NanoMOF in Biomedicine: an update

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C. Serre

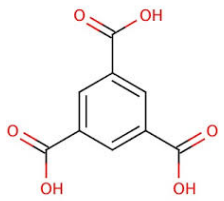
NanoSaclay
Laboratoire d'Excellence en Nanosciences et Nanotechnologies

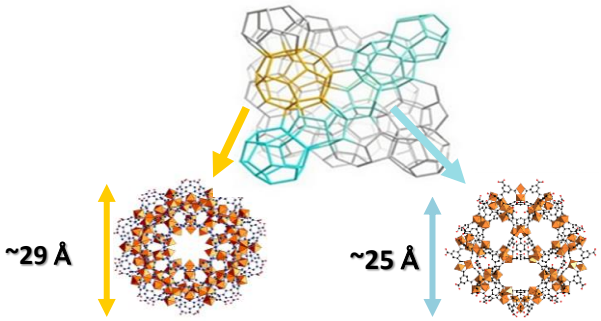
NanoMedecine Flagship

OVERVIEW

MIL100

Iron(III) tricarboxylate





(Material from Institut Lavoisier)

Chem. Commun. 2007

In vivo studies MOFs

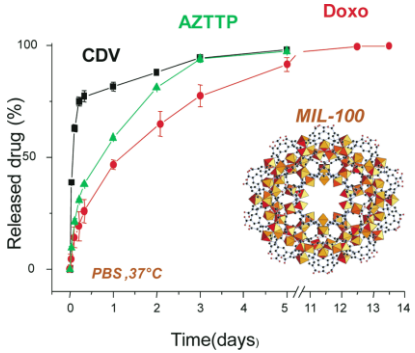
- Toxicity
- Pharmacokinetics (PK)
- Biodistribution (BD)

Chem. Rev. 2012
Chem. Sci. 2013

Drug encapsulation and prolonged release

- Ibuprofen
- Antiretroviral (AZT-TP, Cidofovir, Lamivudine)
- Anticancer drugs (Busulfan, Doxo, Gemcitabine)
- Therapeutic gas (NO, H_2S, CO)
- Antibiotics (Isoniazid, Rifampicin, Genistein)
- Etc

Angew. Chem. Int. Ed. 2006
Nat. Mater. 2010
Chem. Rev. 2012



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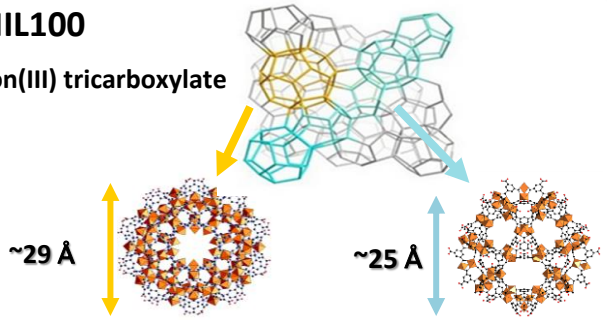

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Theranostic

- Maghemite
- Gold

Sene Saad
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In vivo effectiveness

J. Drug. Target. 2016

- Gemcitabine-MP (Gem-MP)
- Pancreatic cancer

Teresa Simon-Yarza
Rhizlaine Mrini (Idex)

Surface Modification - Biodistribution control

- Heparine (Hep)
- Polyethylen glycol (PEG)

Adv. Healthc. Mater. 2015

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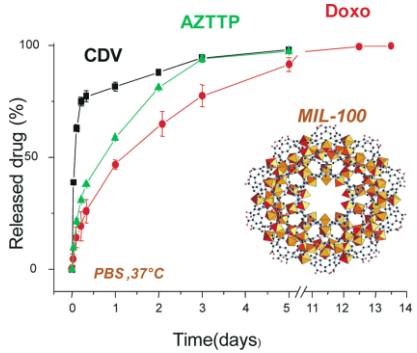

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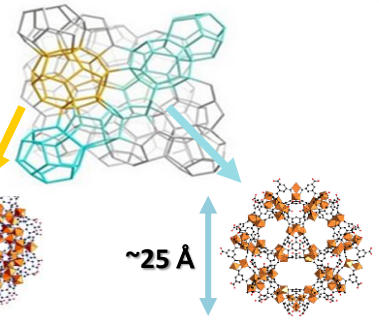

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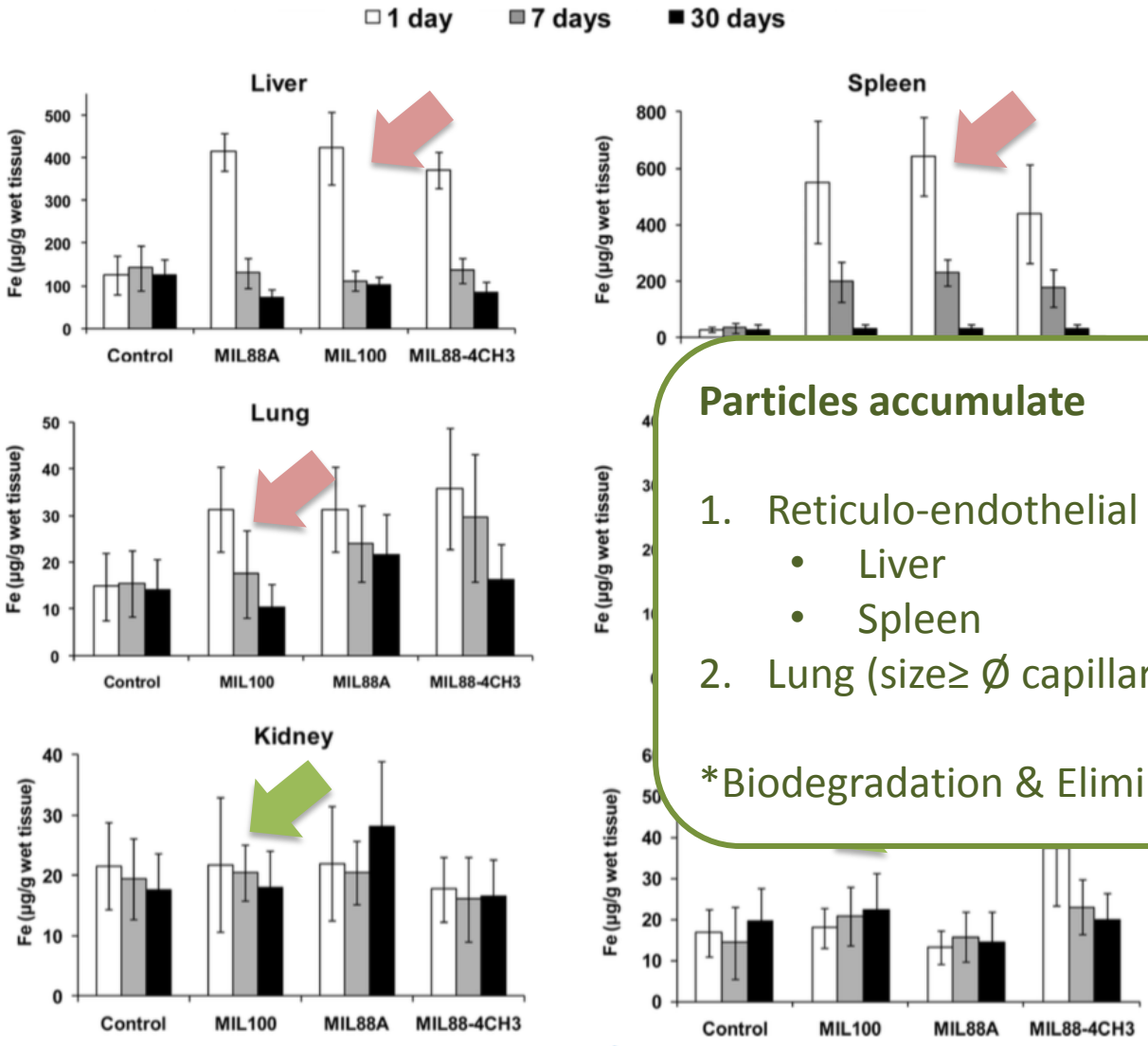
SURFACE MODIFICATION

