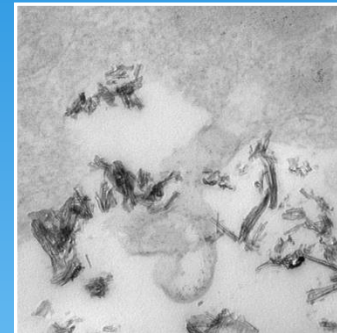
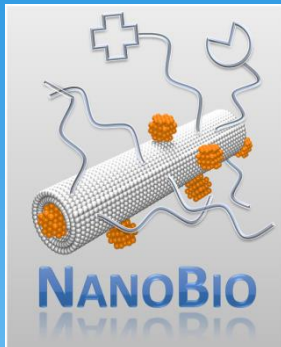


Applications des nanoparticules en santé



Nadine MILLOT

Professeur des Universités

Equipe de Recherche "Bio(Hybrid)-Nanoparticles and Nanostructures"

Département Nanosciences

Laboratoire Interdisciplinaire Carnot de Bourgogne,
UMR 6303 CNRS/Université Bourgogne Franche Comté

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PLAN

1. Qu'est-ce qu'un nanomatériau ?
(définition, applications quotidiennes)
2. Applications des nanopoudres dans le domaine biomédical.
Quelques données générales (marché, applications, études cliniques en cours)
3. Les exemples dijonnais :
 - nanoparticules d'oxydes de fer pour l'imagerie médicale multimodale
 - nanotubes de titanates comme nouveaux radiosensibilisants (glioblastome et cancer de la prostate)

Exemple d'ordres de grandeur dans le monde du vivant

NANOMONDE

Etre humain



1 m

Papillon



10 cm
= 10^{-1} m

1 cm
= 10^{-2} m

Puce



1 mm
= 10^{-3} m

Cheveux



100 μ m
= 10^{-4} m

10 μ m
= 10^{-5} m

Cellule



1 μ m
= 10^{-6} m

ADN



100 nm
= 10^{-7} m

Protéine



10 nm
= 10^{-8} m

Molécule



1 nm
= 10^{-9} m

Atome



0,1 nm
= 10^{-10} m



Voiture



Téléphone Portable



Carte puce



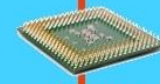
Micro-processeur



Photo transistor



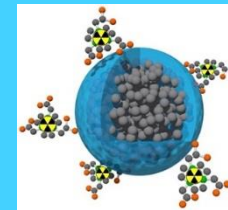
Transistor



Nano transistor



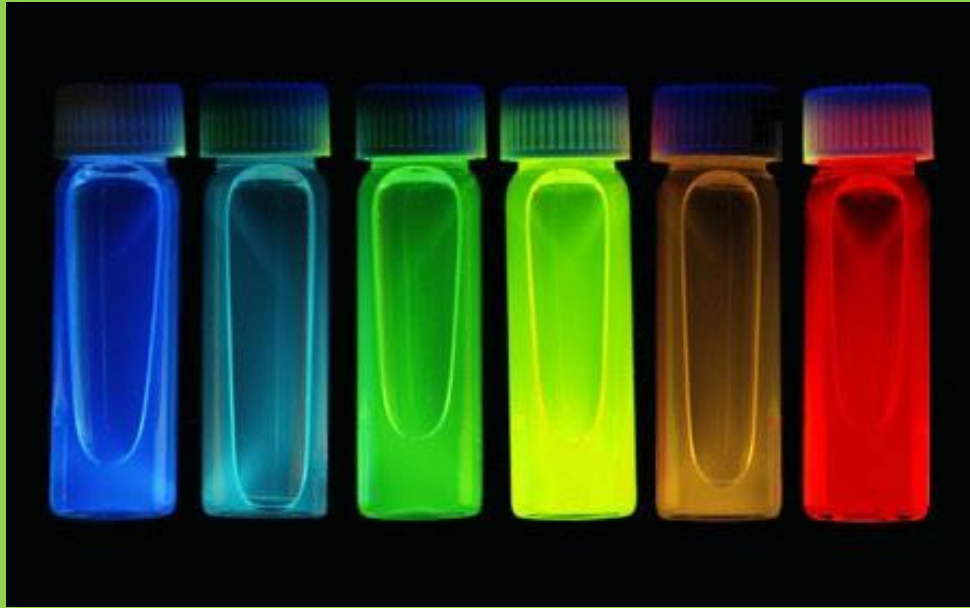
Agrégat d'atomes



Nanoparticules en médecine

Exemple d'ordres de grandeur dans le monde des produits fabriqués par l'homme

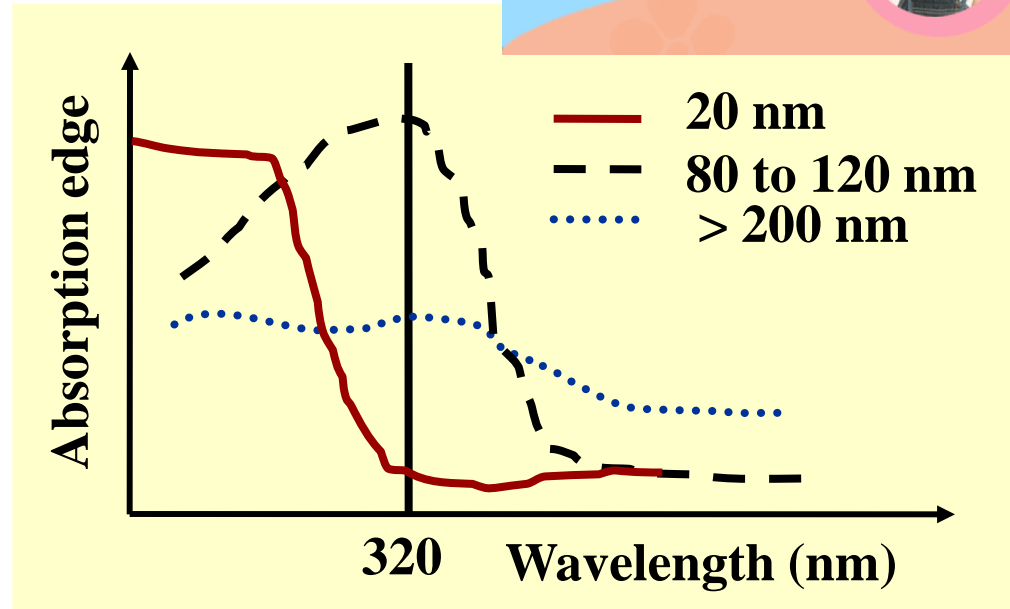
Les propriétés des matériaux dépendent de la taille de leurs grains (pour des dimensions < 100 nm)



Chaque couleur correspond à une taille de grains différente

Exemples d'applications quotidiennes des nanomatériaux...

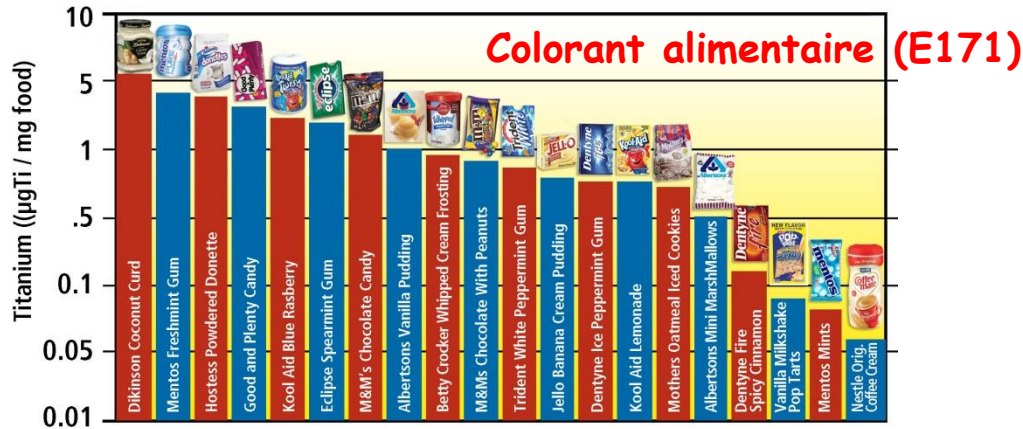
Des filtres solaires (minéraux) plus efficaces



Evolution du seuil d'absorption de TiO_2 en fonction de la dimension des grains



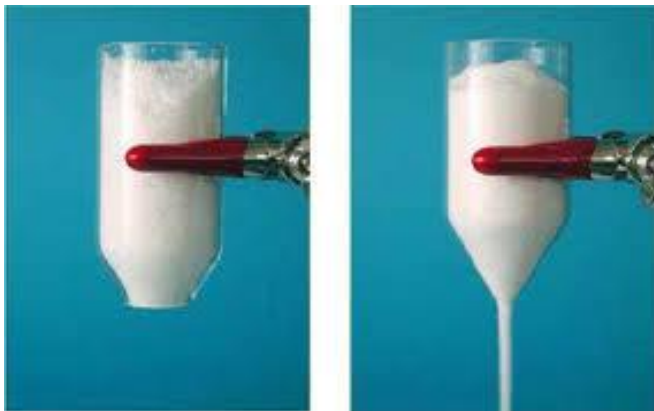
Exemples d'applications quotidiennes des nanomatériaux...



Peintures bactéricides
Peintures virucides
Peintures fongicides



Des peintures, des pansements, des emballages, des colorants *etc.* intelligents !



Sel marin *avant* et *après* introduction de nano-silice

Films propres
Anti-Mûrissement



Pansements désinfectants

Secteurs fortement utilisateurs de nanoparticules

Médecine et Santé



1

Matériel de loisirs



16

17

Alimentation



17

17

Fournitures Maisons



24

24

Vêtements Textiles



29

32

69



Cosmétique Hygiène



Automobile



Electronique



Applications multiples



Bâtiments

PLAN

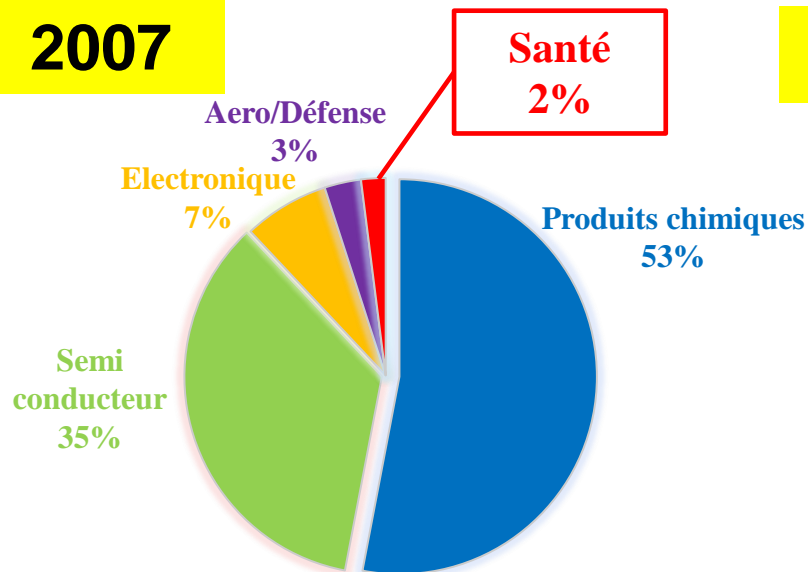
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Nanotechnologie: le MARCHÉ

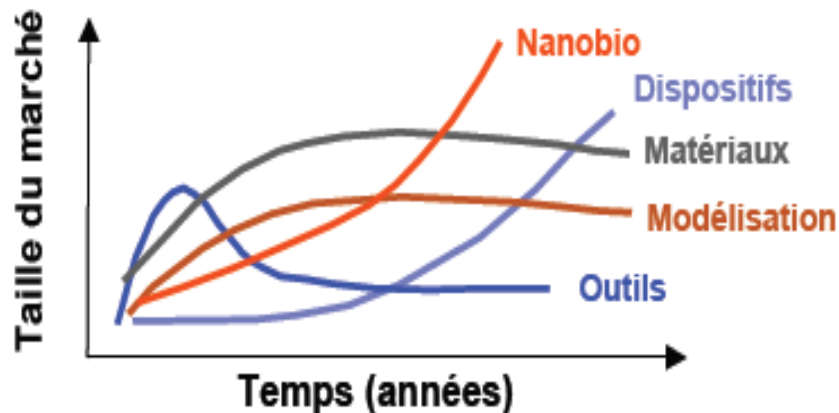
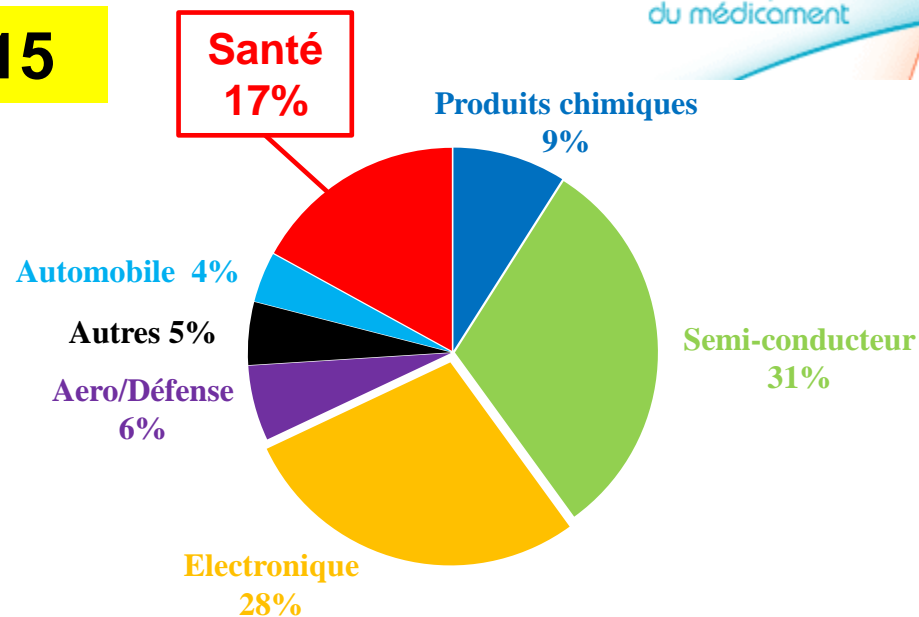
Source BIONEST Partners, Etude LEEM Mars 2009



2007

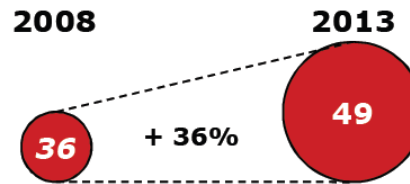
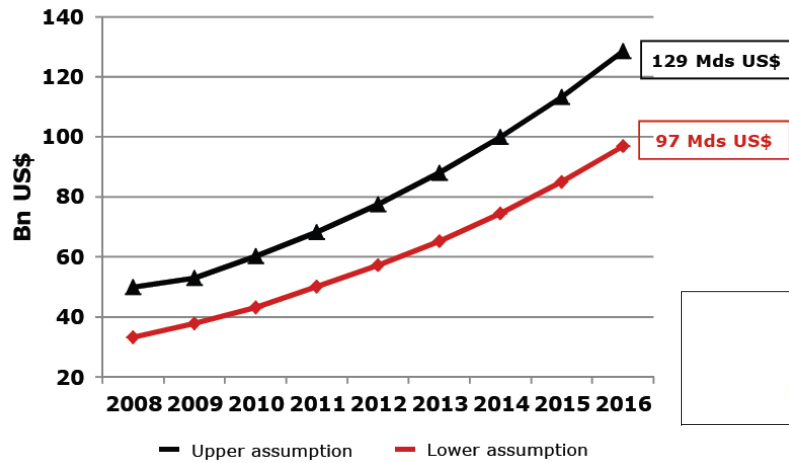


2015

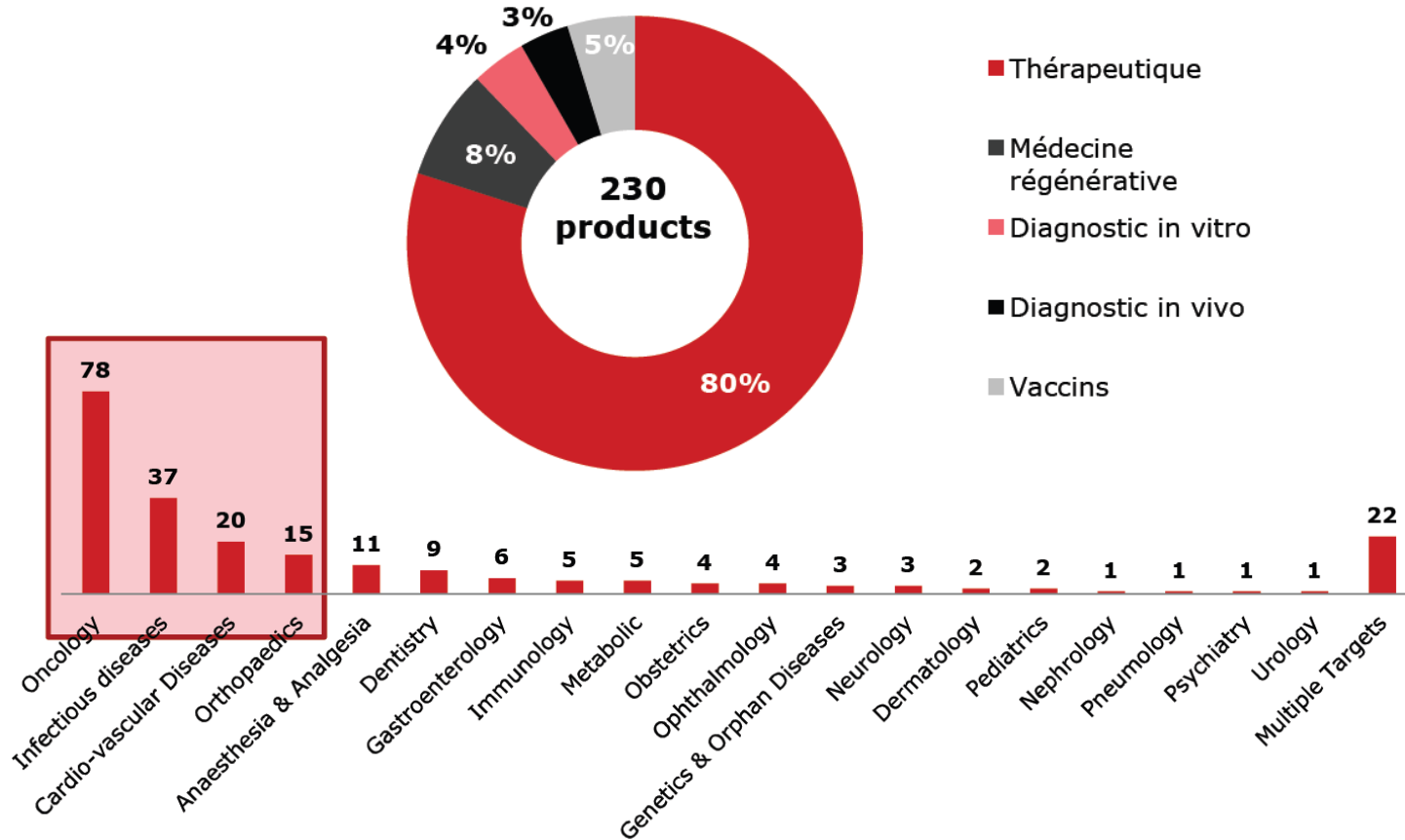


Nanomedicine Market growth

Number of marketed products



NANOMEDECINE :
des médicaments « miniatures » qui font le maximum !

