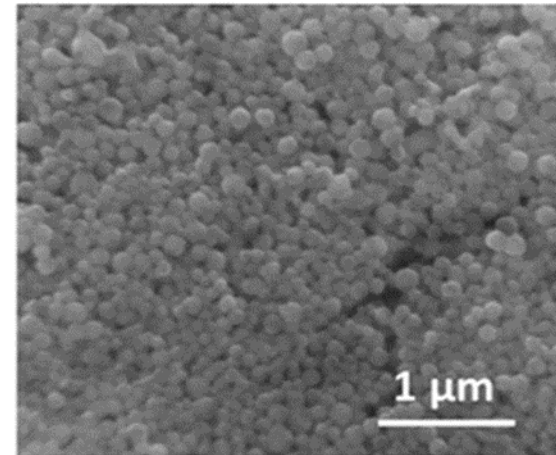
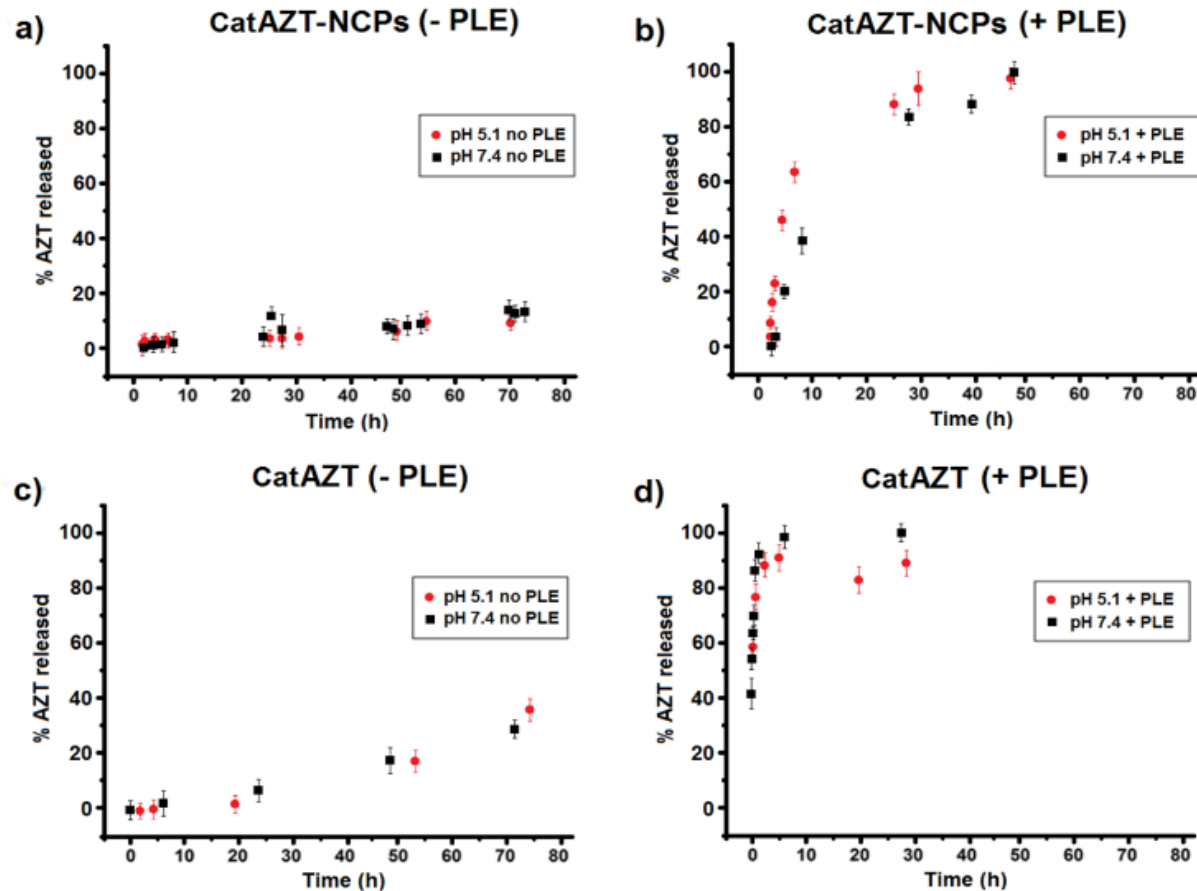
Retroviral Functionalization



Long lasting release...