Previous *in vivo* results with MIL100 (iv route, 220 mg/kg)



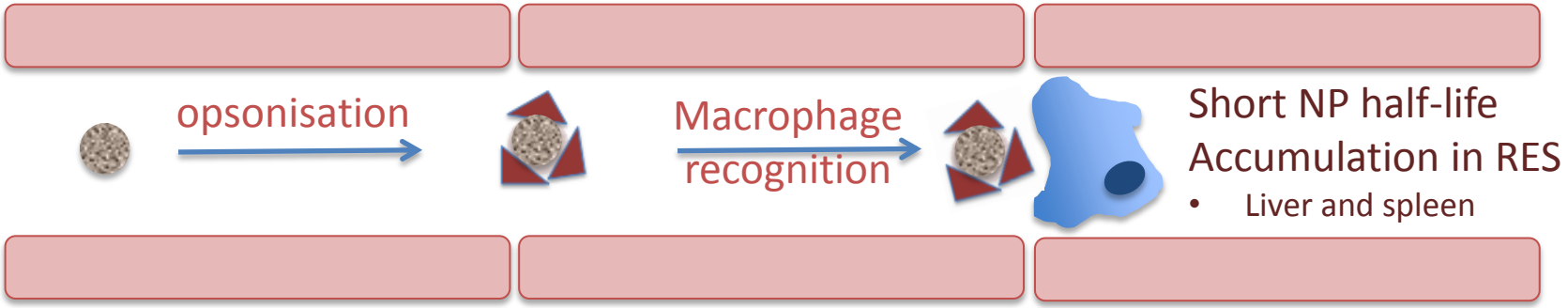
Particles accumulate

1. Reticulo-endothelial system (RES)
   - Liver
   - Spleen
2. Lung (size≥ Ø capillaries)

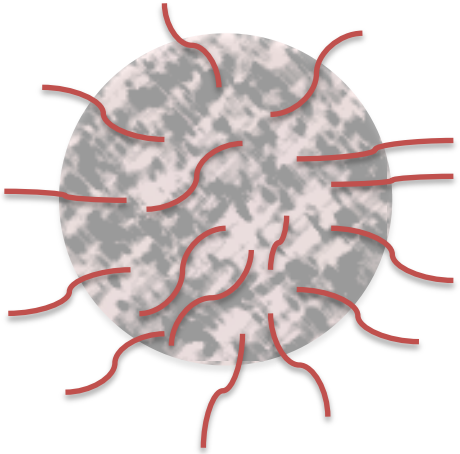
*Biodegradation & Elimination (urine/faeces)

Chem. Rev. 2012

The concept



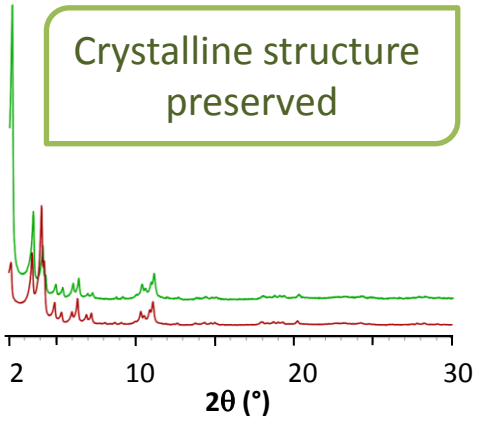
Macrophage clearance and hydrophilicity:
Polyethyleneglycol (PEG), Heparin (Hep)

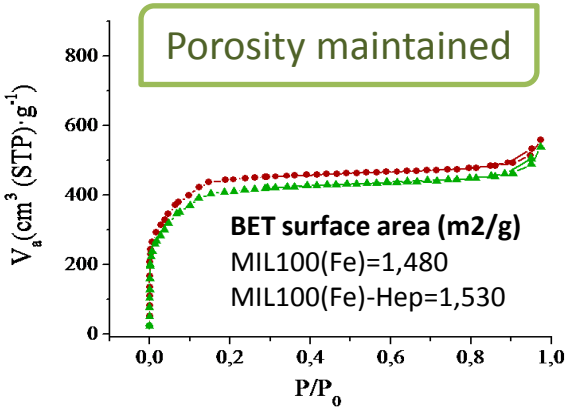


SURFACE MODIFICATION

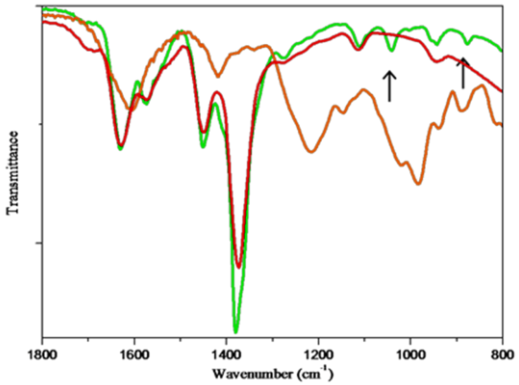
MIL100(Fe)-Hep: Impregnation method

MIL100(Fe)
MIL100(Fe)-Hep

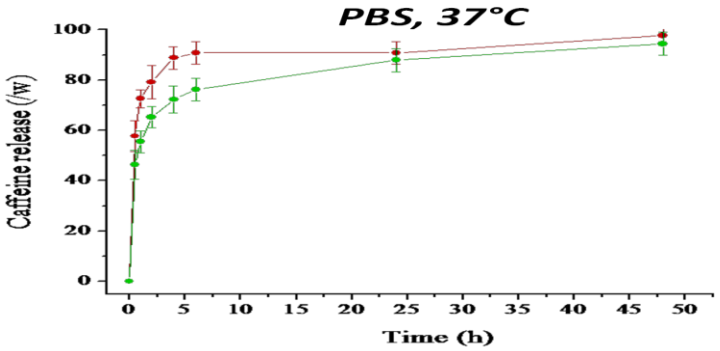




Shift of ν(S-O) and $\upsilon_{as}(Fe_3O)$
→ Hep-SO_3 – Fe-CUS



	MIL100(Fe)	MIL100(Fe)-Hep
Heparin (wt%)		12.5±1.5 (~ 88 %)
Size (nm)	141 ± 43	173 ± 51
ξ-potential (mV)	- 24.1 ± 2.1	– 20.7 ± 5.0
S_{BET} (m^2/g)	1530	1480
Caffeine loading (wt%)	43 ± 2	42 ± 6