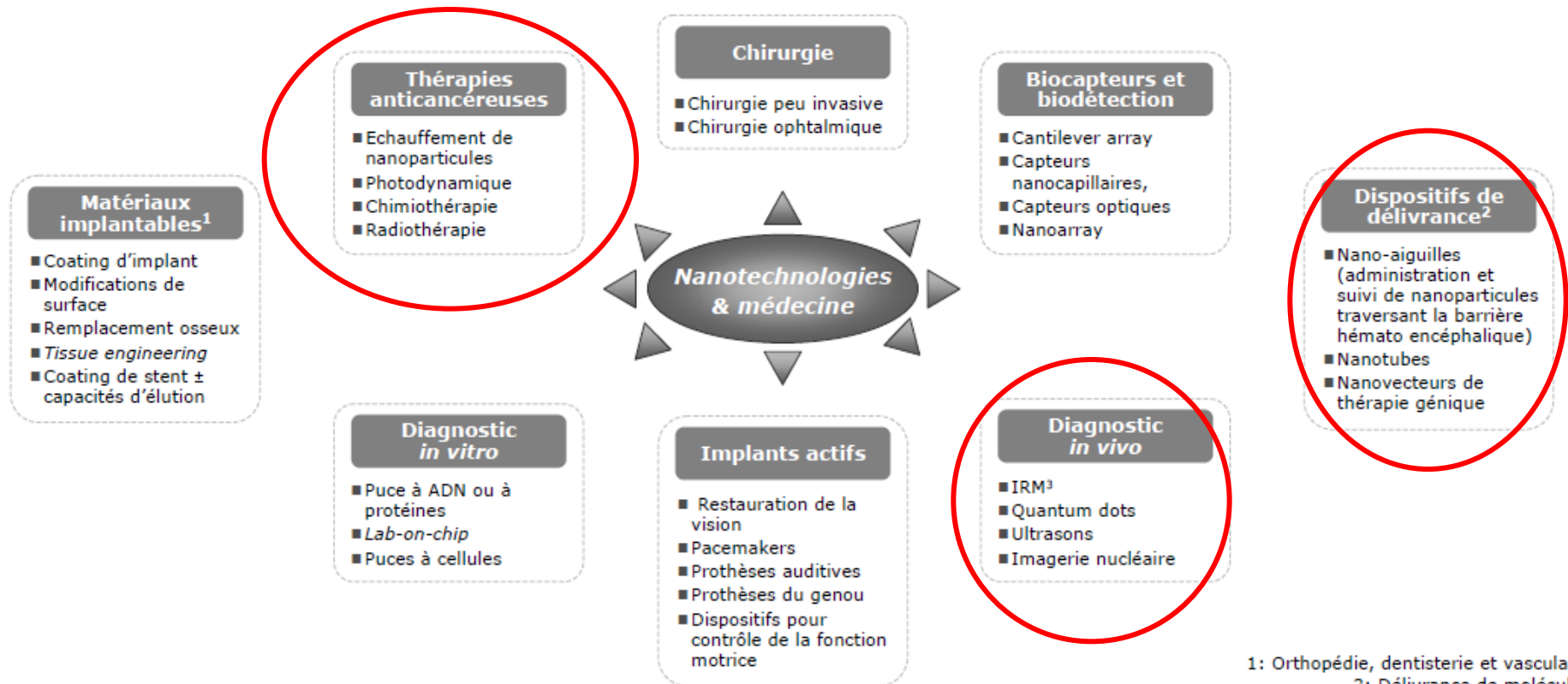


Nanotechnologie: les ENJEUX

Source BIONEST Partners, Etude LEEM Mars 2009



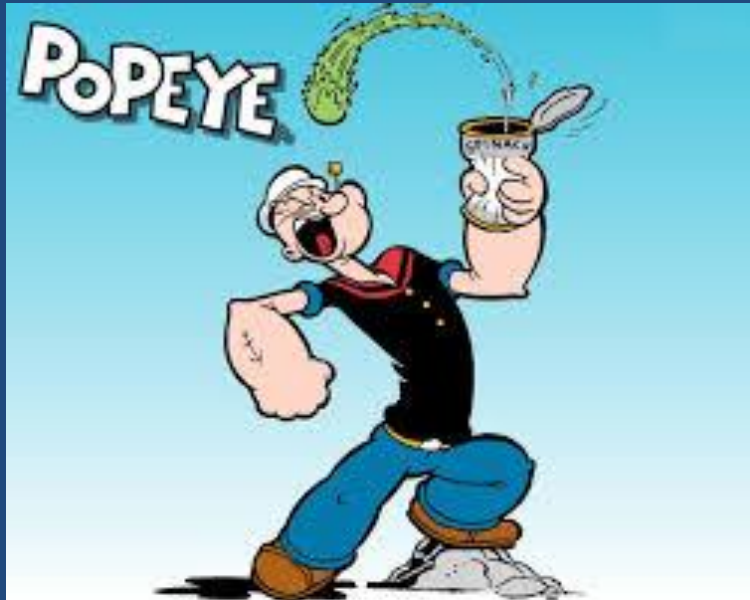
Champ d'application des nanotechnologies en santé



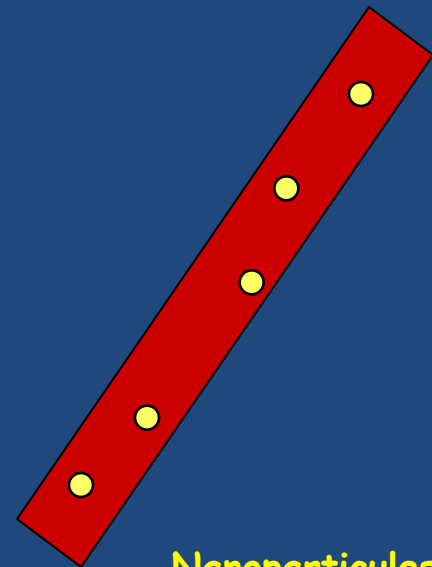
Source: analyse Bionest Partners

1: Orthopédie, dentisterie et vasculaire
2: Délivrance de molécules
3: Imagerie par résonance magnétique

L'exemple historique de nanopoudre utilisée en santé : les nanoparticules d'oxyde de fer

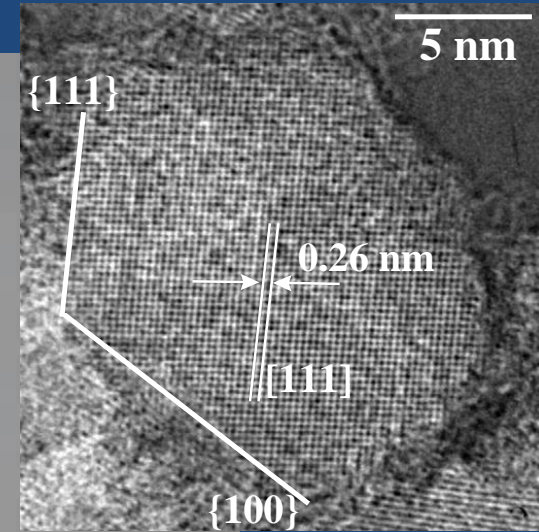
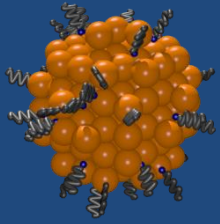


Capillaires sanguins



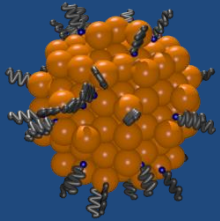
Nanoparticules

Nanoparticules d'oxydes de fer : applications en santé



SPIONS SuperParamagnetic Iron Oxide Nanoparticles

Vecteurs colloïdaux d'oxydes de fer : agents de contraste en IRM



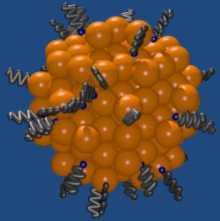
Guerbet
Bayer...



Détection des lésions du foie en IRM

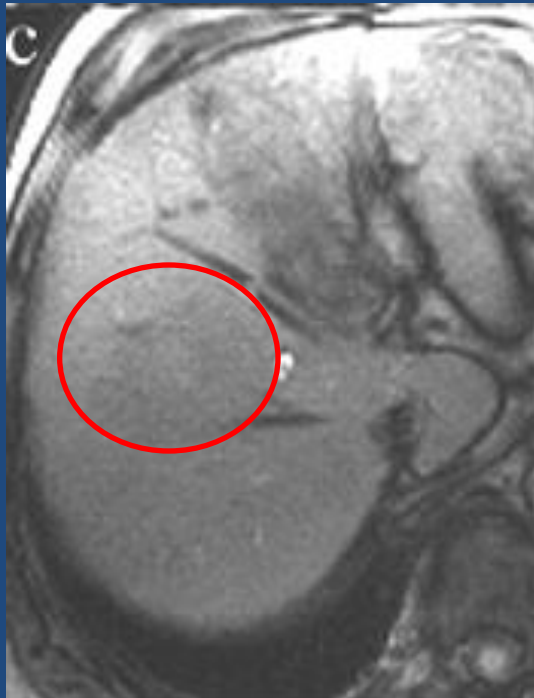
Repérage du tube digestif en IRM (délimitation des organes et localisation de lésions)

Nanoparticules d'oxydes de fer : applications en santé



- Agent de contraste en IRM (contraste négatif : T2)

Sans agent de contraste



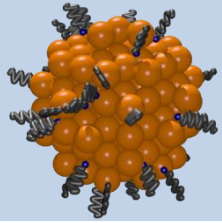
Avec agents de contraste



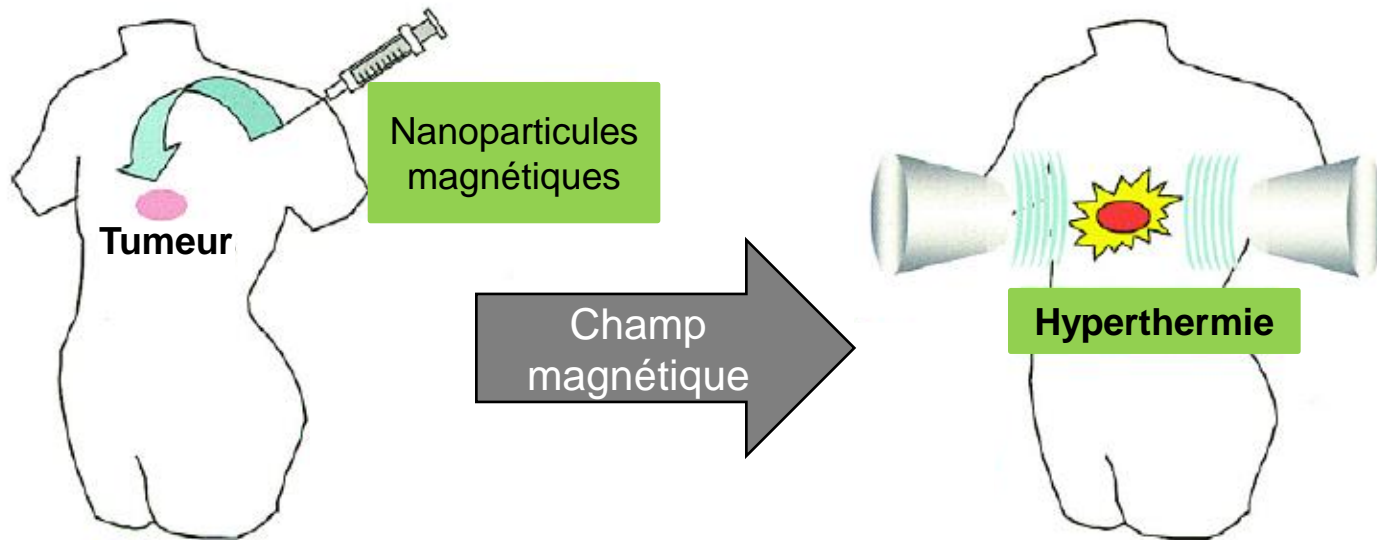
Tumeur dans le foie

SPIONs

SuperParamagnetic Iron Oxide Nanoparticles

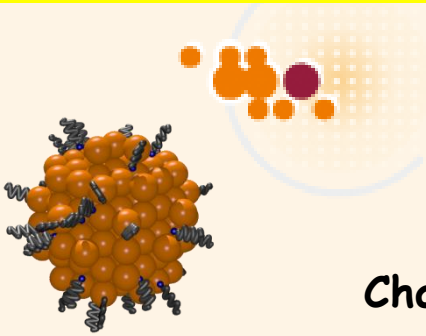


- Hyperthermie



Ito, A et al., *Journal of Bioscience and Bioengineering* 100(1), 2005 ; p 1-11.

Hyperthermie



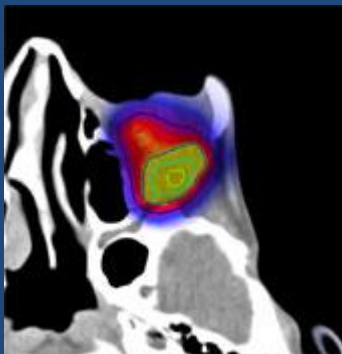
magforce®
NANOTECHNOLOGIES

Charité University Hospital Berlin



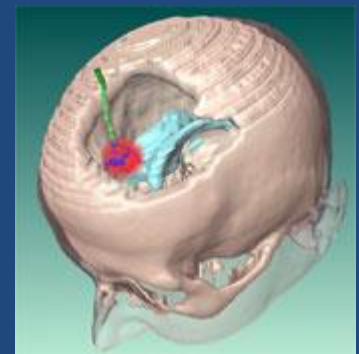
Dr. Andreas JORDAN

*"This approach, which involves the use of nanoparticles containing **iron oxide** and an **alternating current (AC) magnetic field**, allows almost any part of the human body to be thermally targeted with **millimeter precision** and **maximum tumor-cell specificity** at temperatures ranging from **43-46°C (hyperthermia)** to **47-70°C (thermoablation)**"*

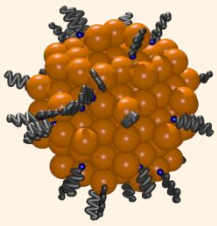


Tests cliniques
sur des dizaines de patients

18 kA/m @ 100 kHz

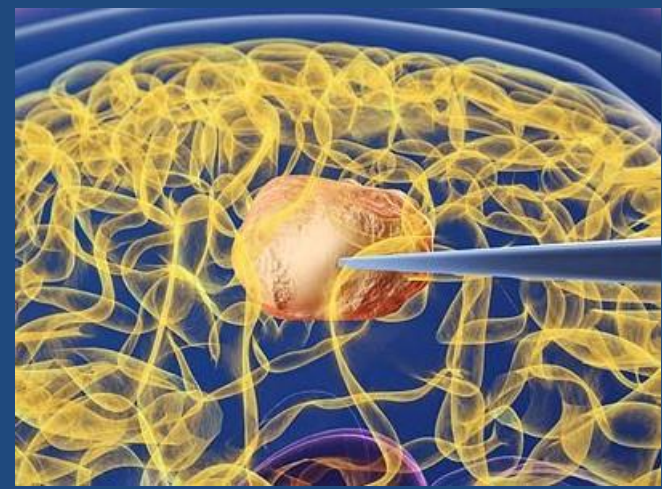


Hyperthermie



magforce®
NANOTECHNOLOGIES

Charité University Hospital Berlin



CLINICAL TRIALS / TUMOR TYPES	ADVANCEMENT		
	Pre-clinical	Phase I Feasibility study	Phase II Efficacy study
Glioblastoma multiforme >>	<div style="width: 100%; height: 10px; background-color: #c00000;"></div>	<div style="width: 100%; height: 10px; background-color: #c00000;"></div>	<div style="width: 100%; height: 10px; background-color: #c00000;"></div>
Prostate cancer >>	<div style="width: 100%; height: 10px; background-color: #c00000;"></div>	<div style="width: 100%; height: 10px; background-color: #c00000;"></div>	<div style="width: 20%; height: 10px; background-color: #c00000;"></div>
Local recurrences or residual tumors eg. cervical and prostate cancer, sarcomas >>	<div style="width: 100%; height: 10px; background-color: #c00000;"></div>	<div style="width: 100%; height: 10px; background-color: #c00000;"></div>	
Esophageal cancer >>	<div style="width: 100%; height: 10px; background-color: #c00000;"></div>	<div style="width: 100%; height: 10px; background-color: #c00000;"></div>	
Pancreatic cancer >>	<div style="width: 100%; height: 10px; background-color: #c00000;"></div>	<div style="width: 20%; height: 10px; background-color: #c00000;"></div>	
Breast cancer >>	<div style="width: 100%; height: 10px; background-color: #c00000;"></div>	<div style="width: 0%; height: 10px; background-color: #c00000;"></div>	

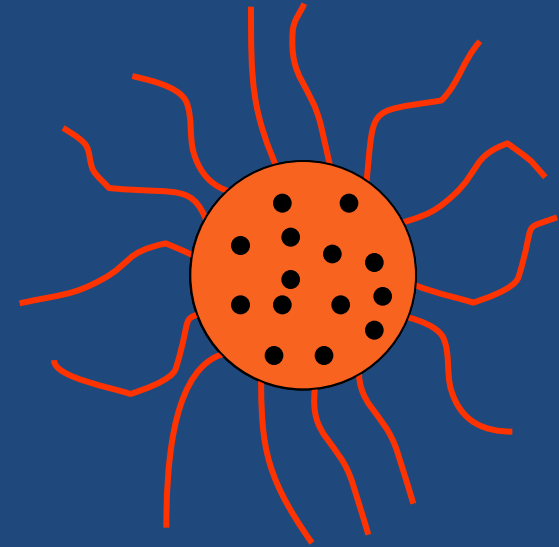
Comment cibler l'administration ?