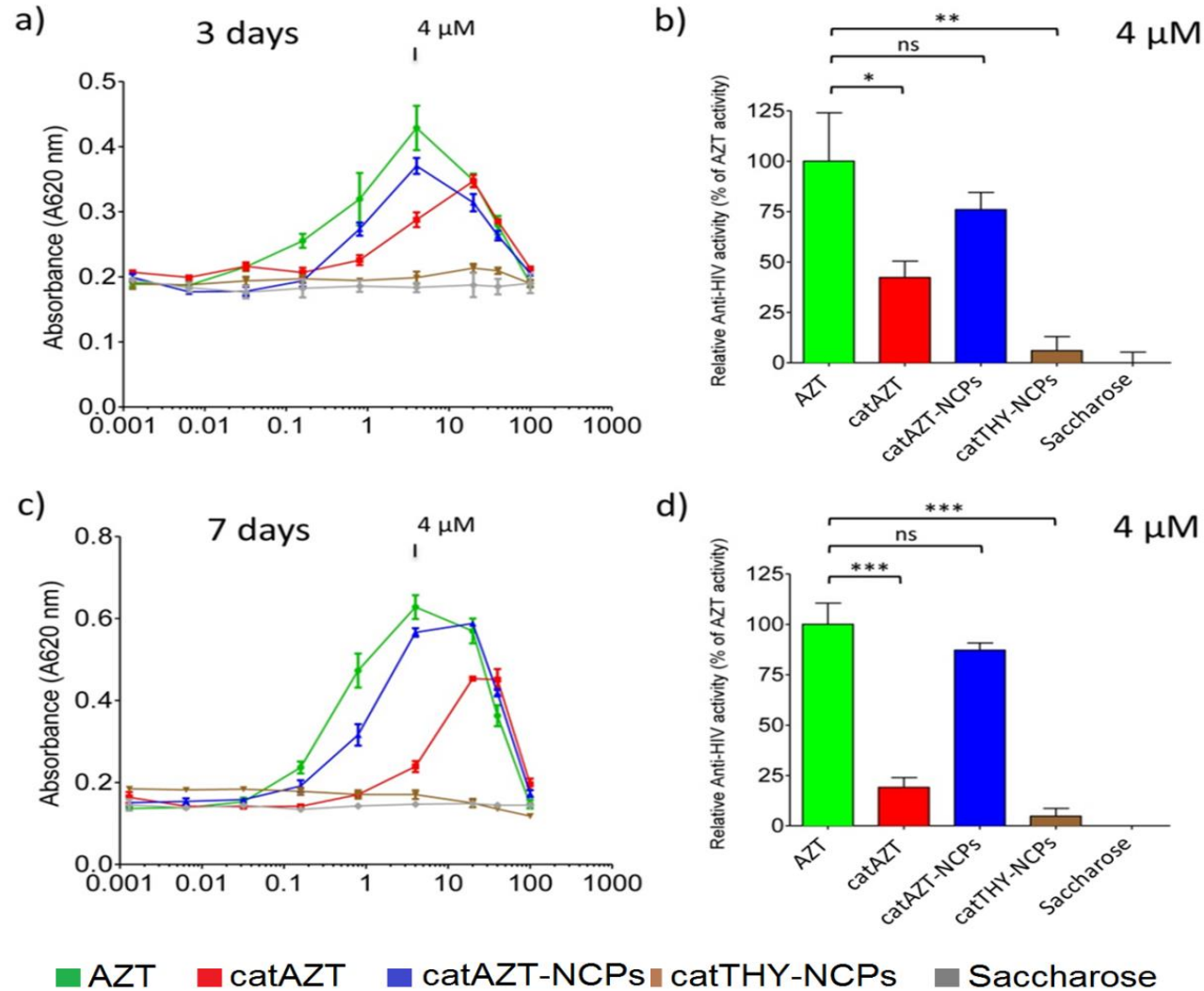


P3 laboratory @ Clinic Hospital

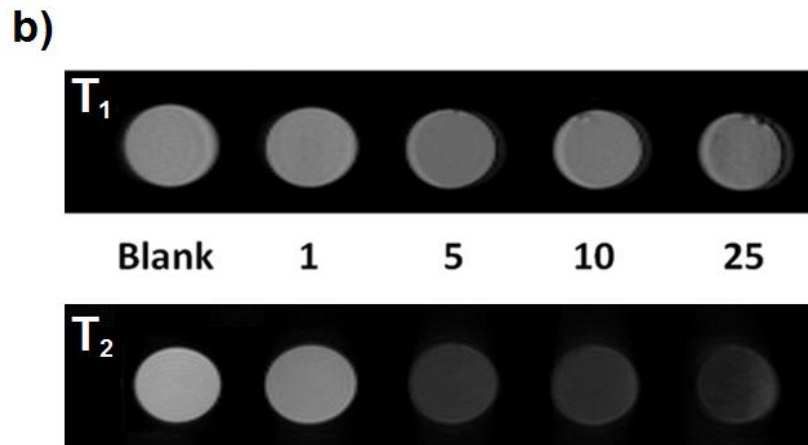
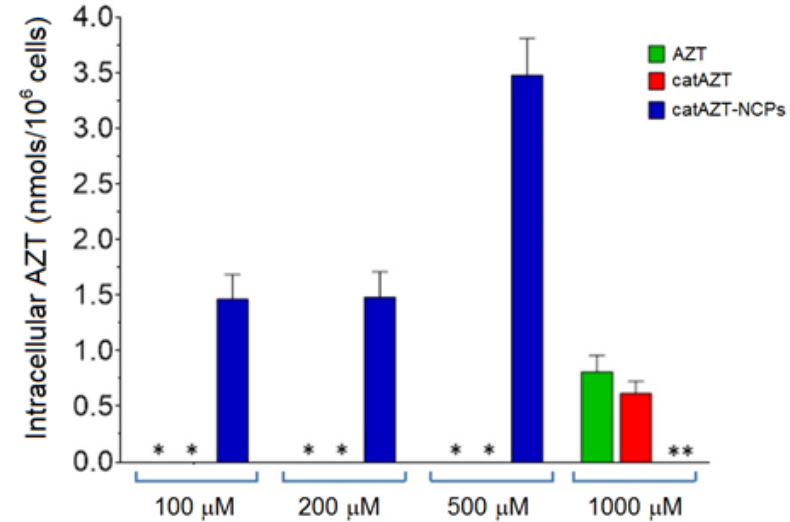
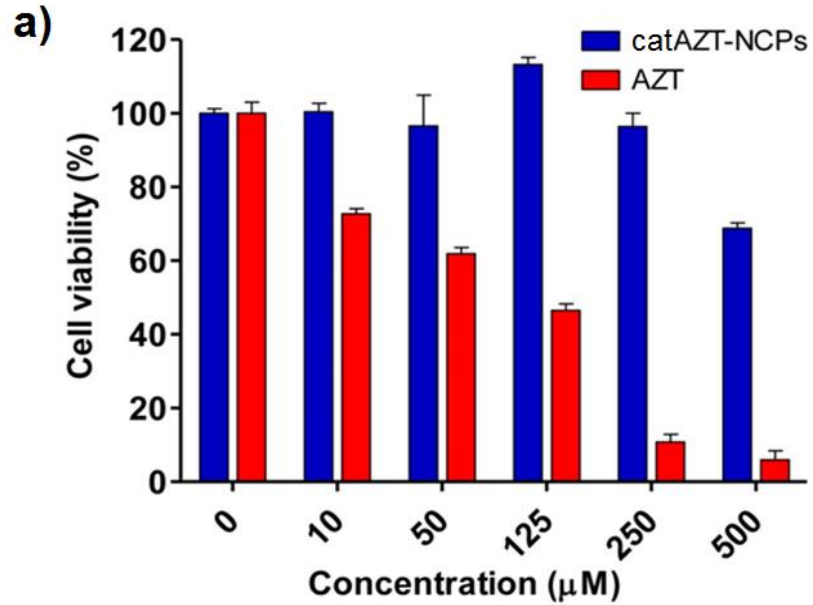


Antiviral effect

Cell viability of different concentrations on HIV-infected MT-2 cell culture



The antiviral effect of the compounds was indirectly measured as an increase in cell viability (increase in absorbance at 620 nm)