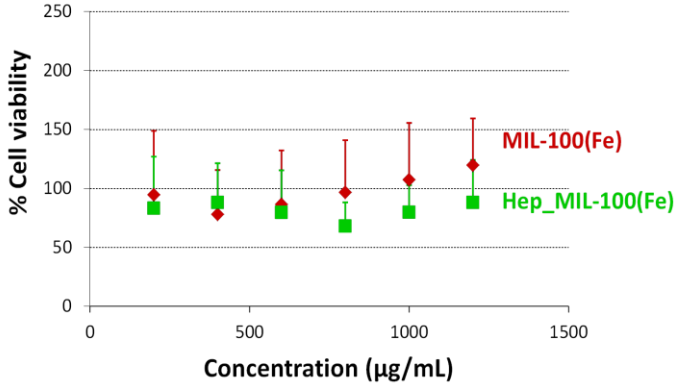


Adv. Healthc. Mater. 2015

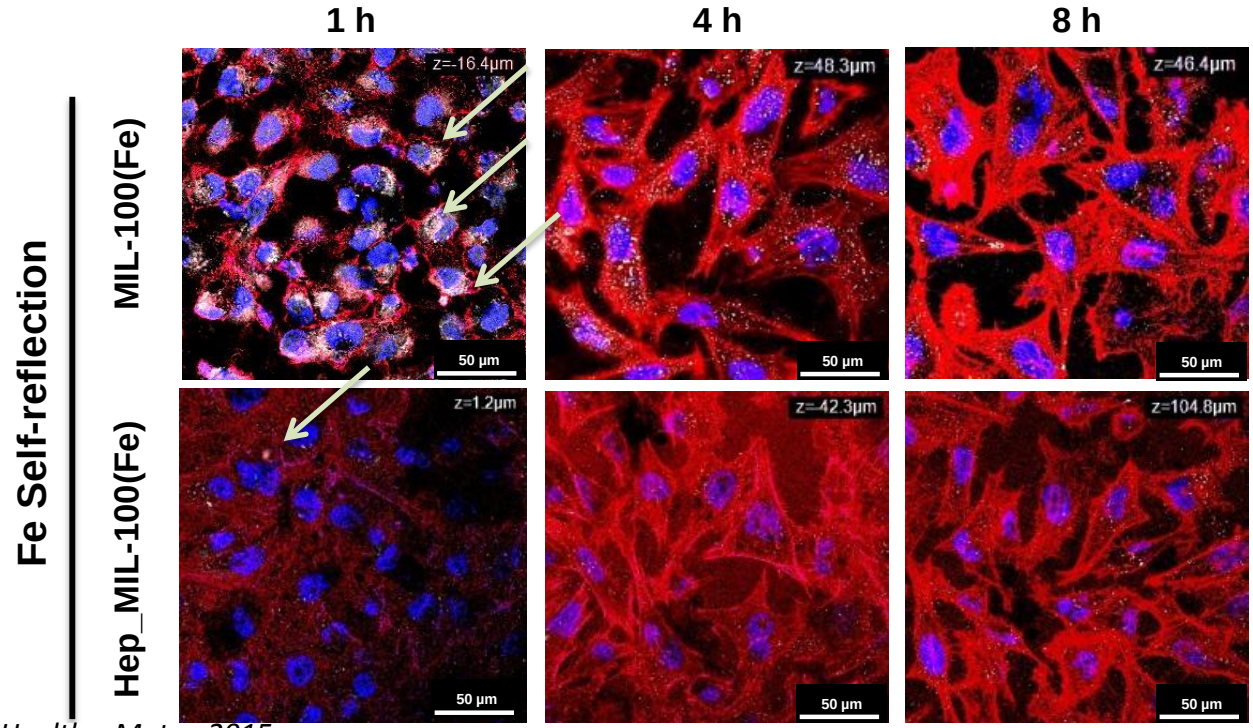
Bars: SD

SURFACE MODIFICATION

MIL100-Heparin



MOF cytotoxicity not affected



Cell uptake slowed-down by the heparin-coating in J774 macrophages

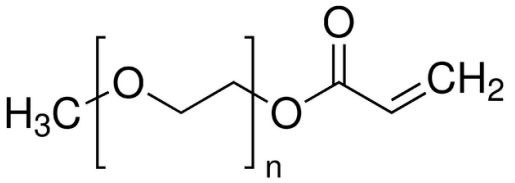
Adv. Healthc. Mater. 2015

Bars: SD

SURFACE MODIFICATION

MIL100-PEG

Acryl-PEGs Low MW: 450 Da, 2 kDa and 5 kDa



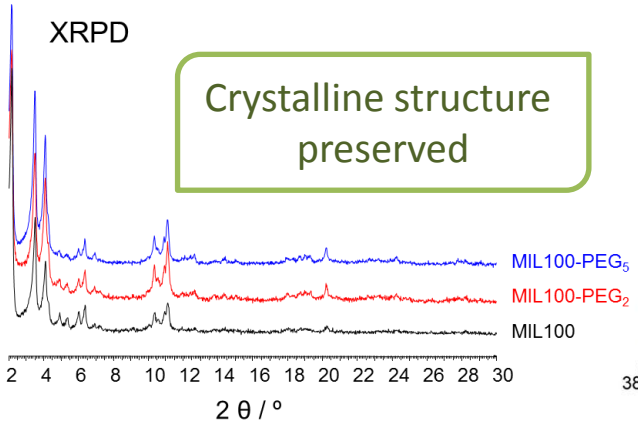
Synthetic procedure

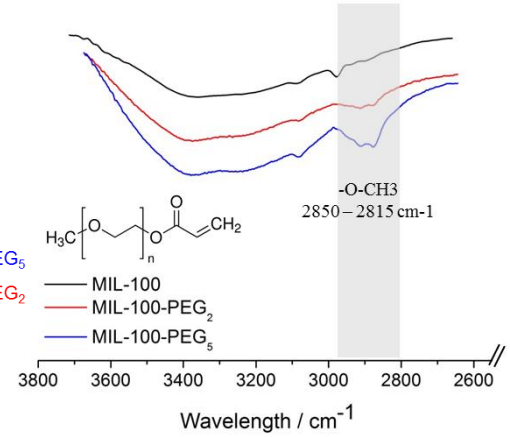
Synthesis by GraftFast®

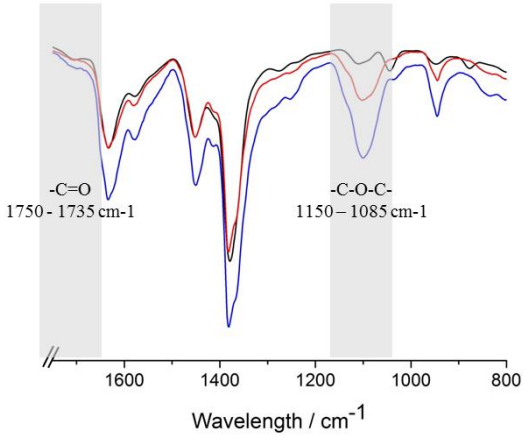
Molar ratio MIL100:PEG of 10:1

Physico-chemical charaterization

	Size (nm)	Potential (mV)	TGA (wt %)	BET ($m^2.g^{-1}$)
MIL-100	135 ± 20	–13 ± 3	-	1570
MIL-100@PEG_2	152 ± 11	–20 ± 4	18 ± 3	1600
MIL-100@PEG_5	167 ± 25	–23 ± 3	25 ± 5	1600