Administration intraveineuse (IV)

- ciblage du foie
(nanoparticule "nue")

Vecteurs de première génération

ailleurs que dans le foie
(avec PEG ou dextran)



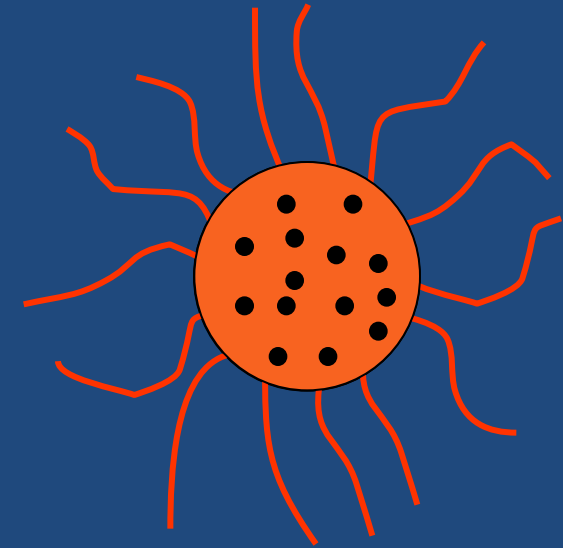
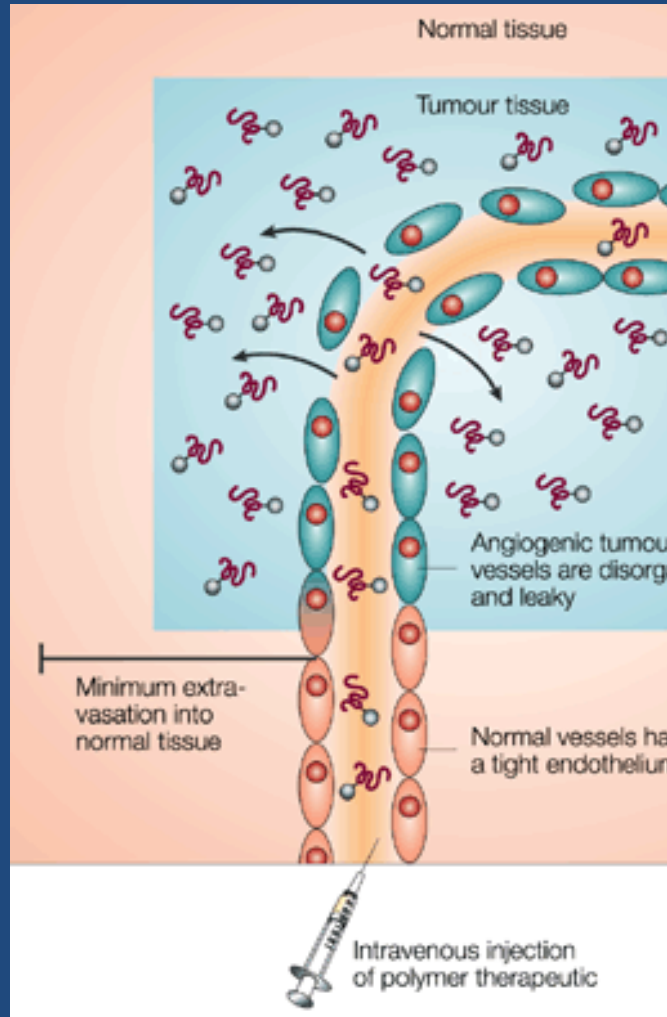
Pour être furtives, la surface des nanoparticules :

- Hydrophile (P.G. de Gennes, 1991) :
les polymères hydrophiles ne fixent pas les protéines)
- Electriquement neutre à pH=7
- Aussi petites que possible

Vecteurs "furtifs"
dits de deuxième génération
recouverts de PEG ou de dextran

Ciblage passif

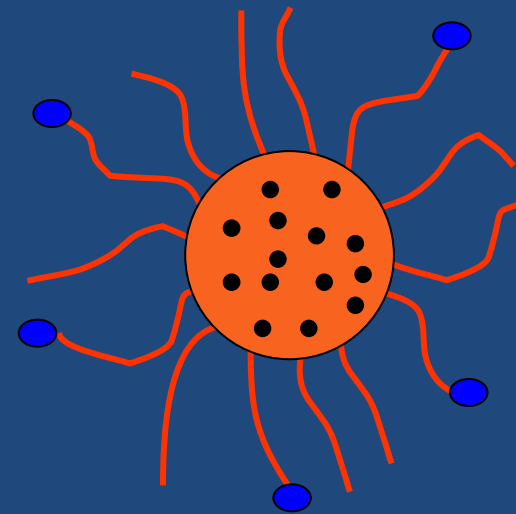
Enhanced Permeability and Retention (EPR) effect



Vecteurs "furtifs"
dits de **deuxième génération**
recouverts de PEG ou de dextran

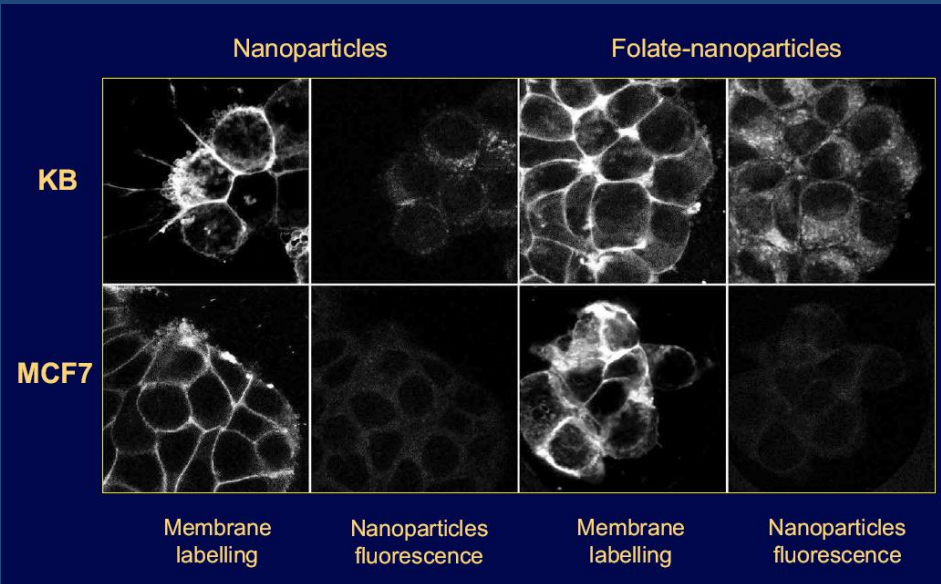
Ciblage actif

Vecteurs de troisième génération

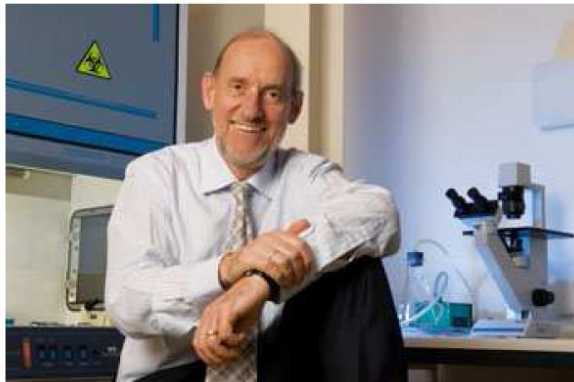


acide folique

Les cellules cancéreuses
ont des récepteurs folates

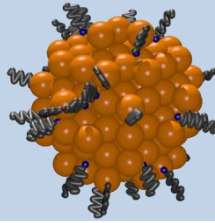


Patrick Couvreur, Biopharmacien
Châtenay-Malabry



SPIONs

SuperParamagnetic Iron Oxide Nanoparticles

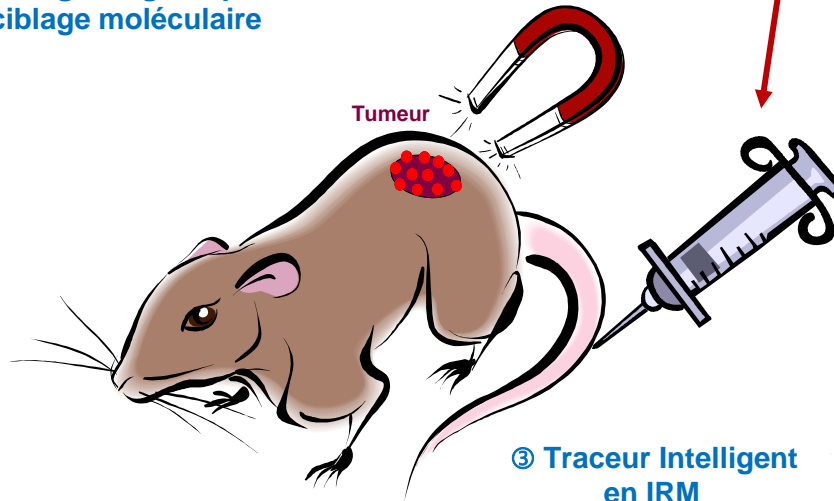


Des nanograins pour vaincre le cancer ?

Des nanohybrides multifonctionnels

- ① Nanovectorisation (anticancéreux)
- ciblage magnétique
- ciblage moléculaire

Champ magnétique



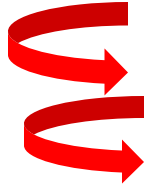
- ② Agent d'hyperthermie magnétique
(cellules cancéreuses détruites à 43-46°C)

Théranostic

- ③ Traceur Intelligent en IRM
(Imagerie par Résonance Magnétique)



+ 19 %



167 clinical trials with

nanoparticles

(June 2014)

+ 19 %

198 clinical trials with

nanoparticles

(June 2015)

236 clinical trials with

nanoparticles

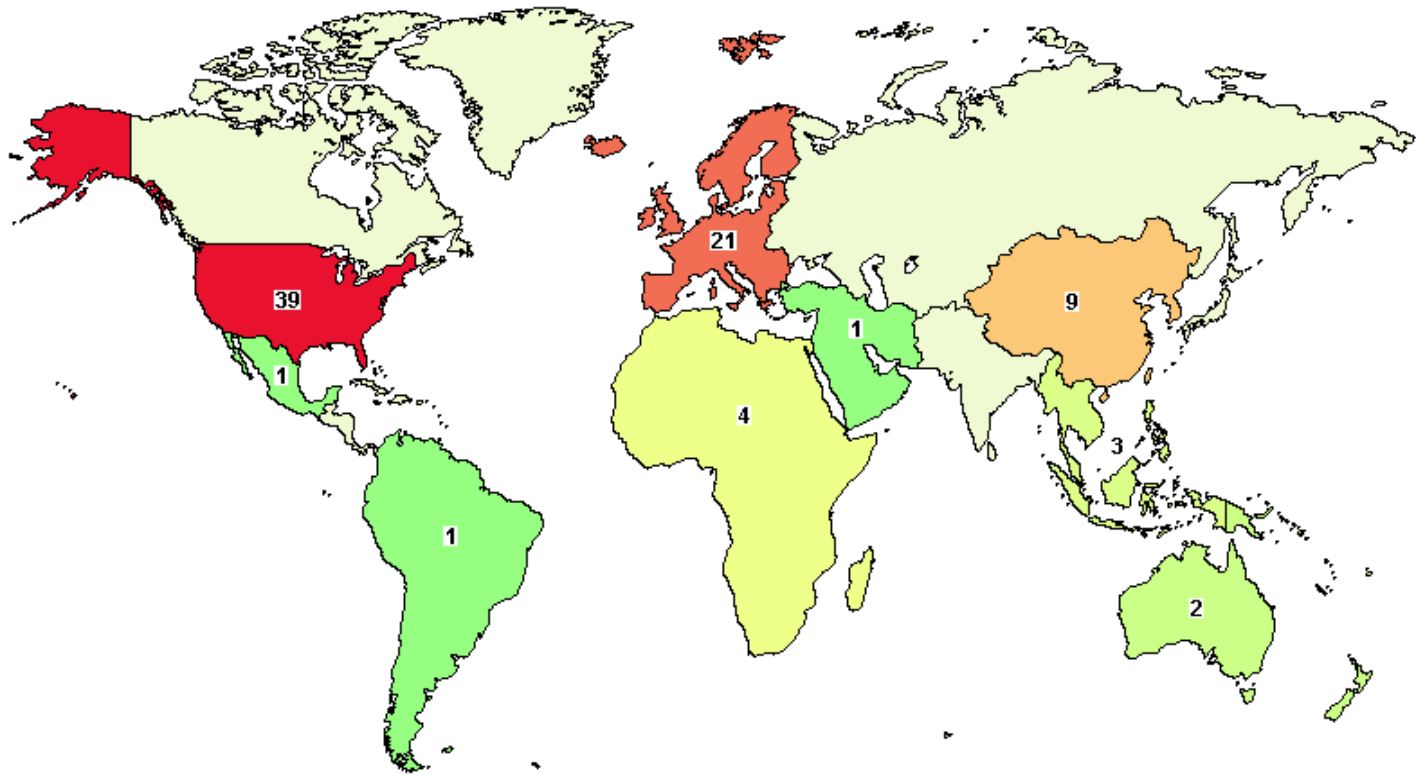
(June 2016)

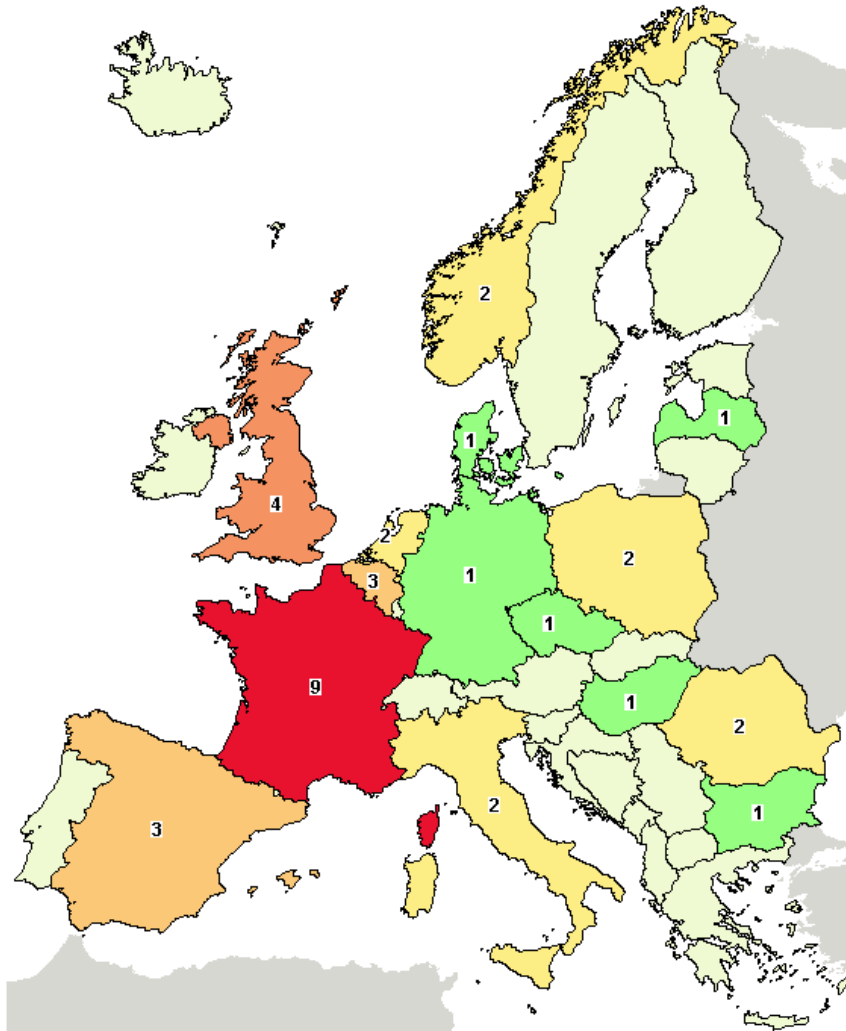
289 clinical trials with

nanoparticles

(01/03/2018)