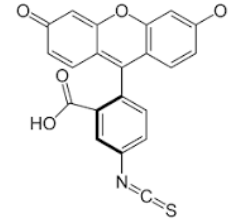
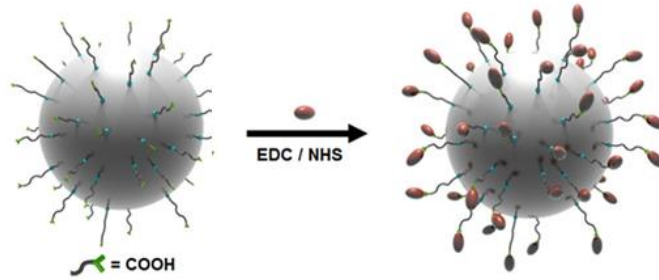


Our nanoparticles also allow for:

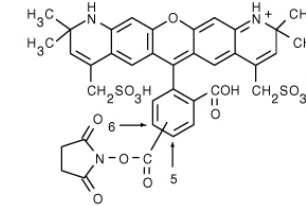
- *an enormous decrease of its cytotoxicity*
- *a remarkable colloidal stability, both worth to improve the biodistribution*
- *Better internalization*

Surface functionality:

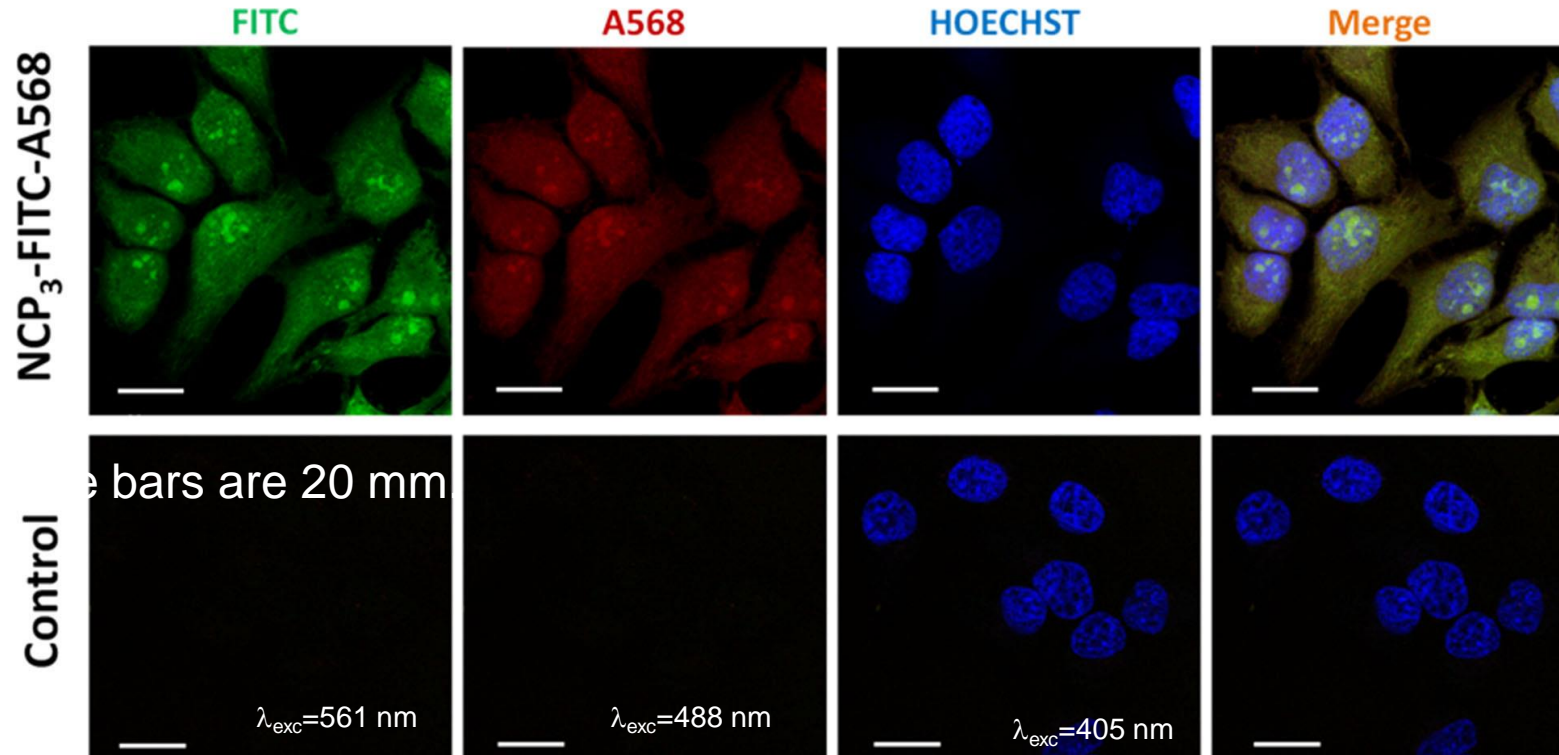
Dye/dual mode

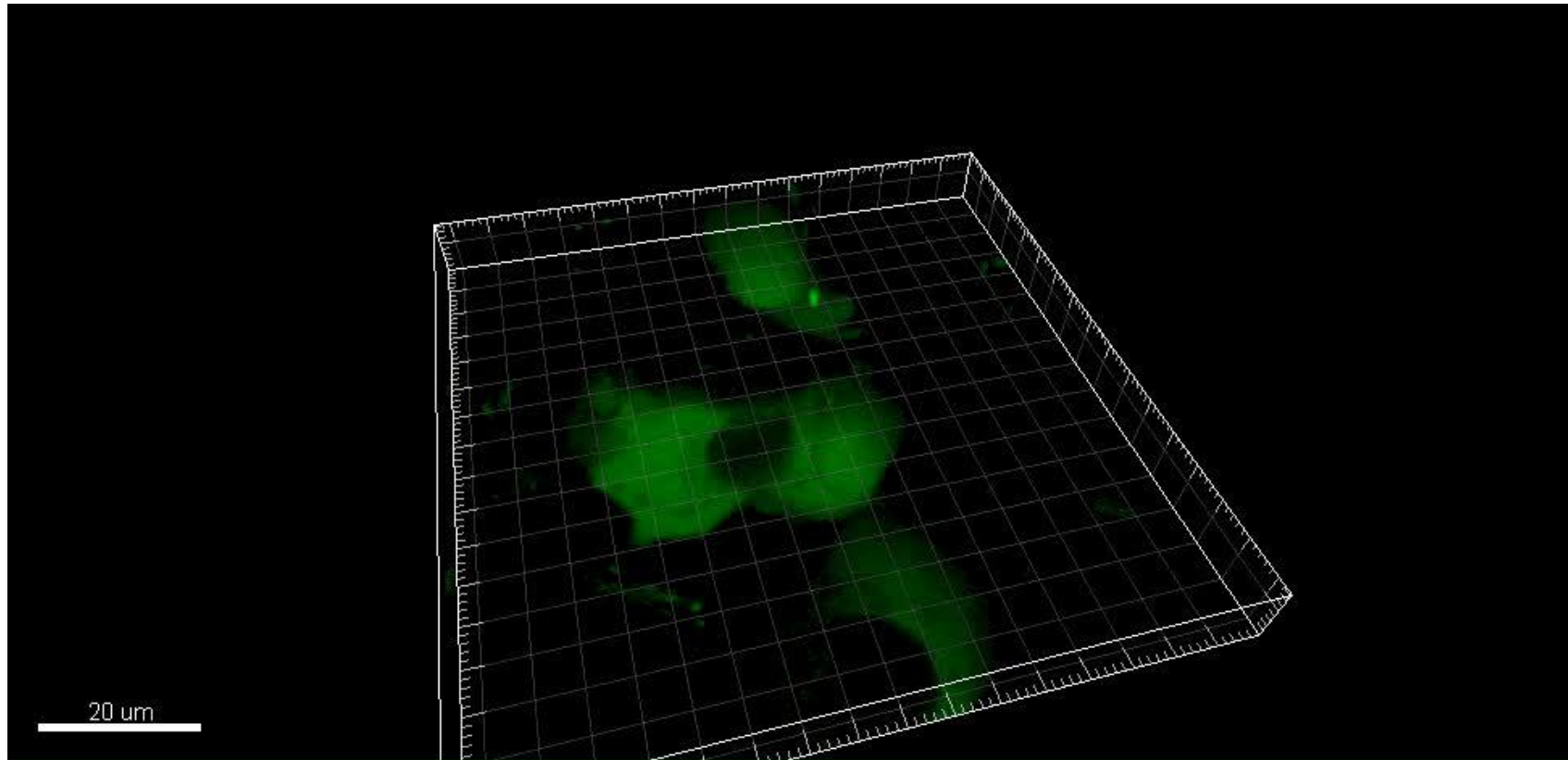


Fluorescein isothiocyanate



Alexa Fluor 568



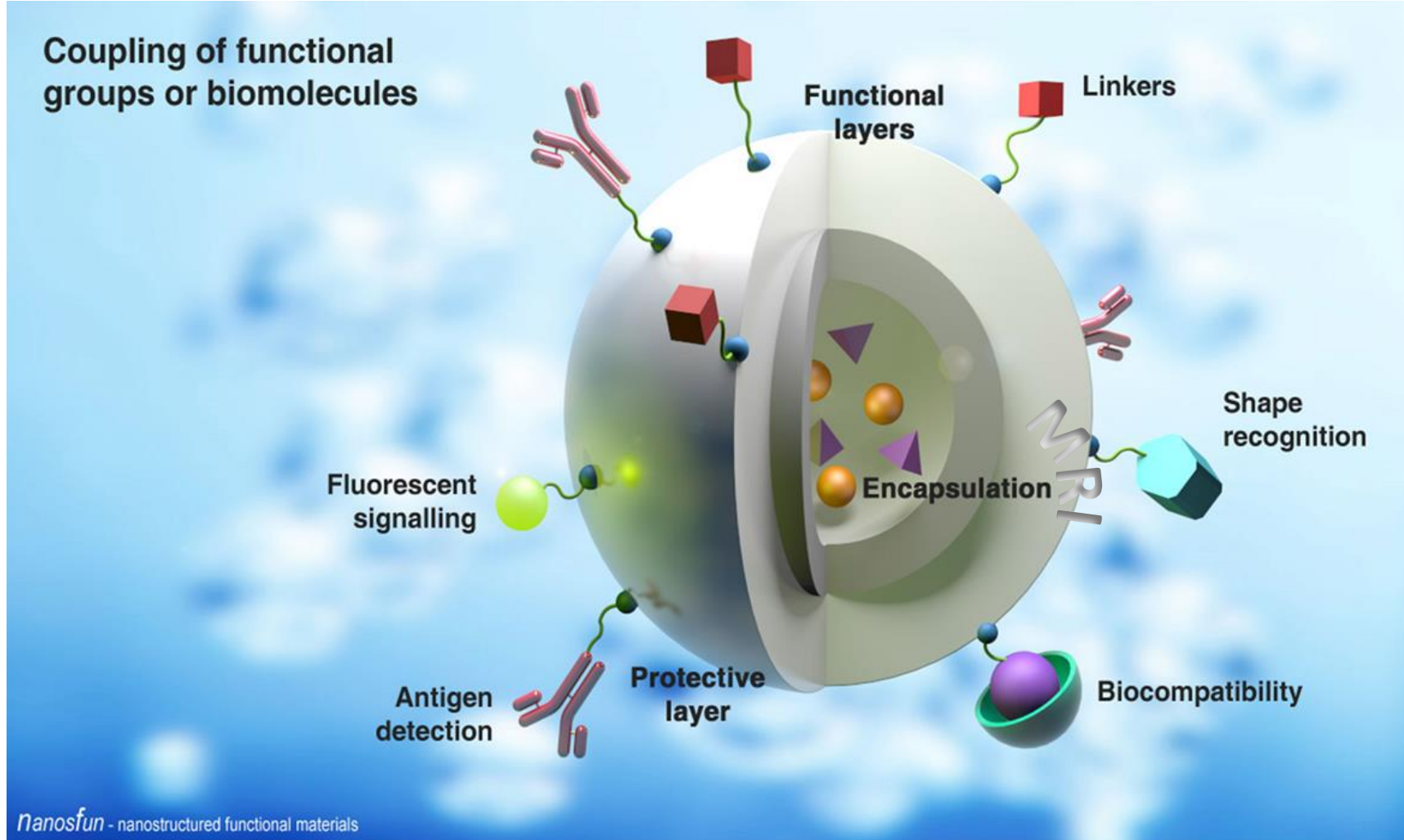


mammary humane adenocarcinoma: MCF7 cells

Quantitative

1. MCF-7 cells incubated with $100 \text{ mg}\cdot\text{mL}^{-1}$ of CPPs for 24 hours and lysed in PBS-1% SDS
2. The cell lysate was quantified in a spectrofluoremeter
3. The relative cell internalization of the nanoparticles was **40%**

Take home message





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dani.ruiz@icn2.cat

Thank you 