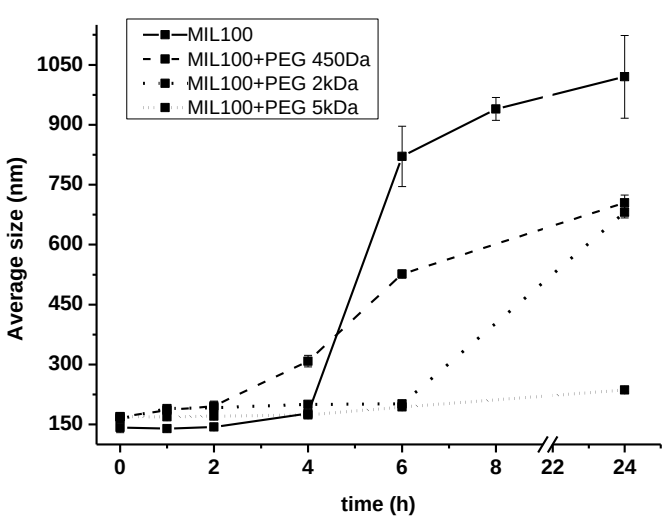


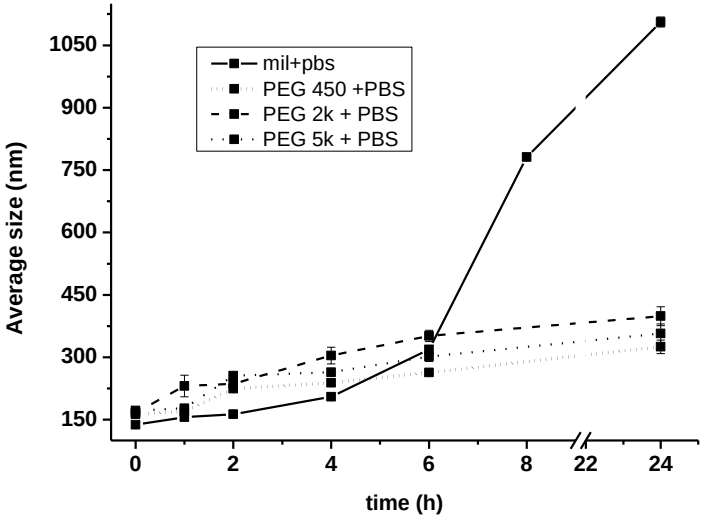


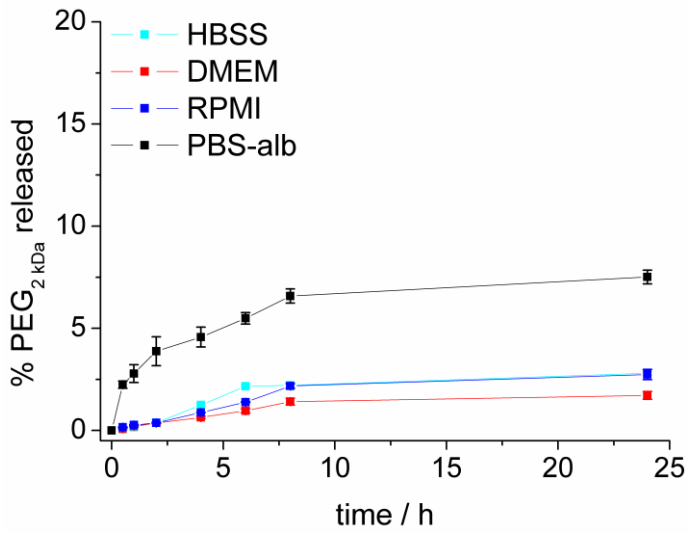
SURFACE MODIFICATION

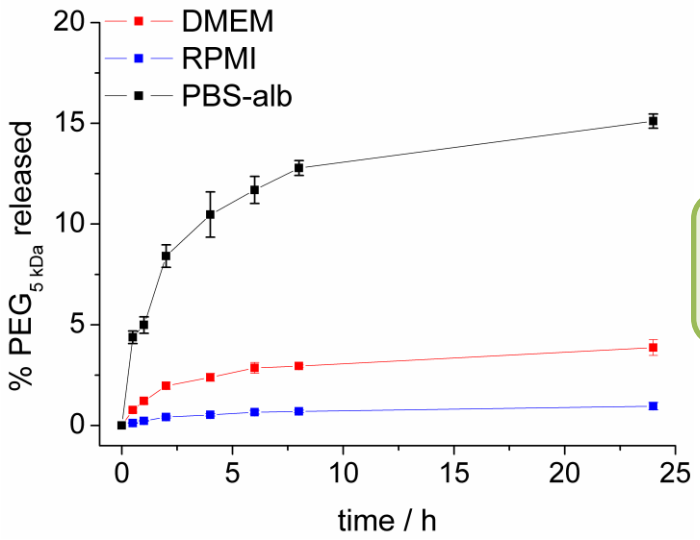
MIL100-PEG

Colloidal stability









PEG release

Bars: SD

SURFACE MODIFICATION

In vivo impact: PK & BD

Wistar rats (220-250 g)

Dose: 25 mg/kg of MIL100 NPs intravenously administered (without considering the Hep/PEG)

Volume administered: 0.5 ml

Pharmacokinetics (PK)

MIL100(Fe)
MIL100(Fe)-Hep
MIL100(Fe)-PEG5kDa
C- [10 % Glc]

Blood extraction (300 mcl) from jugular vein at 0.25, 0.5, 3, 8 and 24 h.
n=6

Biodistribution (BD)

MIL100(Fe)
MIL100(Fe)-Hep
C- [10 % Glc]*

Organs (spleen, kidneys, liver, lungs and heart) collected at 0.25, 0.5,1, 3, 8 and 24 h.
n=6/group
* Only at 24h.