66 recruiting





1. Presence of Nanoparticles in the Amniotic Fluid
2. Radiosensitization of Multiple Brain Metastases Using AGuIX Gadolinium Based Nanoparticles
3. Exhaled Breath Olfactory Signature of Pulmonary Arterial Hypertension
4. Clinical and Genetic Study of Familial Sarcoidosis (SARCFAM)
5. Nanoparticles Emitted by Aircraft Engines, Impact on the Respiratory Function (Air France Company's Employees Working in the Marseilles and Paris Airports)
6. Evolution of Albumin on AOA1 Patients Supplemented With Coenzyme Q10
7. NBTXR3 Crystalline Nanoparticles and Radiation Therapy in Treating Patients With Locally Advanced Squamous Cell Carcinoma of the Oral Cavity or Oropharynx
8. NBTXR3 Crystalline Nanoparticles and Stereotactic Body Radiation Therapy in the Treatment of Liver Cancers
9. NBTXR3 Crystalline Nanoparticles and Radiation Therapy in Two Arms With Soft Tissue Sarcoma of the Extremity and Trunk

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PET/MRI integrated scanner



Equipex IMAPPI : Integrated Magnetic resonance And Positron emission tomography in Preclinical Imaging

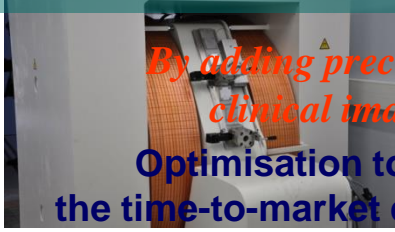
MR SOLUTIONS

**Academic research
3MIM Project (trilateral**

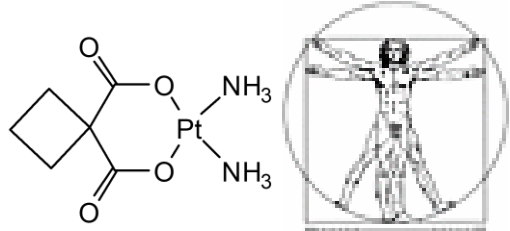


Cyclotron

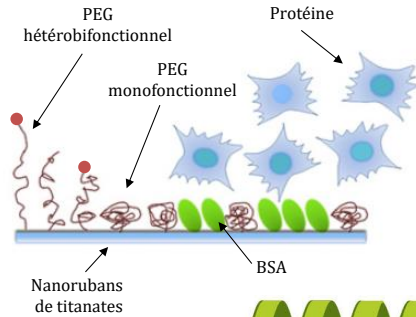
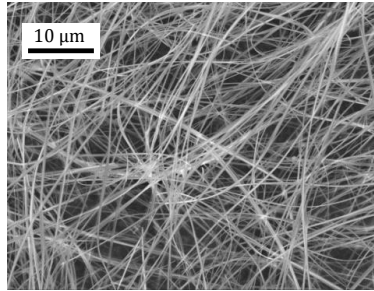
PHARMIMAGE® = « Pharmacology and Imaging »



By adding preclinical and clinical imaging =
Optimisation to reduce the time-to-market development of new pharma-drugs



Titanate nanoribbons: TiONrs



Regenerative Medicine



Perspectives

Ingénierie tissulaire



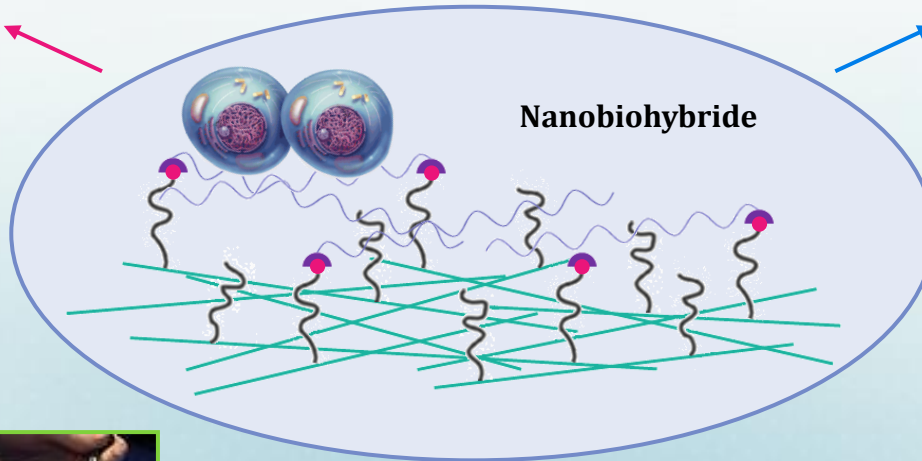
Hémostase



Ulcère du diabétique



Nanobiohybride



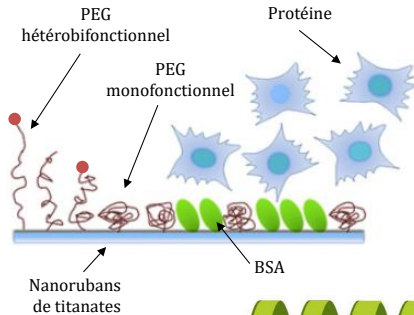
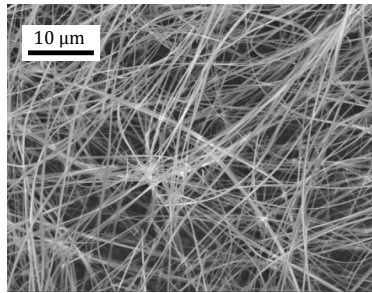
Cardiologie



Odontologie



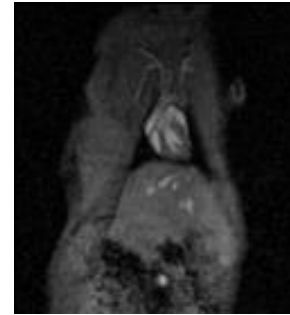
Titanate nanoribbons: TiONrs



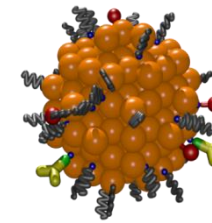
Regenerative Medicine



SuperParamagnetic Iron Oxide Nanoparticles (SPIONs)



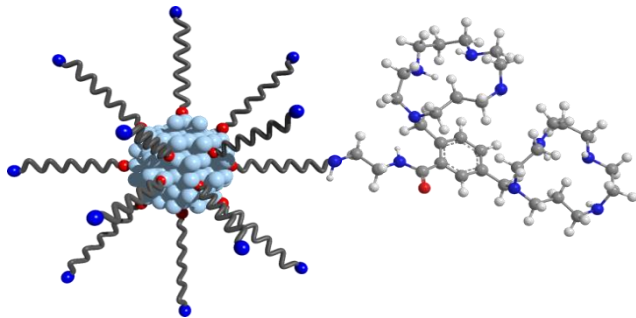
Mouse (heart)



SPIONs as new multimodal imaging probes

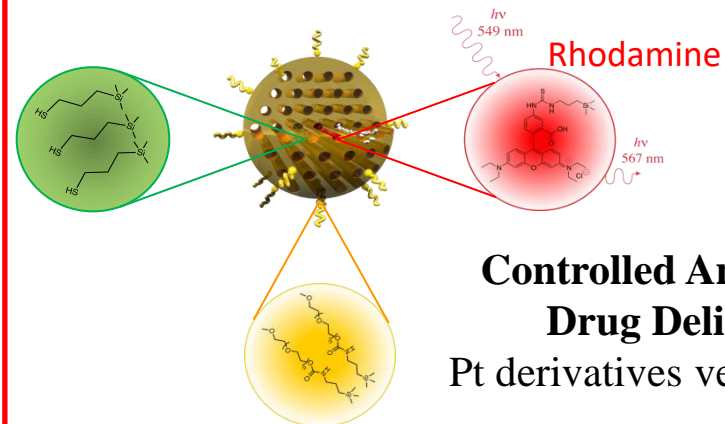
Bimodal contrast agent
Biodistribution

Tantalum Oxide Nanoparticles



- Theranostic agent : CT contrast agent
- Nanovectorization of AMD3100 (CXCR4+)

Mesoporous Silica Nanoparticles (MSNs)



Controlled Anticancer
Drug Delivery:
Pt derivatives vectorization



Different medical imaging techniques: coupled imaging techniques

MRI/PET

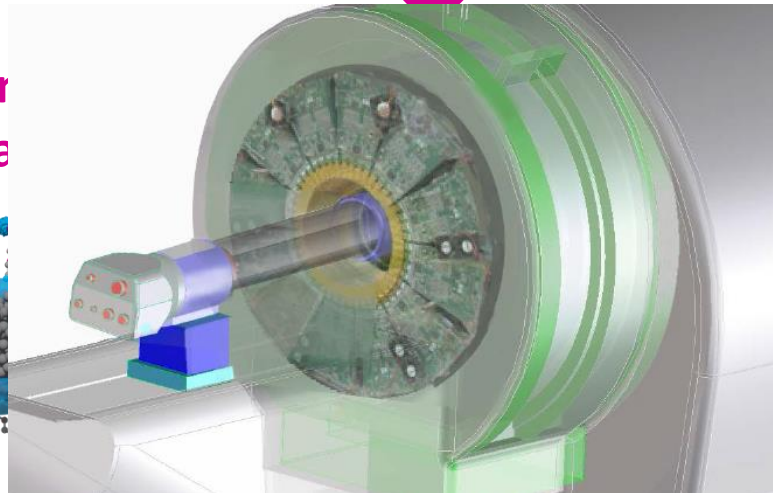
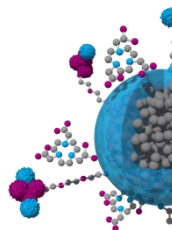
A technology combining MRI and PET detection techniques in the same imaging camera is currently built up in Dijon (Bourgogne, France) *for early detection of tumors and diagnosis of cardiac dysfunctions*



IMAPPI (*Integrated Magnetic resonance And Positron emission tomography in Preclinical Imaging*)
The IMAPPI Project: An example of successful public-private R&D partnership



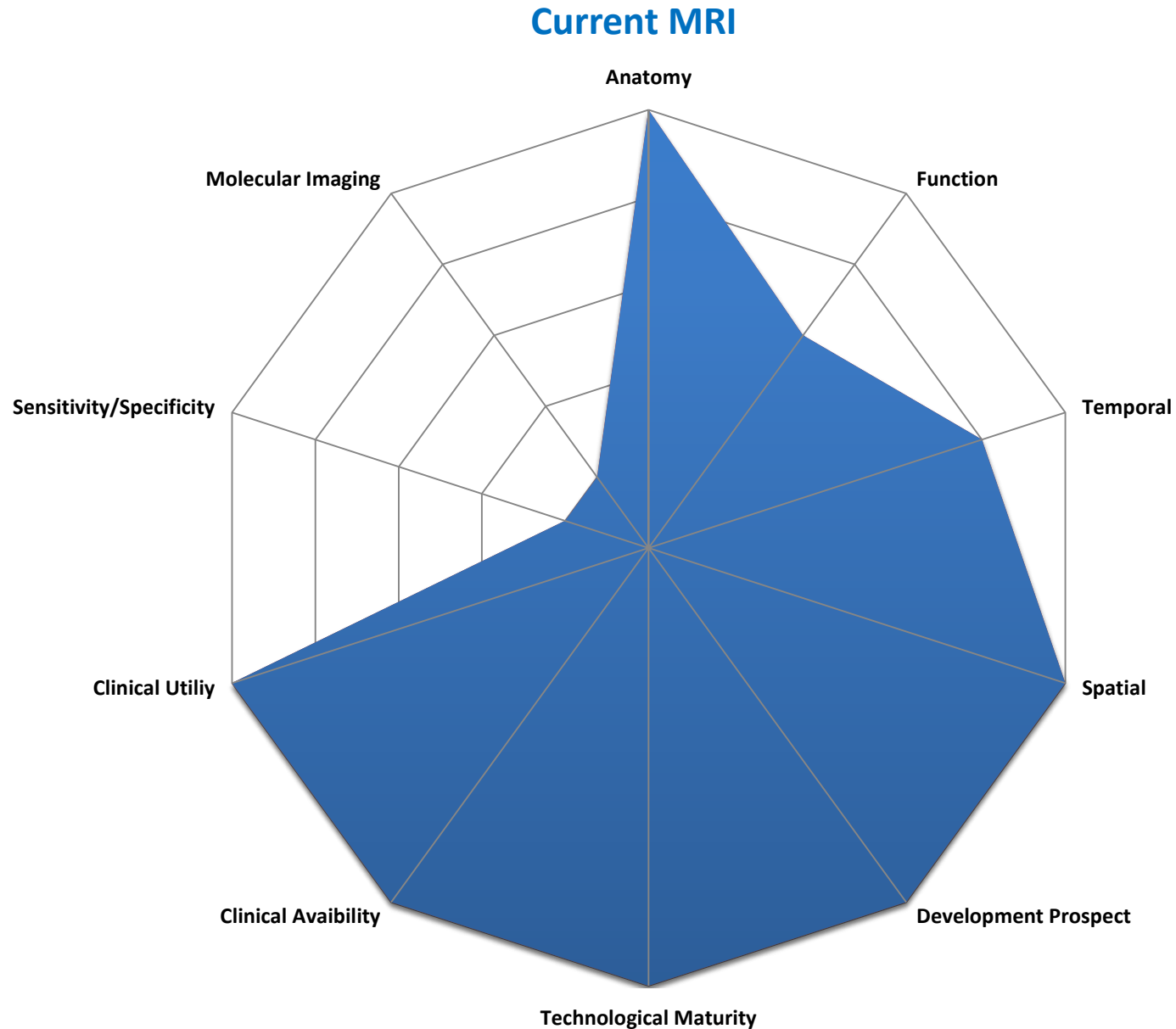
Bimodal contrast agents based on nanoparticles



articles?

contrast agents (theranostic)
high signal-to-background ratio
long residence time

Different medical imaging techniques : coupled imaging techniques

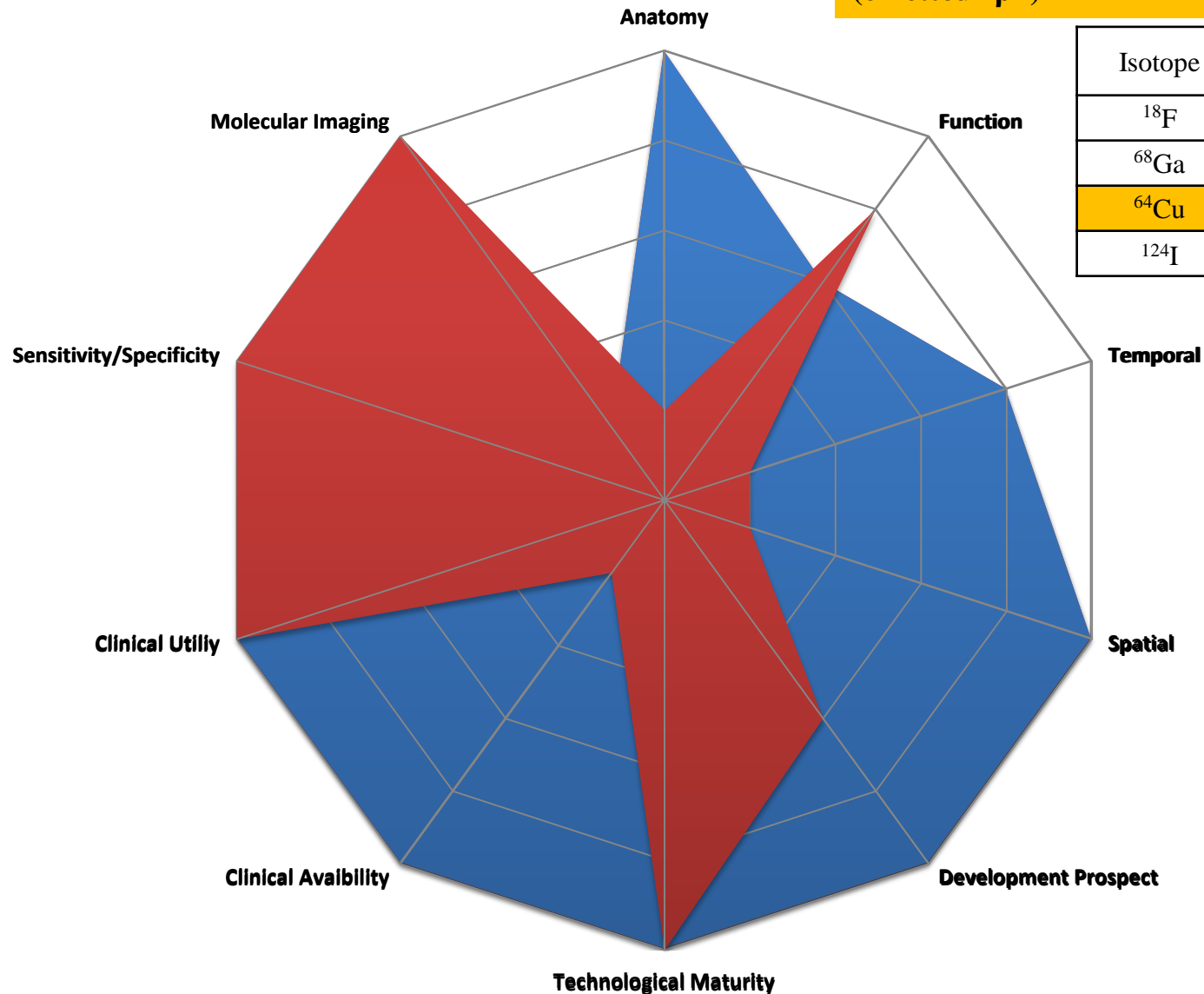


From N. John Shah, Institute of Neuroscience and Medicine, Jülich, Germany

Different medical imaging techniques : coupled imaging techniques

Current PET

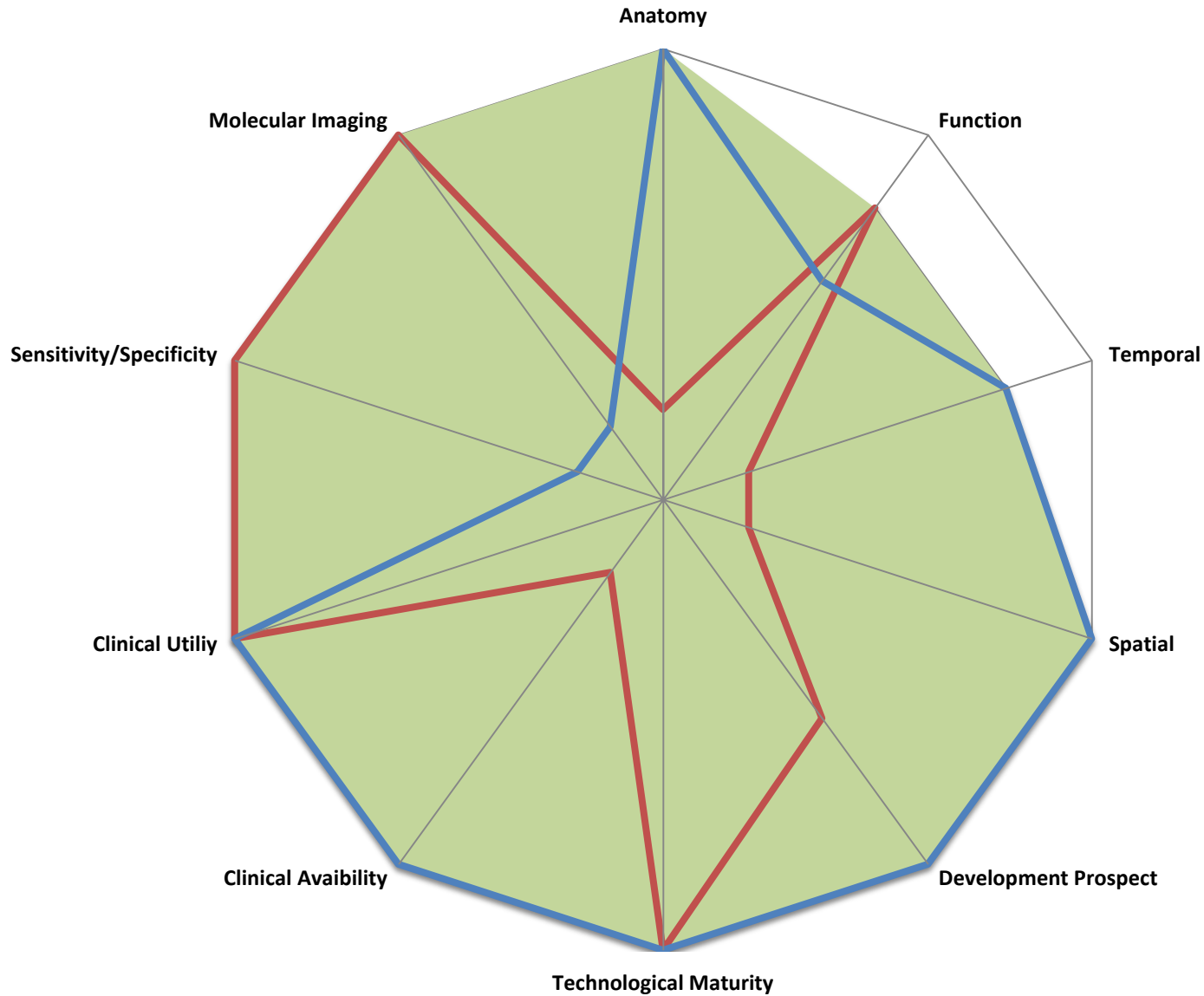
PET : Tomographie par émission de positons (émetteur β^+)



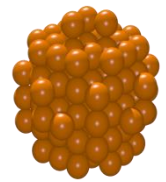
Isotope	Temps de demi-vie (heures)
^{18}F	2
^{68}Ga	1
^{64}Cu	12,7
^{124}I	100

Different medical imaging techniques: coupled imaging techniques

Hybrid MRI-PET built up in Dijon



Synthèse des SPIONs

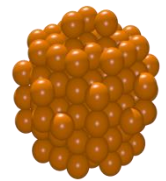


Chimie douce :
Synthèses batch
classiques
de coprécipitation



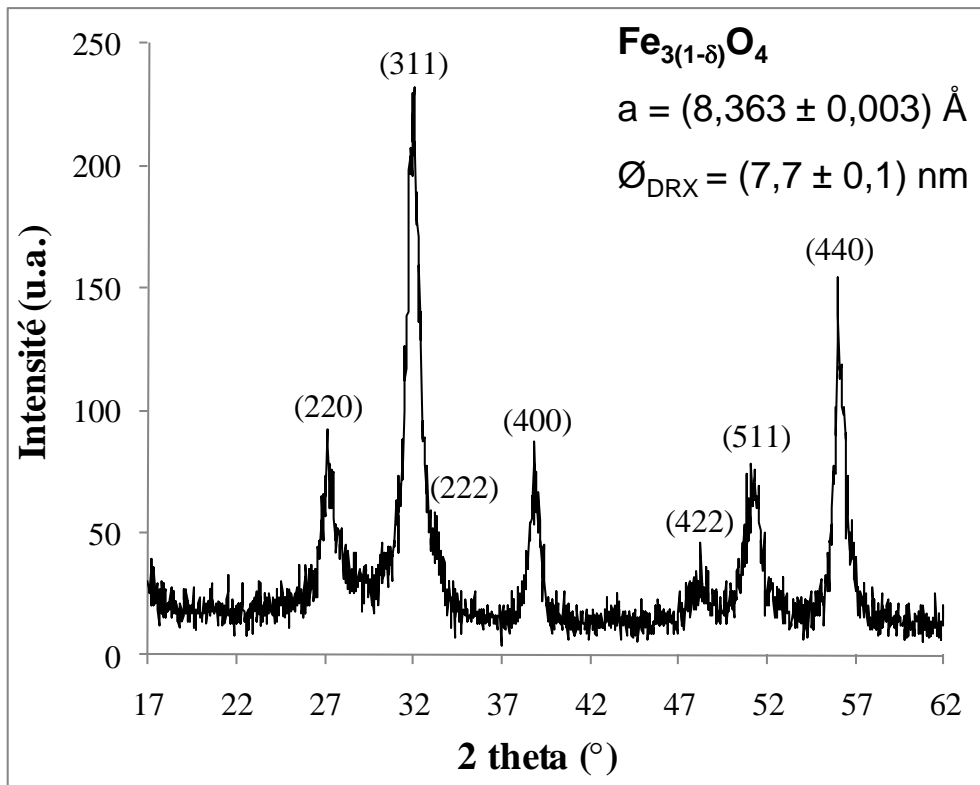
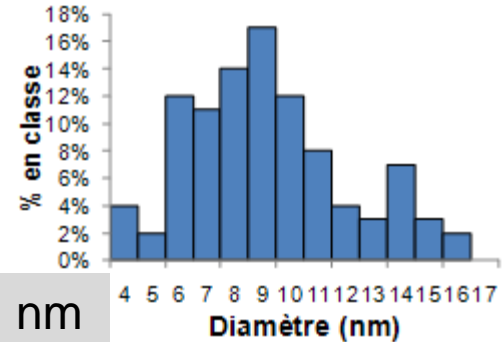
- Synthèse hydrothermale en continu :**
1 Contrôle accru de la distribution de taille
- Grande versatilité et forte productivité
 - Coprécipitation + greffage en une étape
 - Précipitation à l'incubation
 - Hydrothermal à l'incubation
 - Suspension (pH = 3) → post-fonctionnalisation

Synthèse batch de $\text{Fe}_{3(1-\delta)}\text{O}_4$

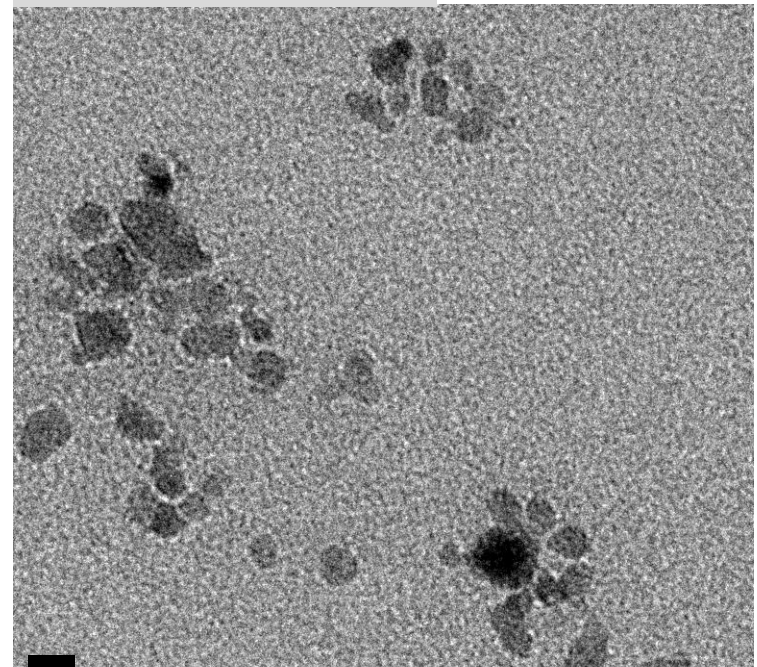


pH = 3

- $a = 8,363 \text{ \AA}$: composition entre la magnétite Fe_3O_4 ($a = 8,396 \text{ \AA}$) et la maghémite $\gamma\text{-Fe}_2\text{O}_3$ ($a = 8,345 \text{ \AA}$).
- Tailles DRX des cristallites : $7,7 \pm 0,1 \text{ nm}$
- Diamètre hydrodynamique (d_H) = $23 \pm 1 \text{ nm}$
- Surface spécifique $110 \pm 1 \text{ m}^2/\text{g}$
- $7 \text{ OH}/\text{nm}^2$ (ATG)

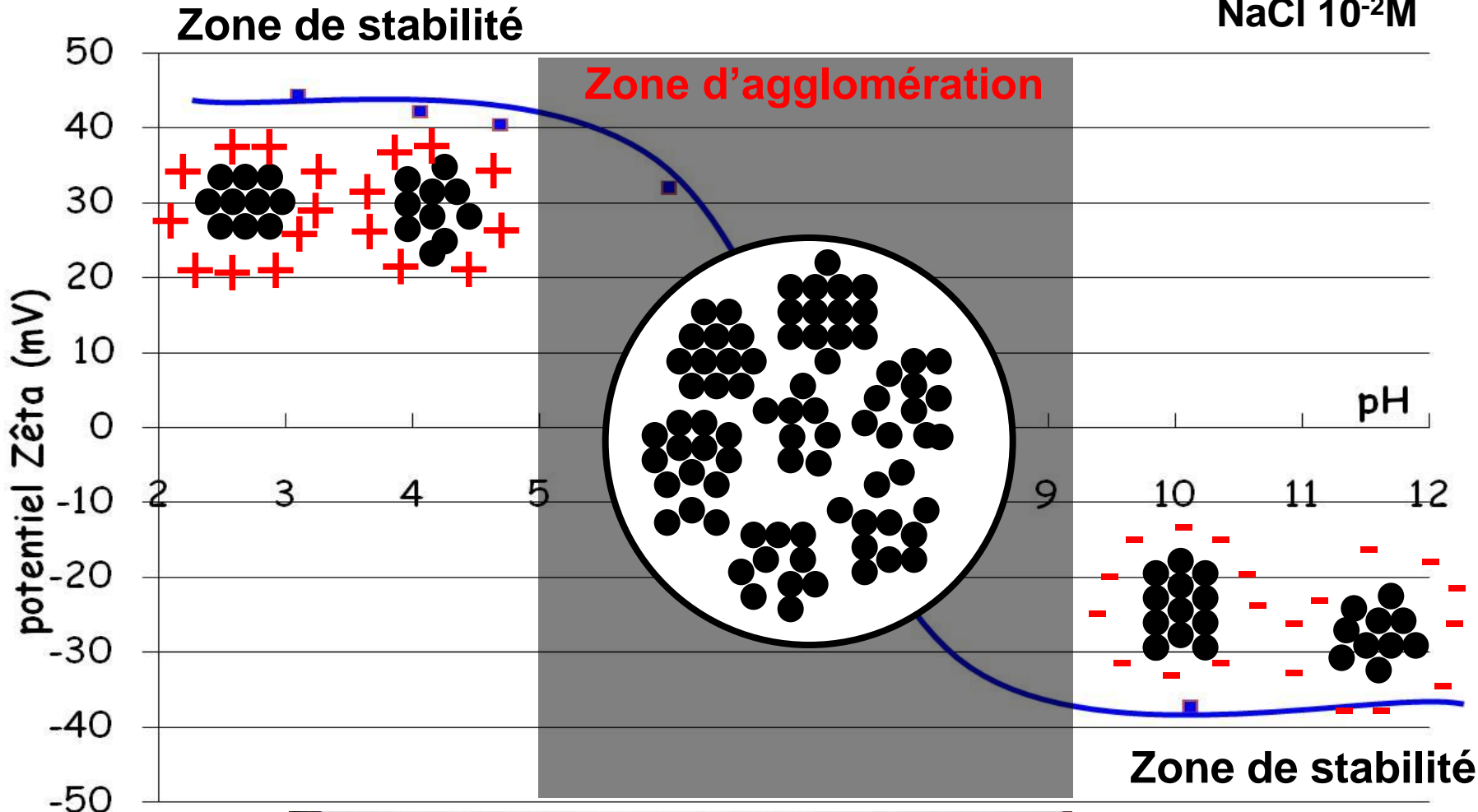


$\varnothing_{\text{MET}} = (9 \pm 2) \text{ nm}$



Pourquoi modifier la surface ?

Fe_3O_4
NaCl 10^{-2}M



Les choix de fonctionnalisation

Instabilité en conditions physiologiques



Fonctionnalisation nécessaire

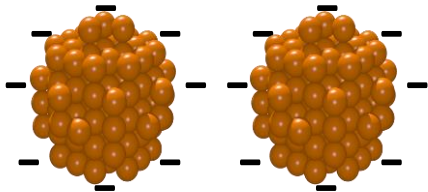


Agents électrostatiques



DMSA

Le DiMercaptoSuccinic Acid



Les choix de fonctionnalisation

Instabilité en conditions physiologiques



Fonctionnalisation nécessaire

Agents électrostatiques

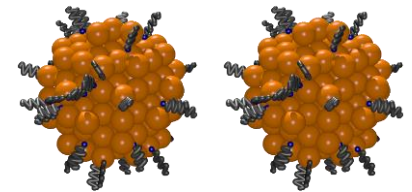
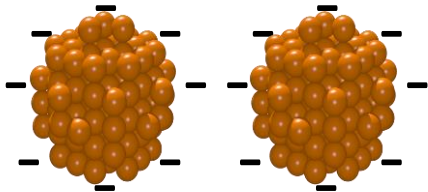


DMSA

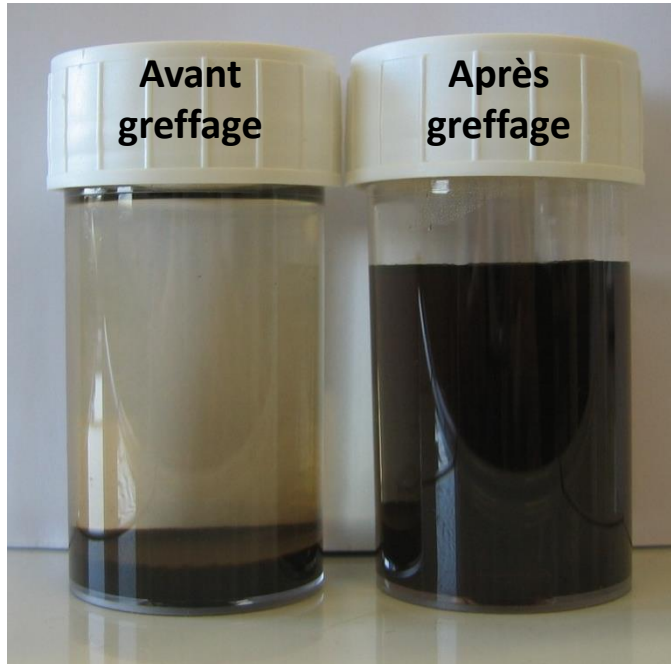
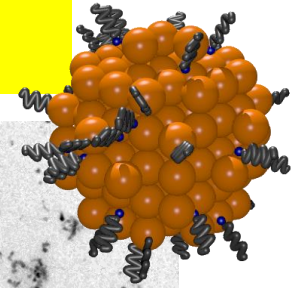
Agents stériques



méthoxy-PEG silanisés

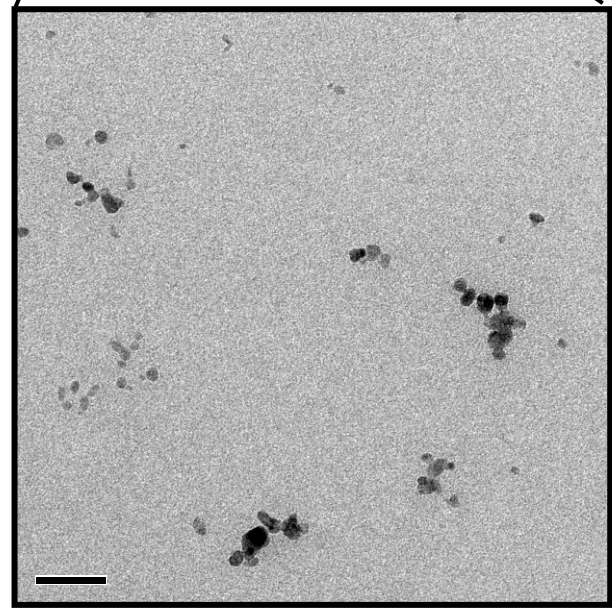
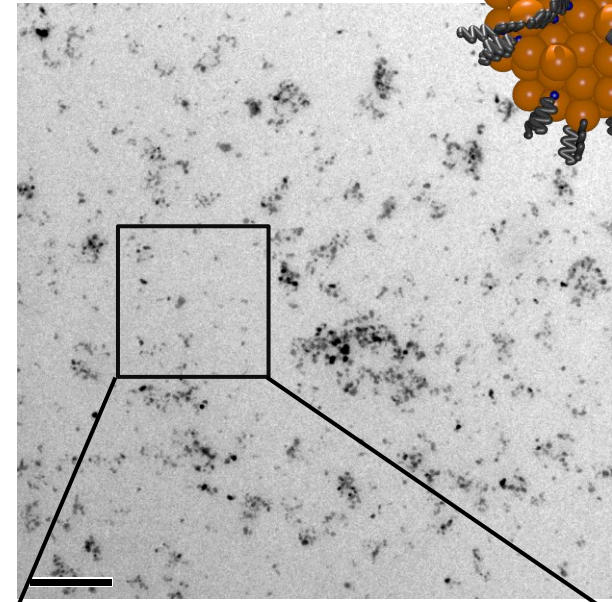