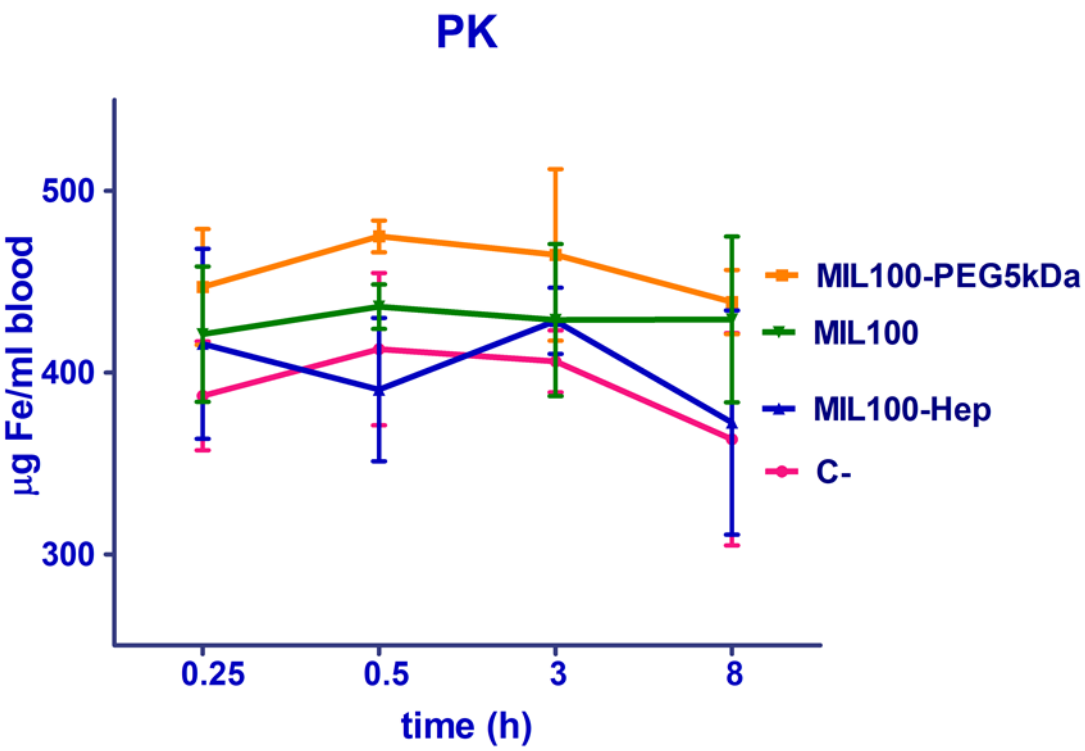
Fe quantification by Atomic Absorption Spectroscopy (AAS)

Organic linker (BTC) quantification by HPLC

J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 2011

SURFACE MODIFICATION

In vivo impact: PK & BD

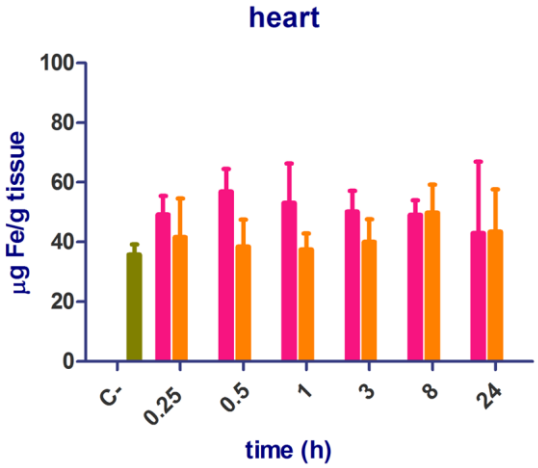


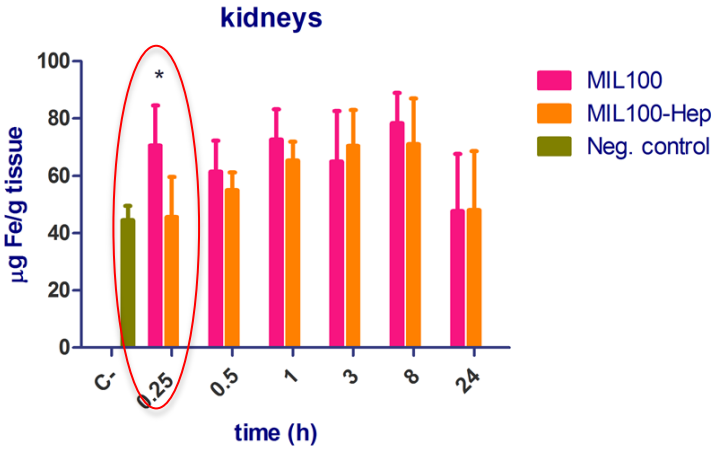
- Slight increase in MIL100-PEG5kDa group
- High variability intra-groups (SD)
- Lack of sensitivity of the method due to the Fe naturally present in the organism?

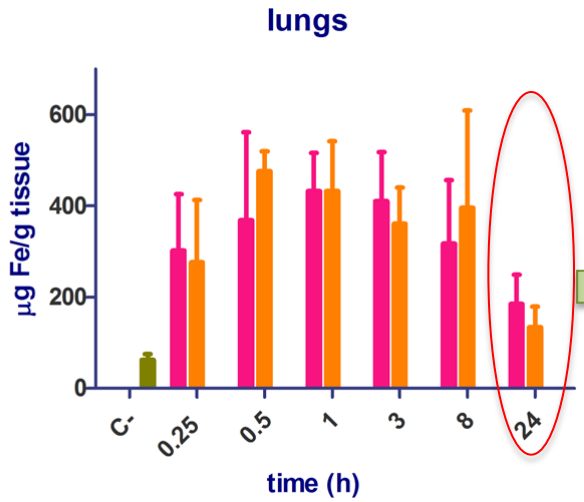
Bars: SD

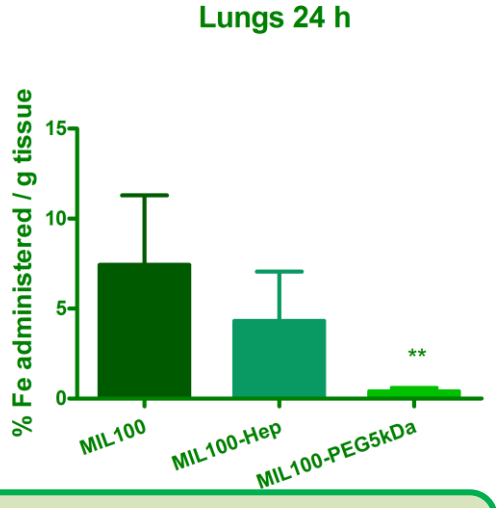
SURFACE MODIFICATION

In vivo impact: PK & BD







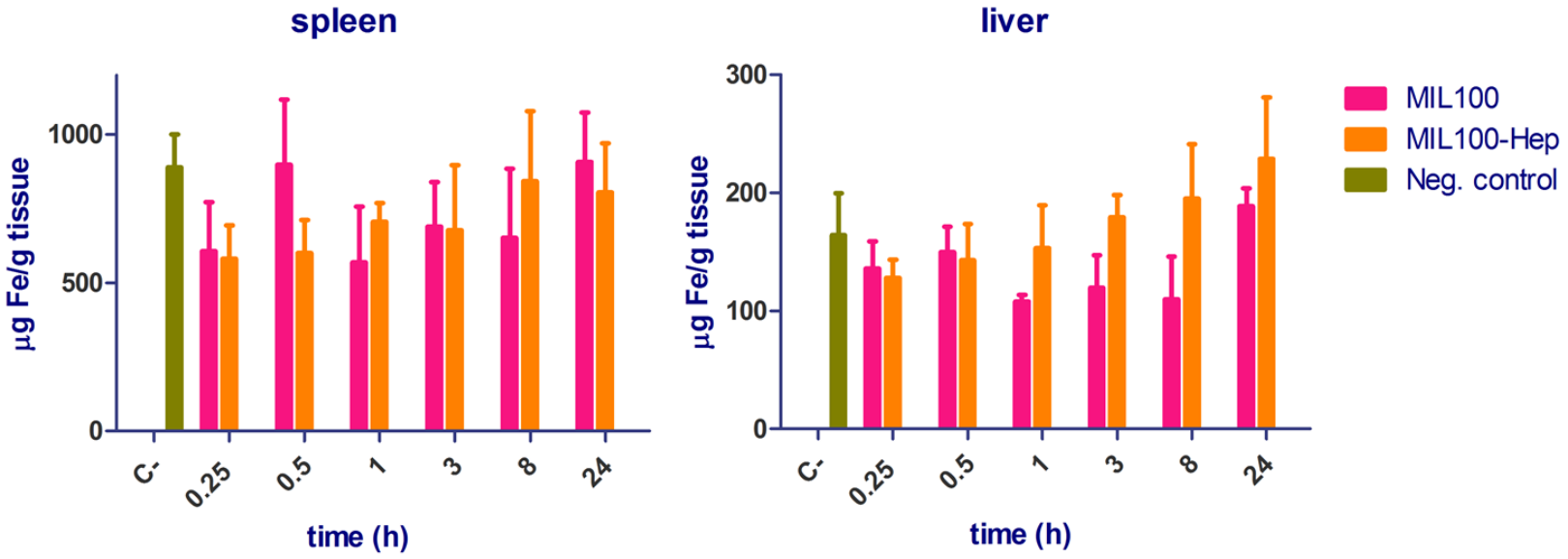


Bars: SD
*p< 0.05
**p<0.01

Better coloidal stability of MIL100-PEG5kDa

SURFACE MODIFICATION

In vivo impact: PK & BD



Reduction in the levels of Fe:

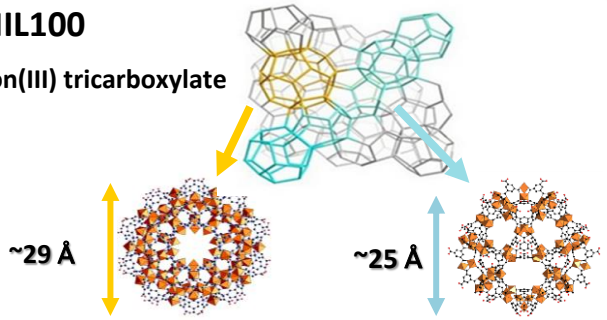
MOF complexation with endogenous Fe→ depletion of Fe stores (ferritine) in **liver** and spleen + reduction of iron recycling in spleen

Bars: SD

OVERVIEW

MIL100

Iron(III) tricarboxylate



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J. Drug. Target. 2016

- Gemcitabine-MP (Gem-MP)
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- Heparine (Hep)
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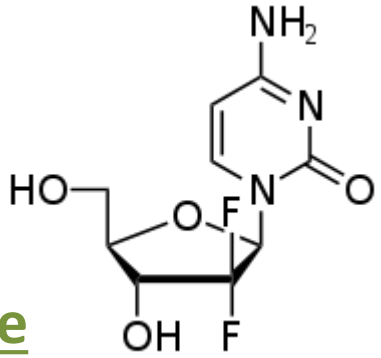
In vivo EFFECTIVENESS

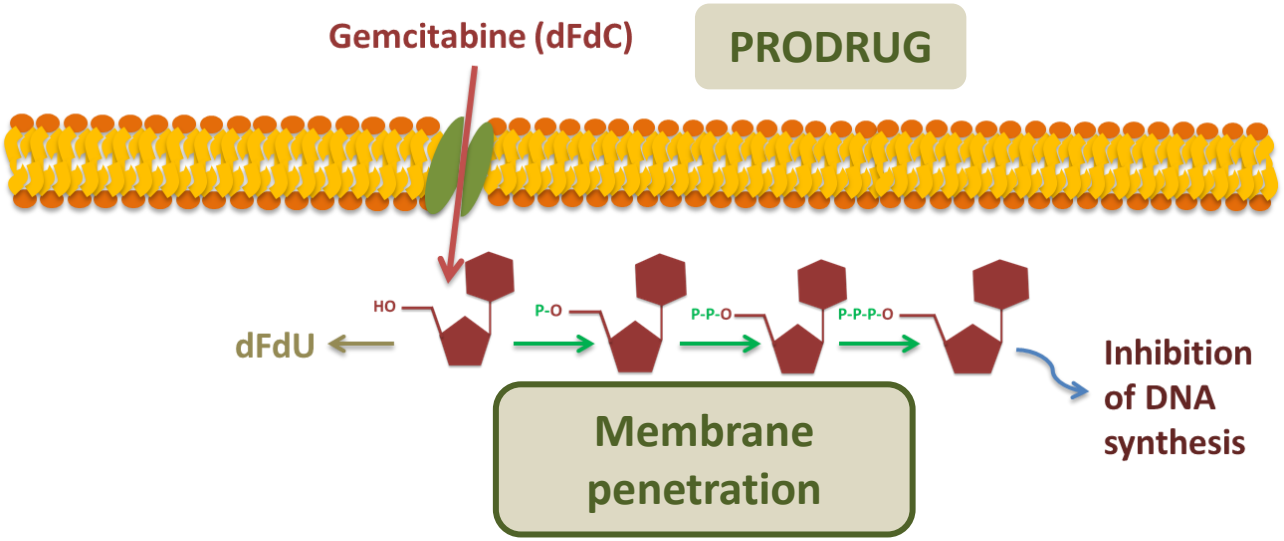
Gem-MP in pancreatic cancer

Drug: Gemcitabine mono-phosphate
Carrier: surface modified MIL100 NPs
Animal model: xenograft pancreatic cancer



Gemcitabine

- ✓ **One of the most relevant alkylating agents**
- ✓ **First line as pre-conditioning agent in CML and other haematological proliferative disorders**
- x **Large differences in drug bioavailability**
- x **Drug crystallization and hepatic veno-occlusive disease**
- x **Limited aqueous solubility**
- x **In contact with aqueous solutions: hydrolyzation and inactivation**

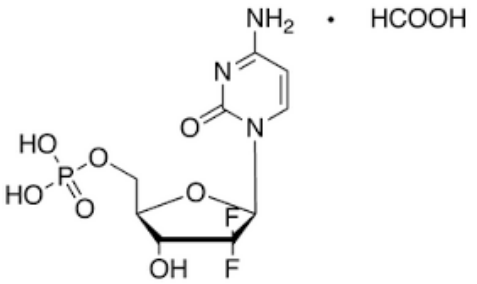


Encapsulation of Gem-MP into nanoparticles

In vivo EFFECTIVENESS

Gem-MP in pancreatic cancer

Drug: Gemcitabine mono-phosphate
Carrier: surface modified MIL100 NPs
Animal model: xenograft pancreatic cancer



- *Green* encapsulation by simple impregnation in **aqueous solutions**
- Maximal **loading of 31 wt%** and an **encapsulation efficiency of 98** % *vs.* Gem (10 % loading and 1 % efficiency)

IC50 (Panc-1 MTT assay)	1h	5h
Gem-MP	> 36 µM	28 µM
Gem	> 36 µM	17.5 µM
nanoMOF	> 36 µM	> 36 µM
Gem-MP nanoMOF	**450 nM**	**45 nM**