Stabilisation stérique : mPEG₂₀₀₀-Si

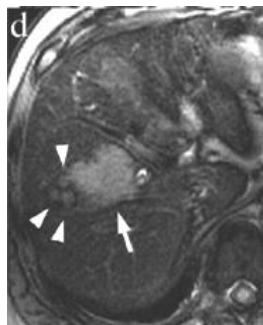


pH = 7,4 ; NaCl = 0,15 M

- Nanoparticules pegylées stables et redispersables en milieu physiologique

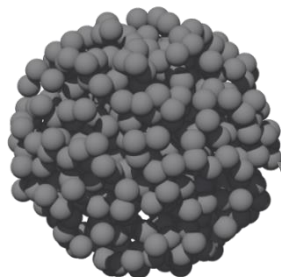


Development of bimodal contrast agents based on nanoparticles (MRI/PET)



Magnetic core

Magnetite phase
 Fe_3O_4



Size under 20 nm

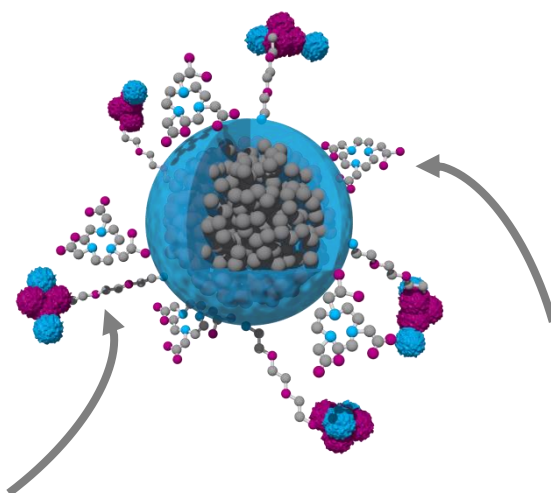
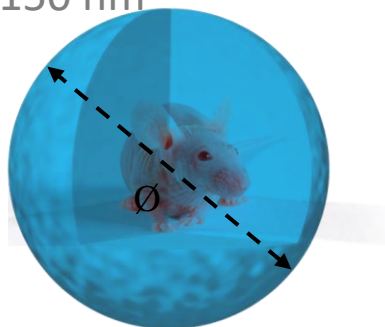


MRI

SPIONs
Iron oxide core
T₂ contrast agent

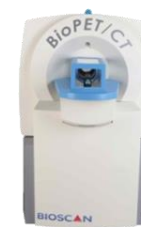
PEG grafting:
Stability of NP suspension
Biocompatibility / Stealth

Hydrodynamic size
between 10-150 nm

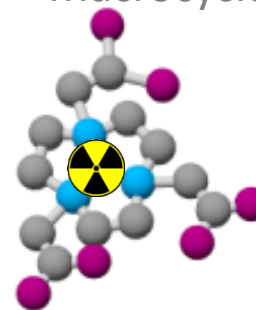


Radioelement	$t_{1/2}$ (h)
^{18}F	2
^{68}Ga	1
^{64}Cu	12.7
^{124}I	100

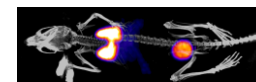
PET



Macrocycle



Chelating agent

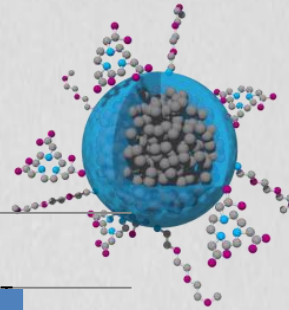
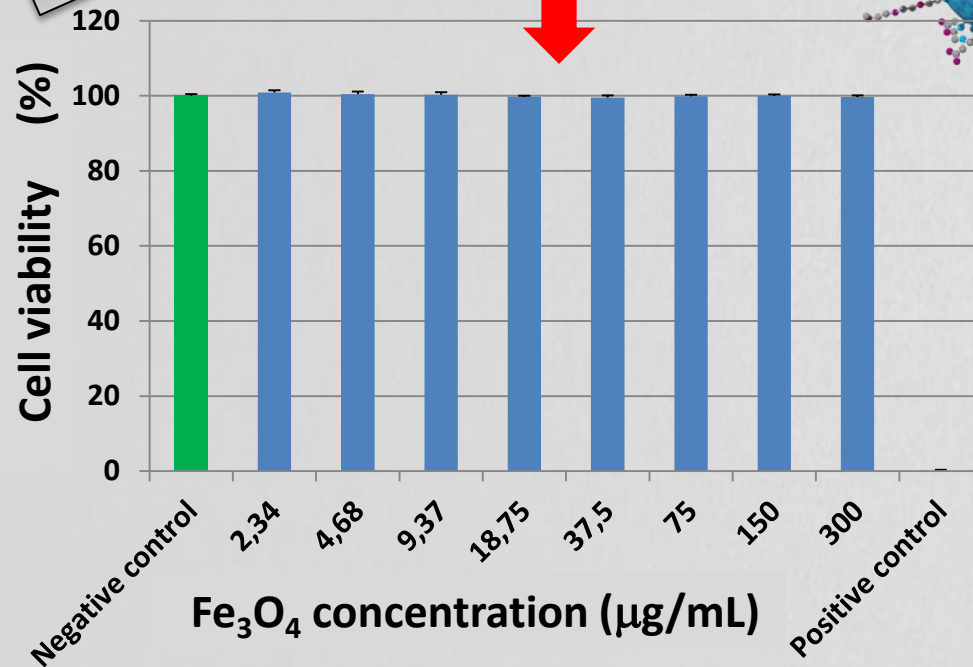


Avoid opsonization (→ stealth)

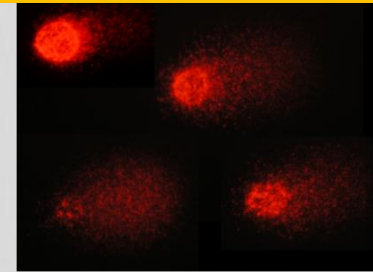
In vitro evaluation: cytotoxicity of the nanohybrid SPIONs-LDOPA-PEG₂₀₀₀-MANOTA

Alamar Blue

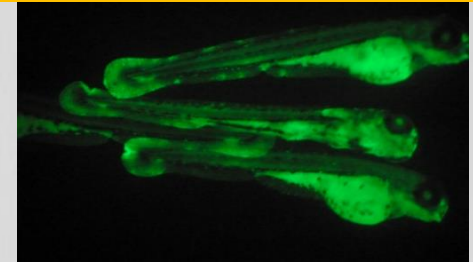
Injected dose
(in vivo experiments)



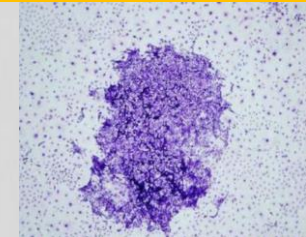
Genotoxicity (Comet assay)



Ecotoxicity (Zebrafish model)



Carcinogenicity
(Cell transformation assay)



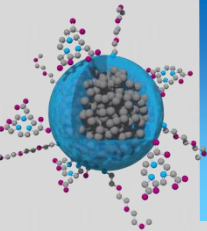
No cytotoxicity, no dose effect

HepG2

(human liver carcinoma cell line)

T- : Without nanoparticles

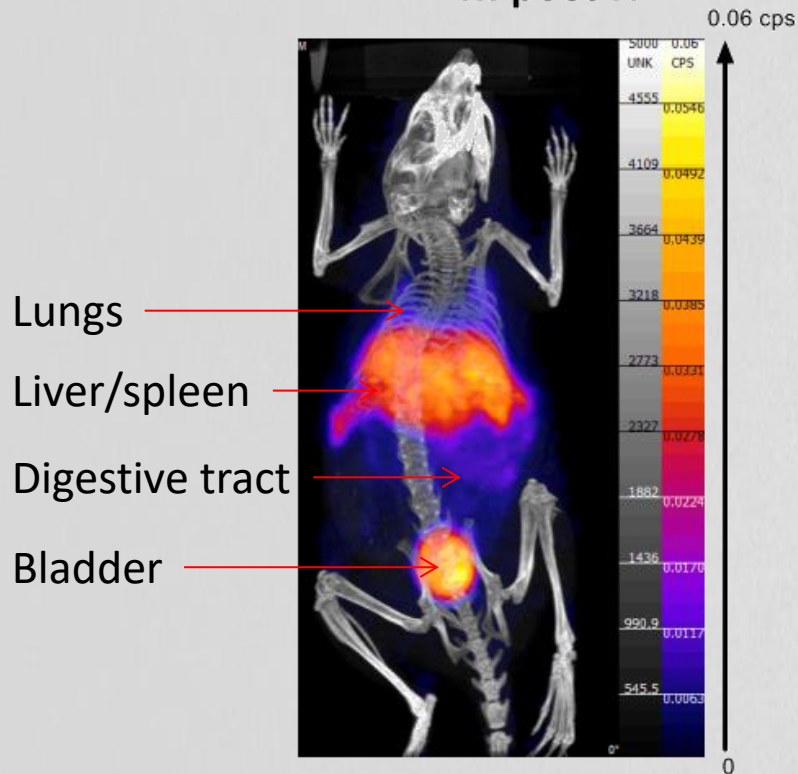
T+ : Dodecylsulfate (3%)



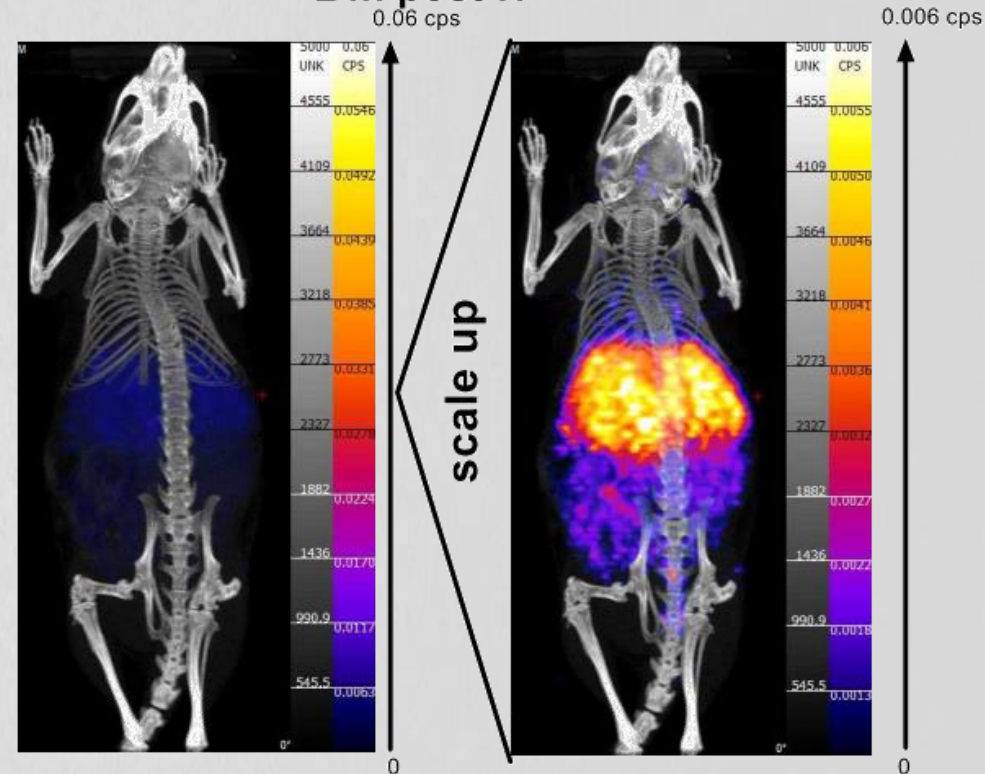
In vivo evaluation: TEP/CT biodistribution

t_0 : 2,5-3 MBq/mouse

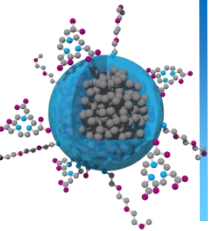
1h post-iv



24h post-iv



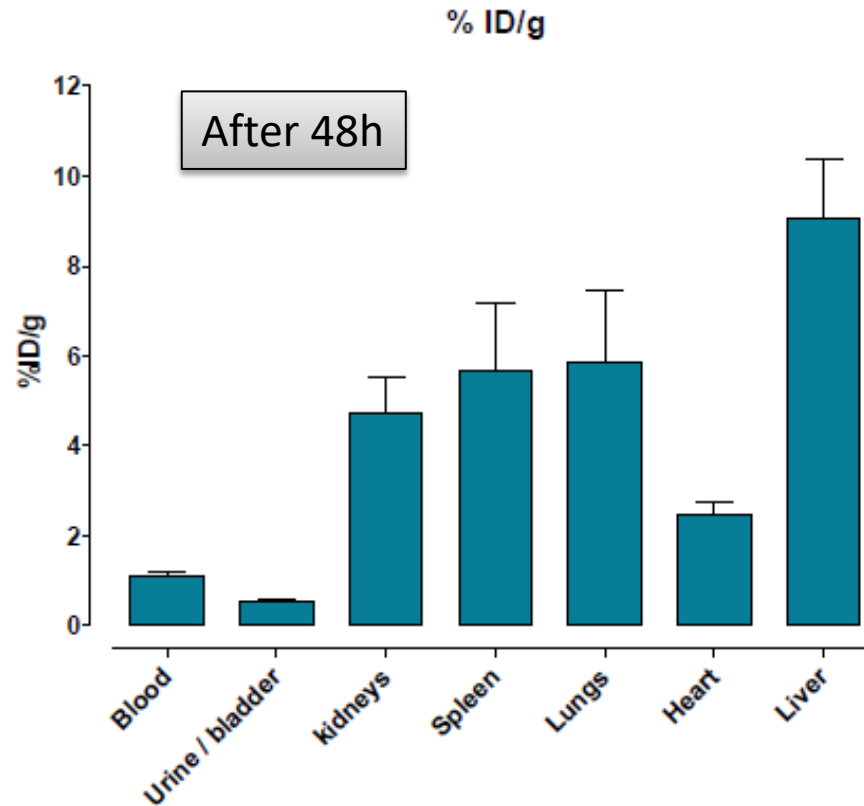
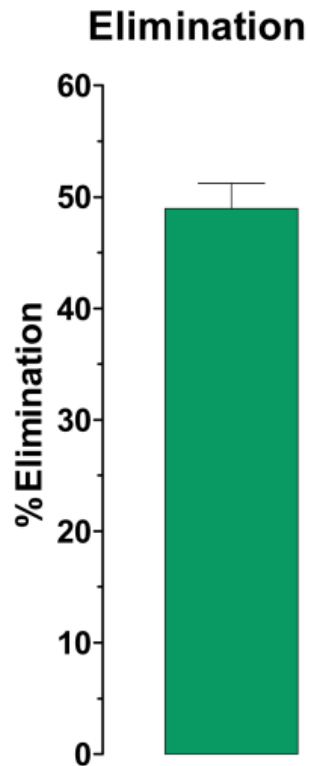
- 1h post-iv, radioactivity was mainly localized in liver, spleen and bladder. Pulmonary and digestive activity could also be observed
- 24h post-injection time, liver activity could still be observed
- A slighter signal could be detected in heart, digestive tract and spleen



In vivo evaluation: TEP/CT biodistribution

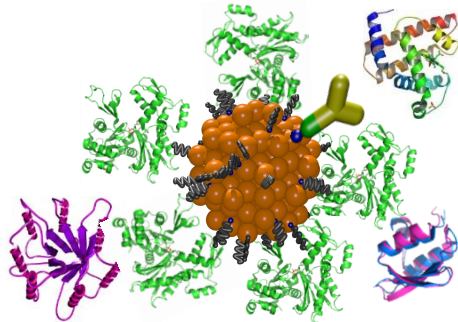
Gamma counting

T_0 : injection time (2.5-3 MBq / mouse)



- Elimination rate, 48h after injection is about 50 % of injected dose
- 48h post injection, there was still an important liver activity (12 %ID)
- Some traces of activity could be also observed in blood, kidneys, bladder, spleen, heart and lungs

Study, understand and control the protein/nanomaterials interactions

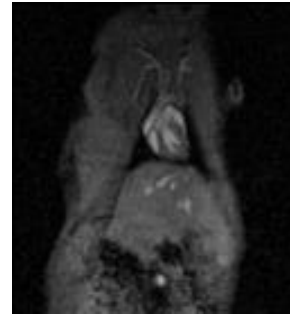


More circulating and more specific nanodrugs

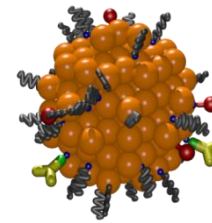
Controlled → specific uptake



SuperParamagnetic Iron Oxide Nanoparticles (SPIONs)



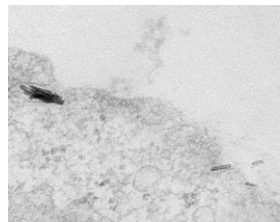
Mouse (heart)



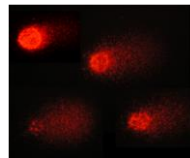
SPIONs as new multimodal imaging probes

Bimodal contrast agent
Biodistribution

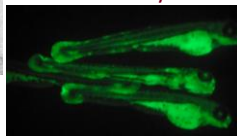
Original evaluation of the toxicity/safety of nanoparticles



Internalization (TEM)



Genotoxicity



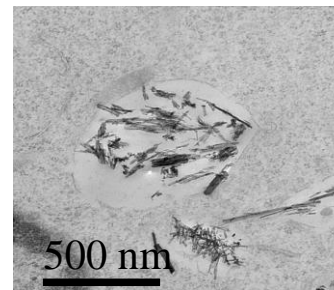
Zebrafish embryo

Nanocare platform

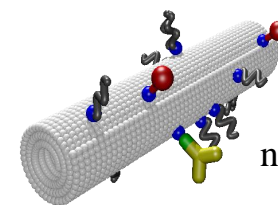
- Cytotoxicity
- Genotoxicity
- Carcinogenicity
- Ecotoxicity...