NEXT
Encapsulation in surface modified nanoMOF
Efficacy in animal model

J. Drug. Target. 2016

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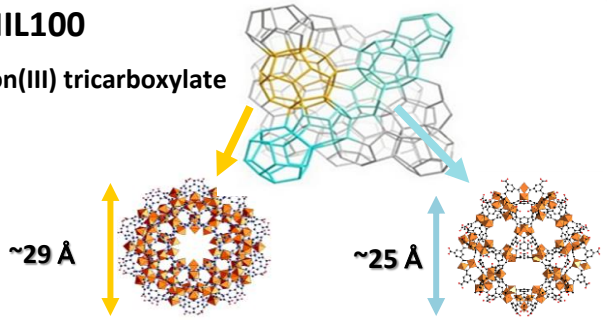

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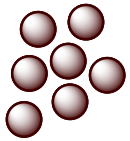
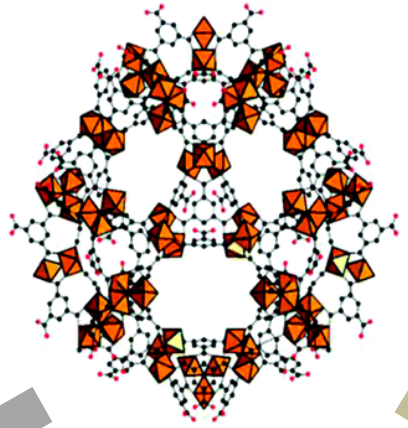
THERANOSTIC

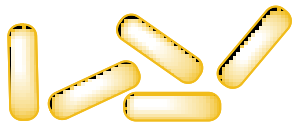
Maghemite and gold nanorods

Maghemite (γ-Fe_2O_3)
contrast agents





Gold Nanorods (Au)



Drug delivery
Imaging (MRI)
Hyperthermia

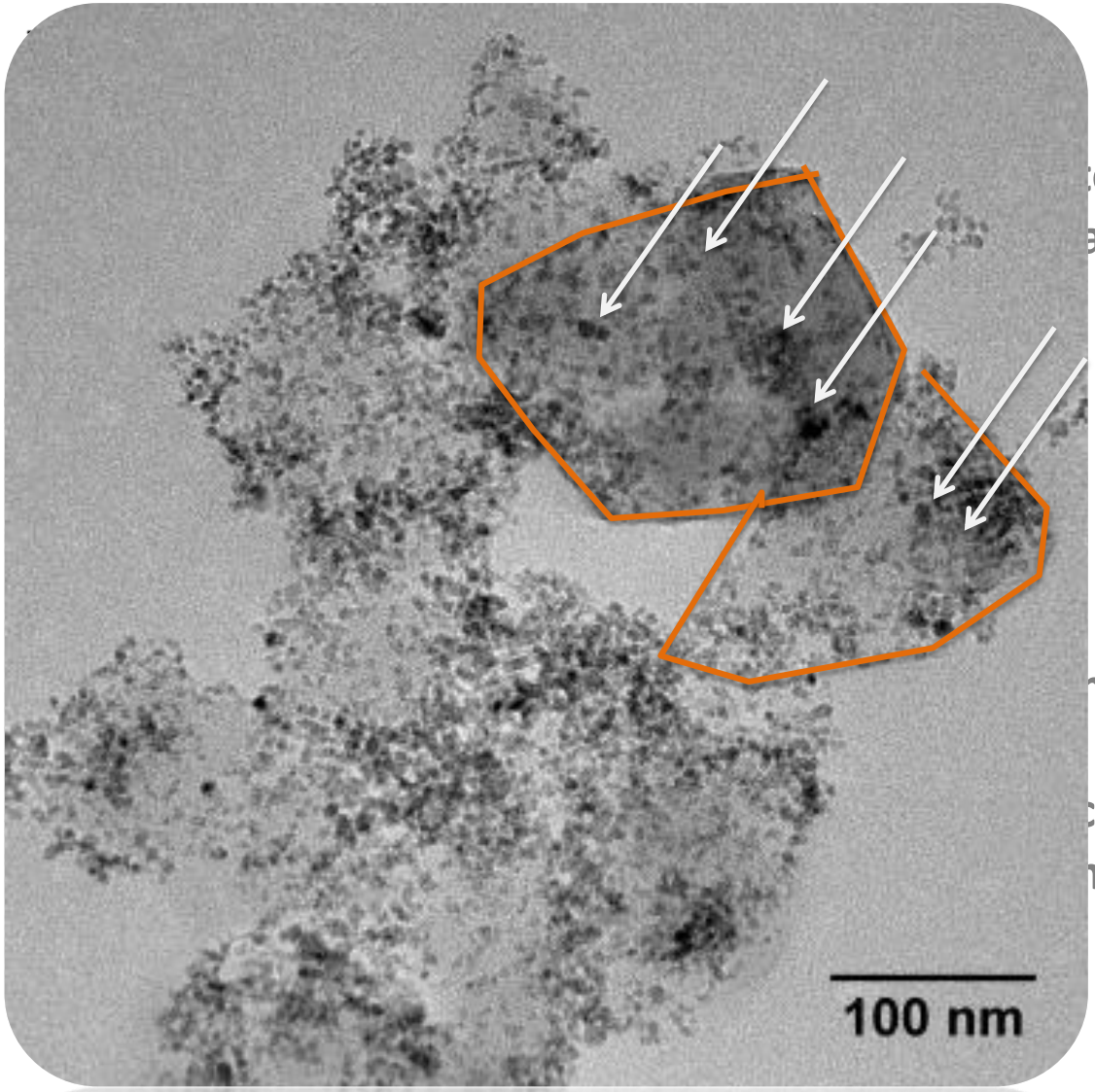
MIL100 has been demonstrated to have image properties

Nat. Mat. 2010

Drug delivery
Imaging (Fluorescence)
Photo thermal therapy

THERANOSTIC

Maghemite adsorption



stability: low pH
e surface charge to
article adsorption

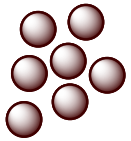
mite adsorption at pH

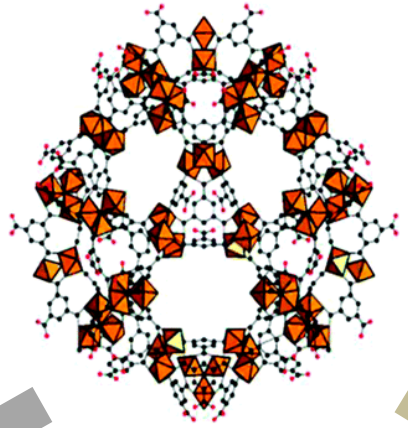
colloidal stability of
mite

THERANOSTIC

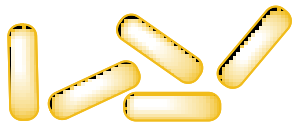
Maghemite and gold nanorods

Maghemite (γ-Fe_2O_3)
contrast agents



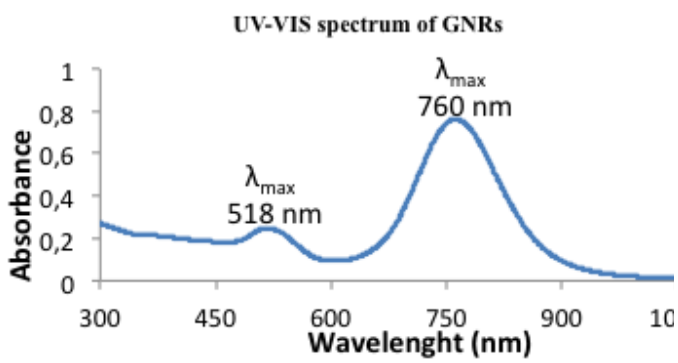


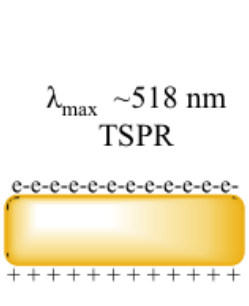
Gold Nanorods (Au)