Titanate nanotubes: TiONts



500 nm



TiONts for nanovectorization

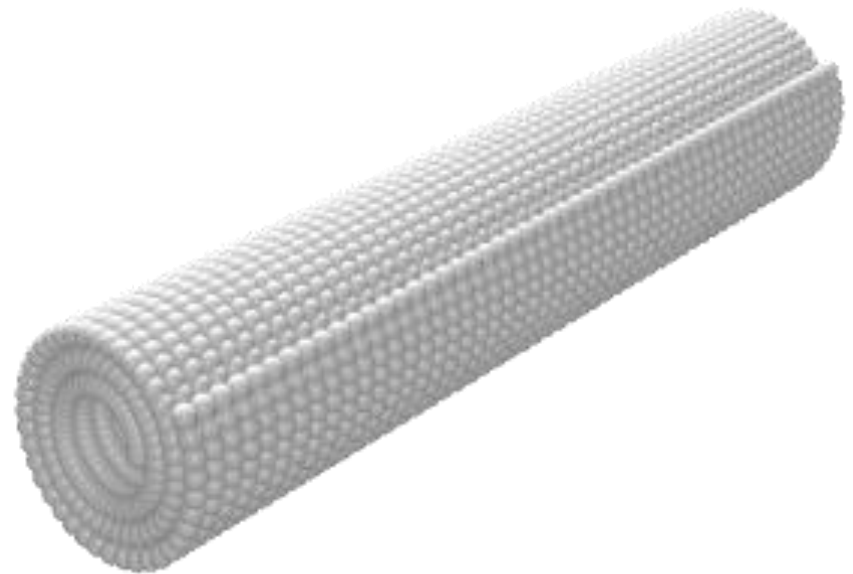
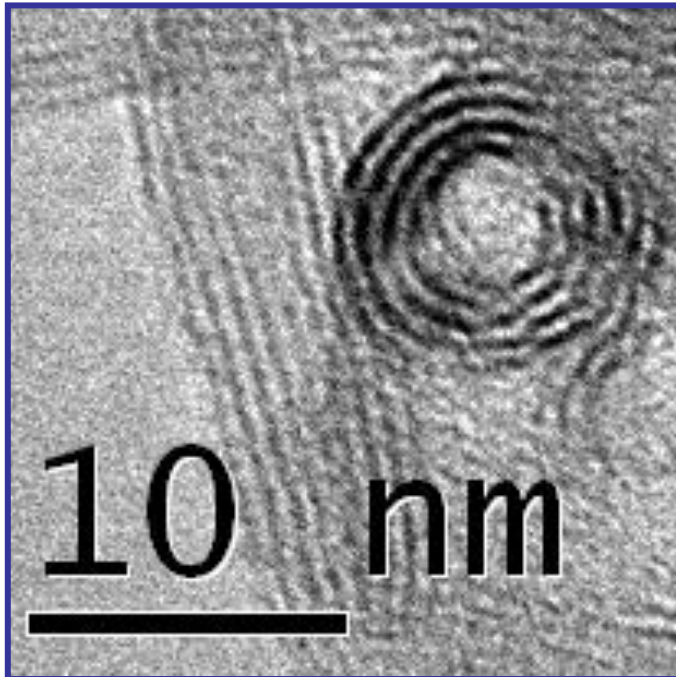
Transfecting DNA in cardiomyocytes cells

Radiosensitizing of tumors



Nanotubes de titanate : des nanocristaux originaux

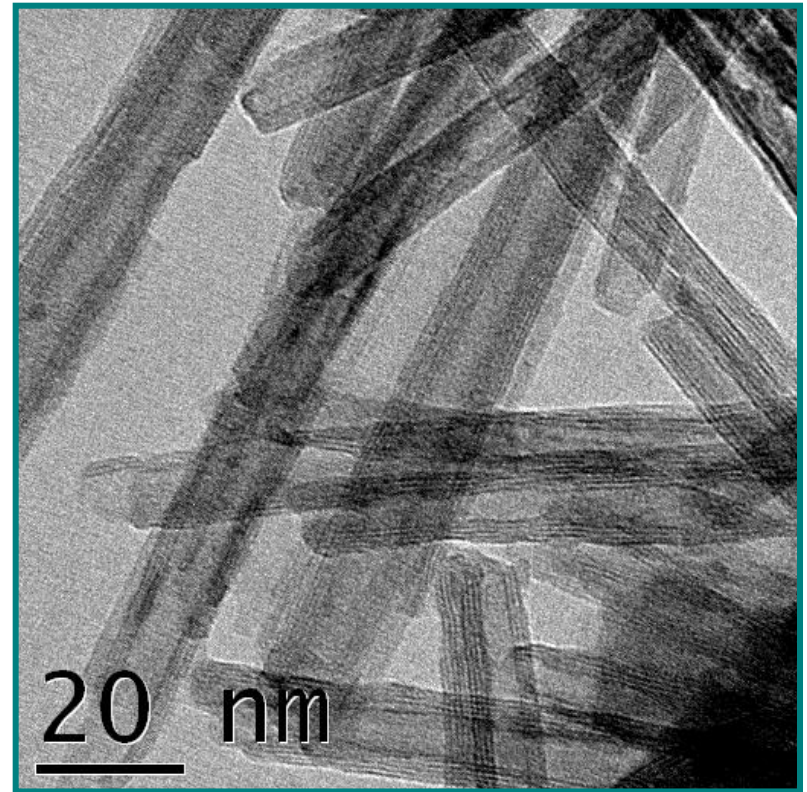
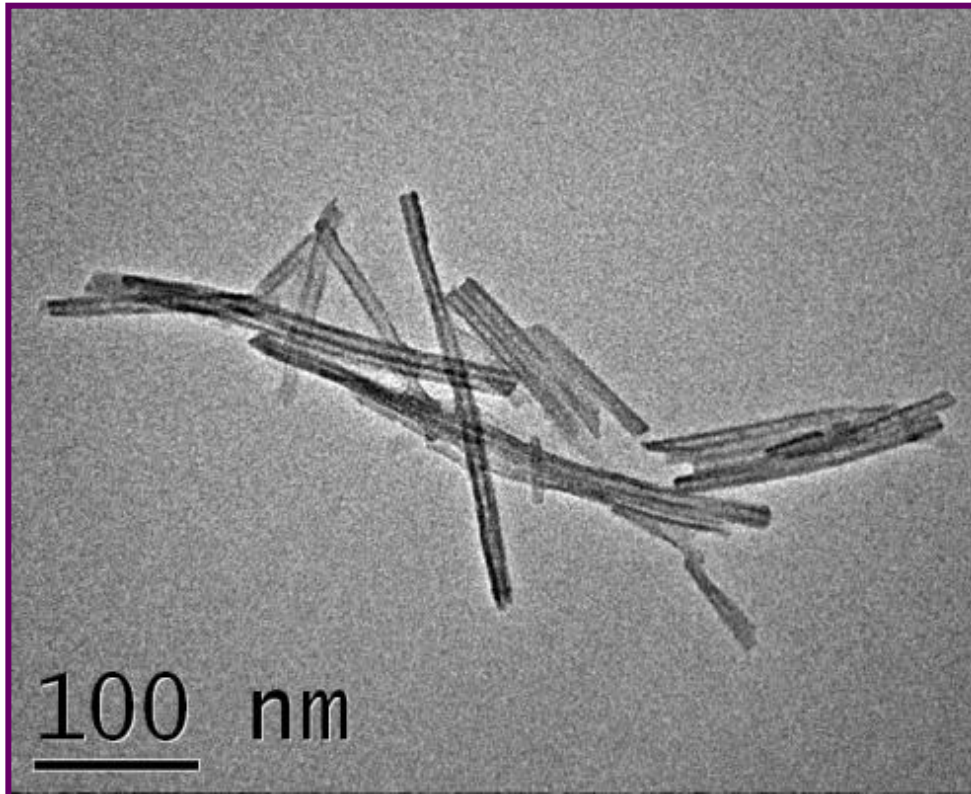
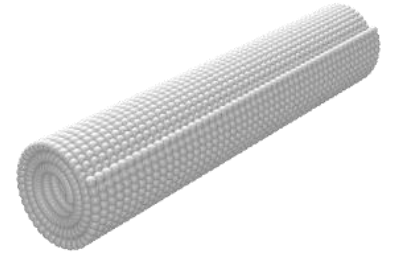
Une nanostructure particulière = des nanofeuilles enroulées



Nanotubes de titanate : des nanocristaux originaux

Morphologie des nanotubes :

- environ **150 nm** de long
- **10 nm** de diamètre
- extrémités ouvertes
- cavité interne de **4 nm**



Synthèse des nanotubes de titanate

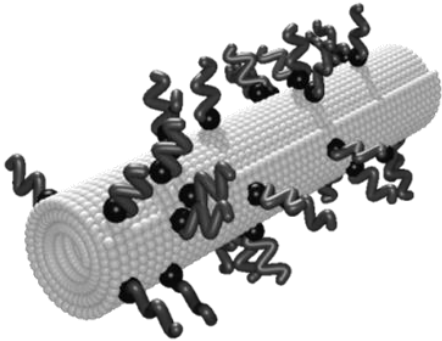
Synthèse hydrothermale :

La synthèse des nanotubes a lieu sous pression et en température (4 bar, 36h, 150°C), dans un milieu **fortement basique** (soude concentrée) **en partant d'une poudre commerciale de TiO_2** .

La poudre est ensuite lavée par dialyse et séchée par lyophilisation.

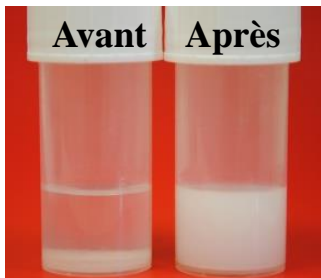


Modifications chimiques nécessaires des nanotubes de titanates pour ces applications en santé

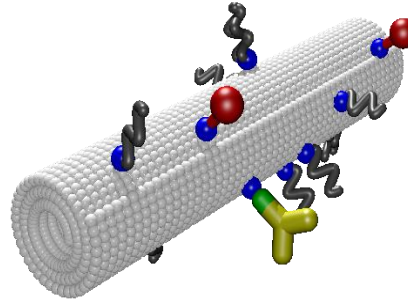


Greffages de polymères :

pour stabiliser les suspensions de nanotubes

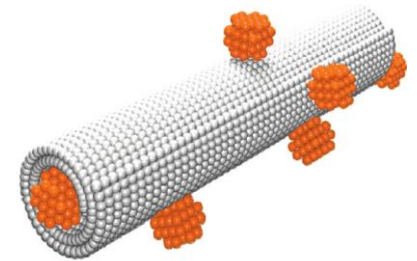


Stabilité sur une période de 48h
pH 7,4 (PBS)



Greffages d'autres molécules :

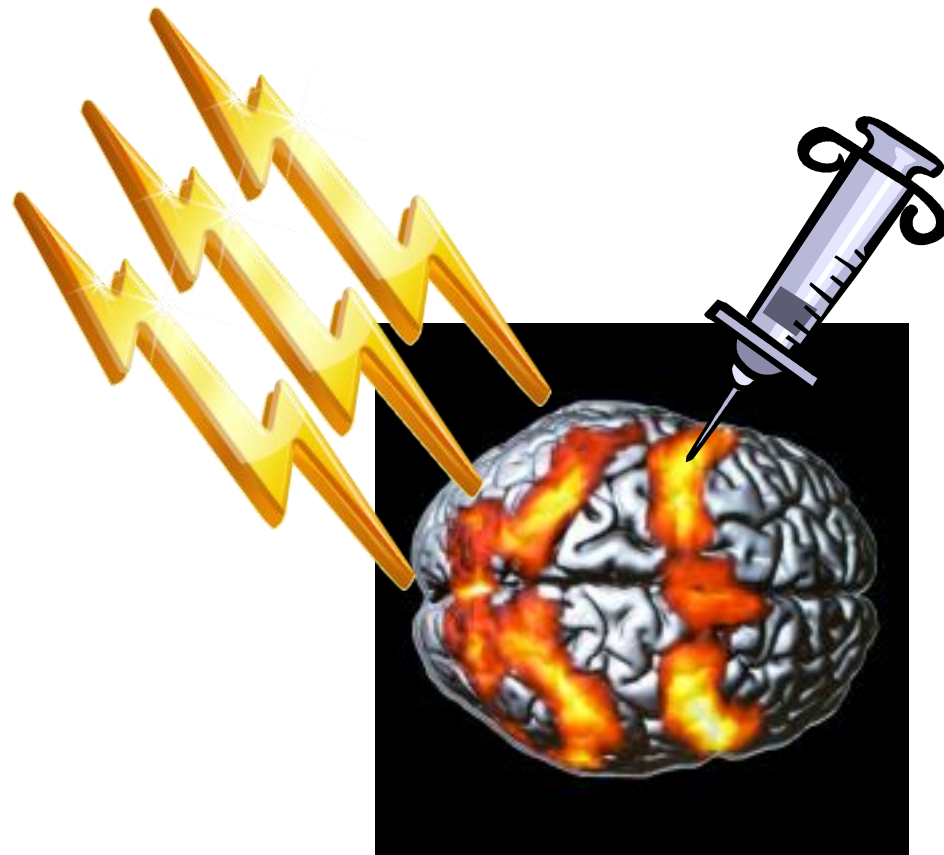
- Molécules thérapeutiques (chimiothérapies)
- Chélatants pour rendre les tubes détectables en imagerie nucléaire
- Anticorps pour cibler la biodistribution des tubes



Association avec d'autres nanoparticules :

- Nanoparticules d'or pour radiosensibiliser des tumeurs
- Nanoparticules d'oxydes de fer magnétiques pour détecter les nanotubes en IRM

Les nanotubes pour radiosensibiliser des tumeurs (rechutes de cancer, tumeurs radiorésistantes)

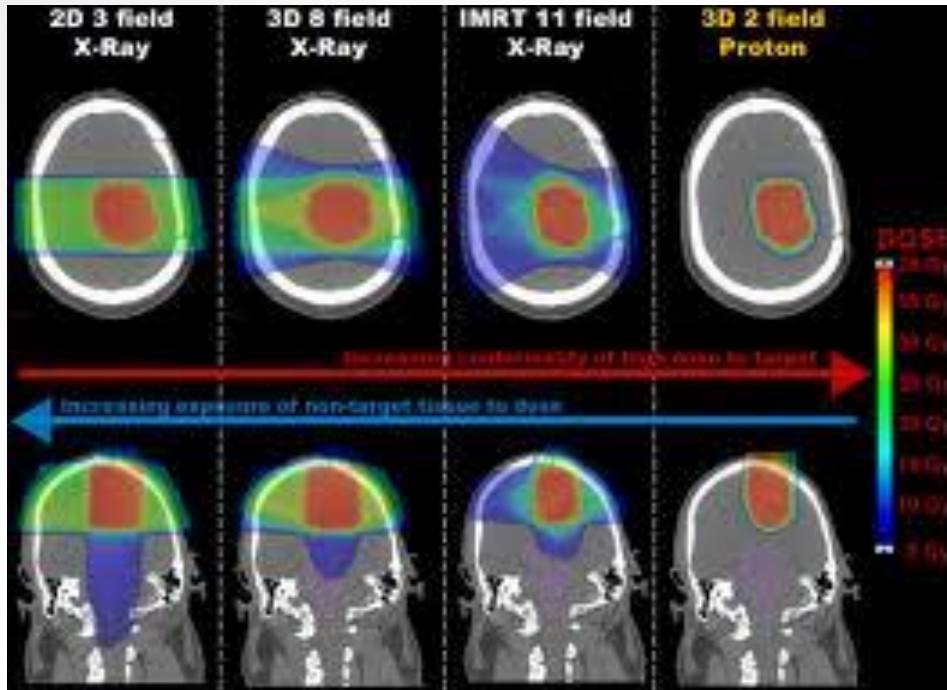
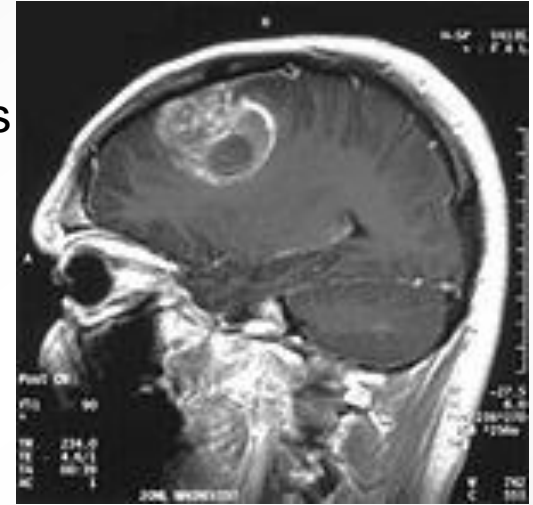