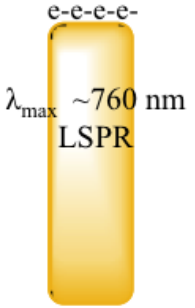


Drug delivery
Imaging (MRI)
Hyperthermia

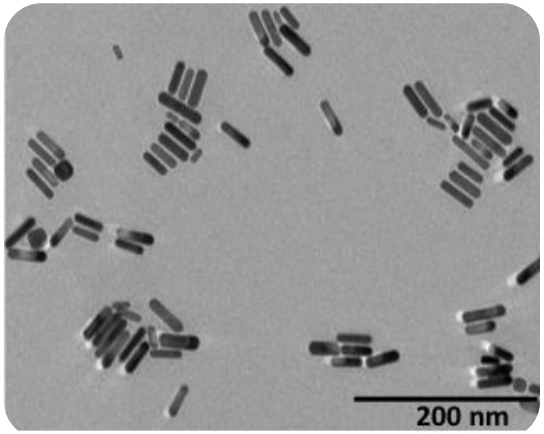
Drug delivery
Imaging (Fluorescence)
Photo thermal therapy

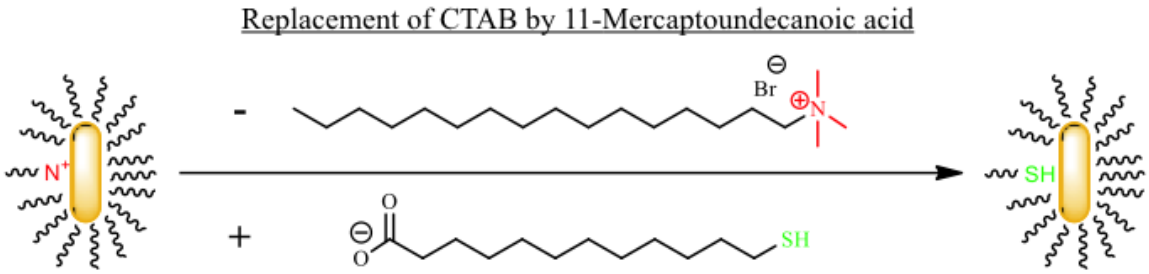


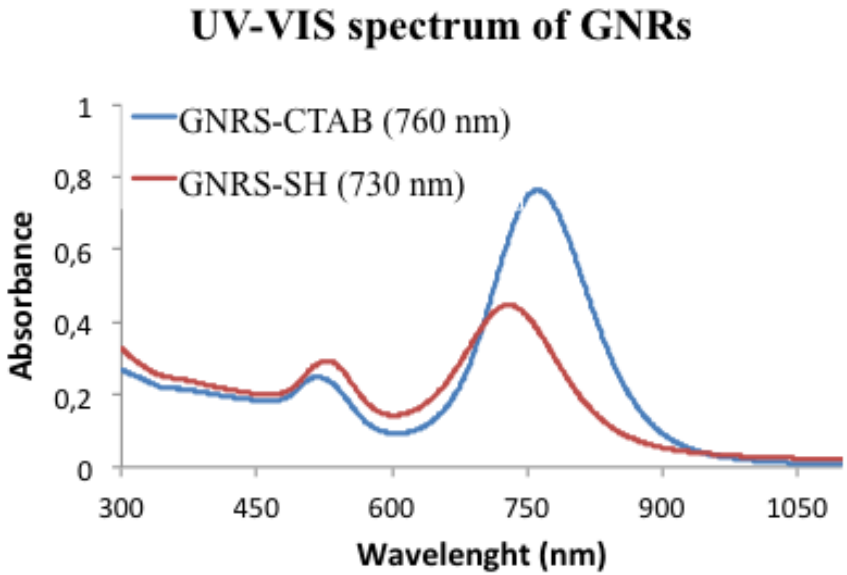




THERANOSTIC







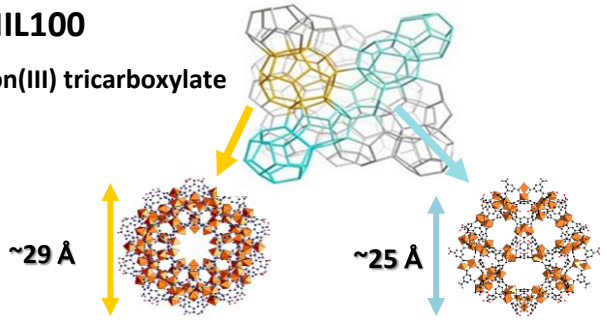
	Zeta potential (mV)
GNRs-CTAB	11.8 ± 8,0
GNRs-SH	-42.9 ± 10,8

CETAB: Cetyl Trimethil Ammonium Bromide (surfactant)

OVERVIEW

MIL100

Iron(III) tricarboxylate



(Material from Institut Lavoisier)

Chem. Commun. 2007

Theranostic

- Maghemite
- Gold

Sene Saad
Teresa Simon-Yarza

In vivo effectiveness

J. Drug. Target. 2016

- Gemcitabine-MP (Gem-MP)
- Pancreatic cancer

Teresa Simon-Yarza
Rhizlaine Mrini (Idex)

Surface Modification - Biodistribution control

- Heparine (Hep)
- Polyethylen glycol (PEG)

Adv. Healthc. Mater. 2015

Elena Bellido
Monica Gimenez-Marques
Teresa Simon-Yarza
Rhizlaine Mrini (Idex)

In vivo studies MOFs

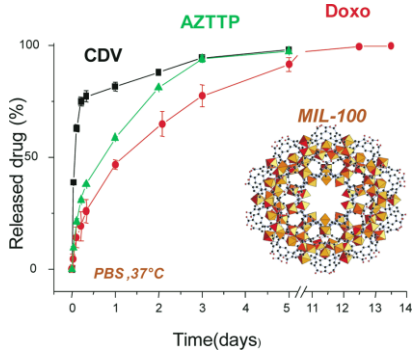
- Toxicity
- Pharmacokinetics (PK)
- Biodistribution (BD)

Chem. Rev. 2012
Chem. Sci. 2013

Drug encapsulation and prolonged release

- Ibuprofen
- Antiretrovirals(AZT-TP, Cidofovir, Lamivudine)
- Anticancer drugs (Busulfan, Doxo, Gemcitabine)
- Therapeutic gas (NO, H_2S, CO)
- Antibiotics (Isoniazid, Rifampicin, Genistein)
- Etc

Angew. Chem. Int. Ed. 2006
Nat. Mater. 2010
Chem. Rev. 2012



NanoMOF in Biomedicine: an update

THANK YOU FOR YOUR ATTENTION

NanoSaclay
Laboratoire d'Excellence en Nanosciences et Nanotechnologies
NanoMedecine Flagship