Glioblastome : 2^{ème} cancer le plus courant chez l'enfant

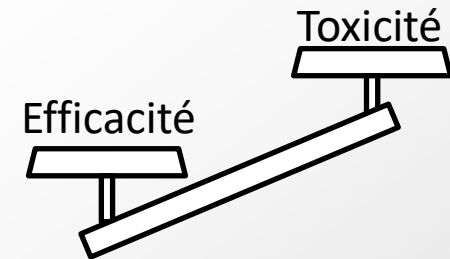
Occurrence : gliome : 7 pour 1 000 personnes
glioblastome multiforme : 2–3 cas pour 100 000 personnes

Pronostic : survie médiane d'environ 14 mois pour les glioblastomes multiformes

Traitement actuel : chirurgie (quand tumeur opérable)
+ radiothérapie + chimiothérapie ? (Temodal®)



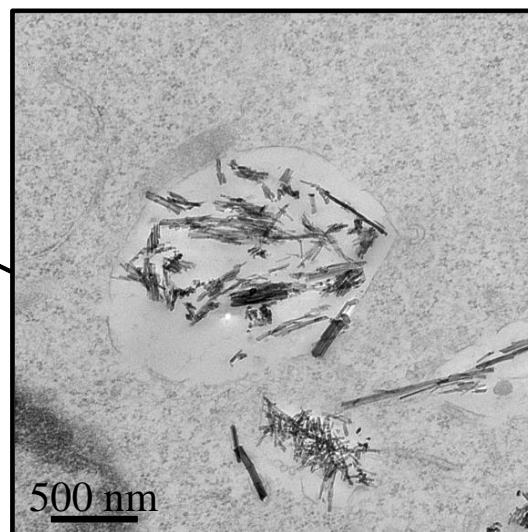
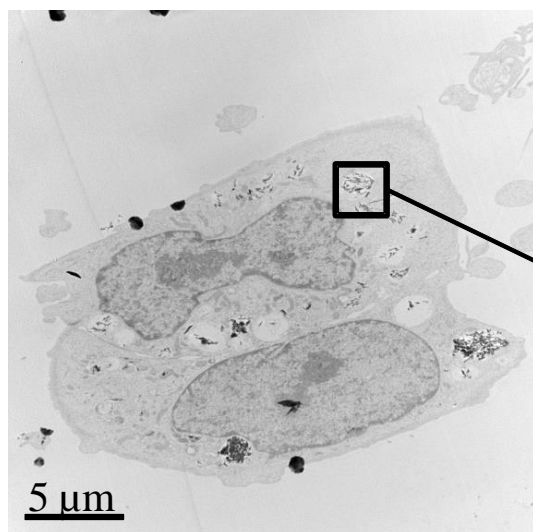
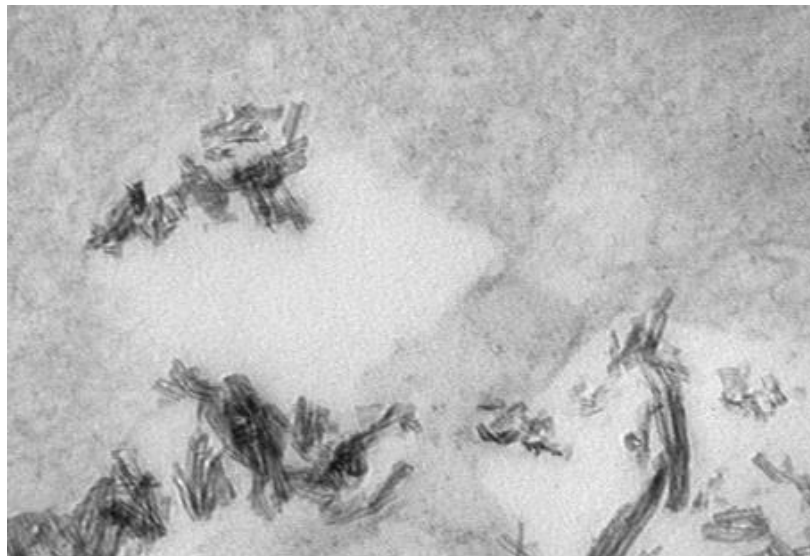
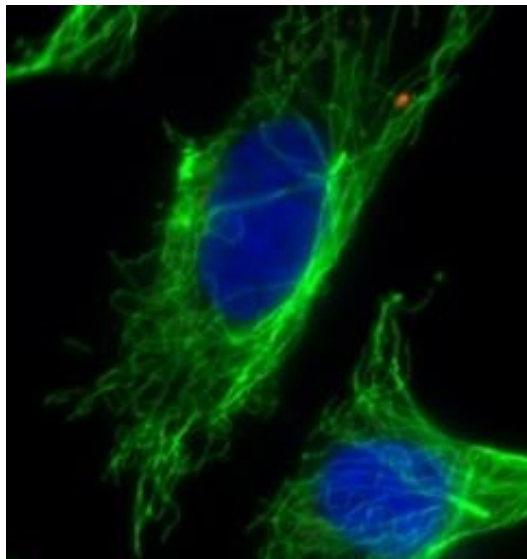
Escalade de doses



- **Toxicité aiguë**
Hypertension intra-crânienne
Céphalées, nausées, vomissements, somnolence
- **Toxicité tardive**
Troubles neuro-cognitifs
Nécrose cérébrale si dose supérieure à 60 Gy

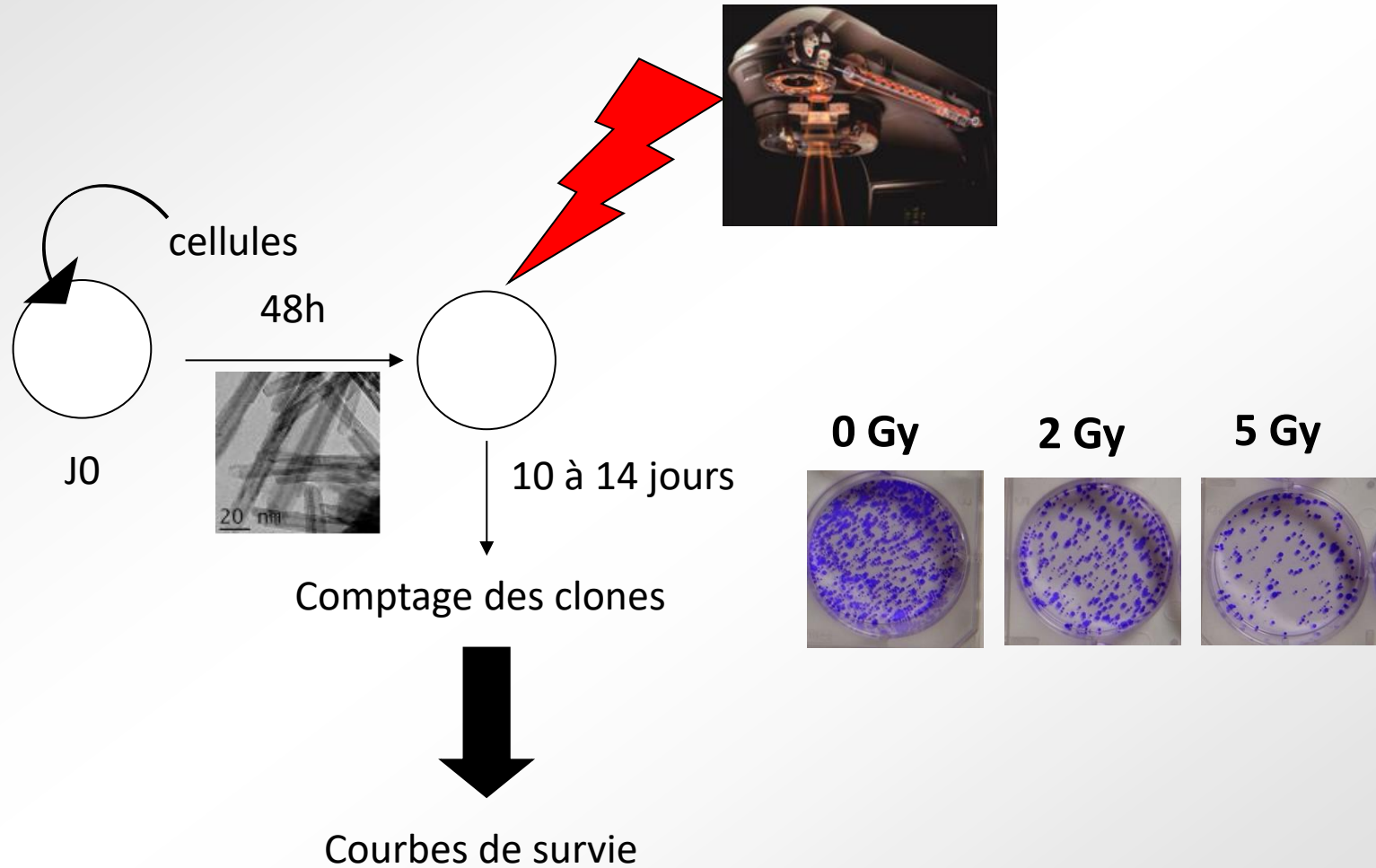
➡ **IL FAUT RADIOSENSIBILISER !**

Très bonne internalisation des nanotubes de titanates dans les cellules cancéreuses

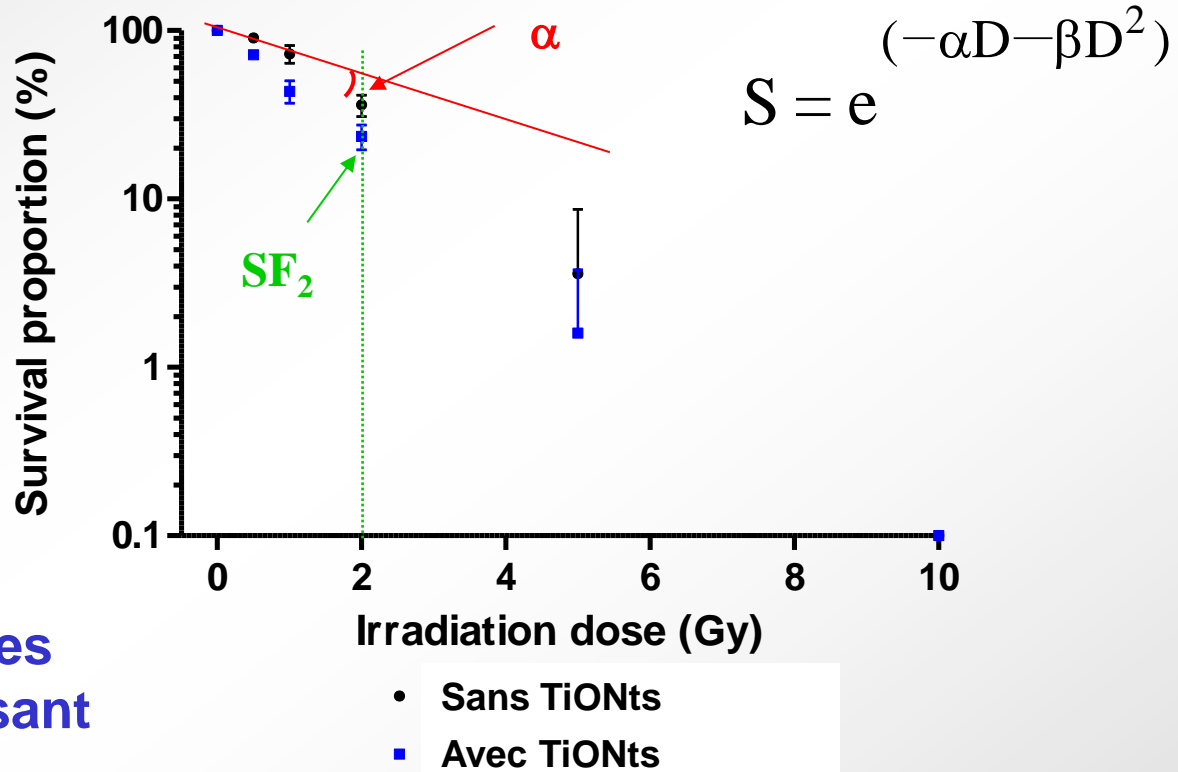


The radiosensitization effect of titanate nanotubes as a new tool in radiation therapy for glioblastoma: a proof-of-concept
C. Mirjolet, A.L. Papa, G. Créhange, O. Raguin, G. Truc, P. Maingon, N. Millot *Radioth. Oncol.* **108**, 136 (2013)

Essai clonogénique



Effet des TiONts sur la radiosensibilité des SNB19



Les nanotubes eux mêmes ont un effet radiosensibilisant

Surviving fraction à 2 Gy (SF2)

SF2 (SNB19) sans TiONts : 0.36 ± 0.05

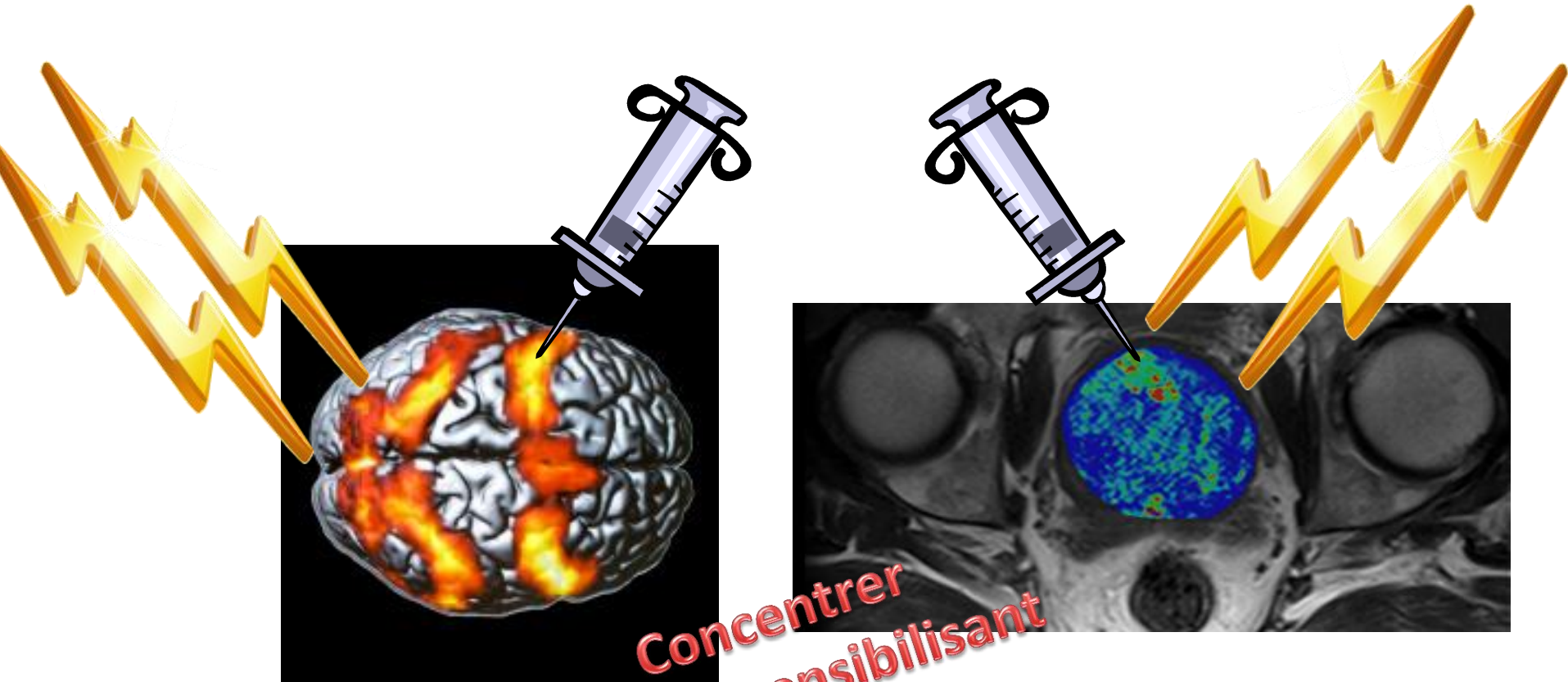
SF2 (SNB19) avec TiONts : 0.23 ± 0.04

α parameter (lié aux évènements létaux)

α sans TiONts : 0.125

α avec TiONts : 0.768

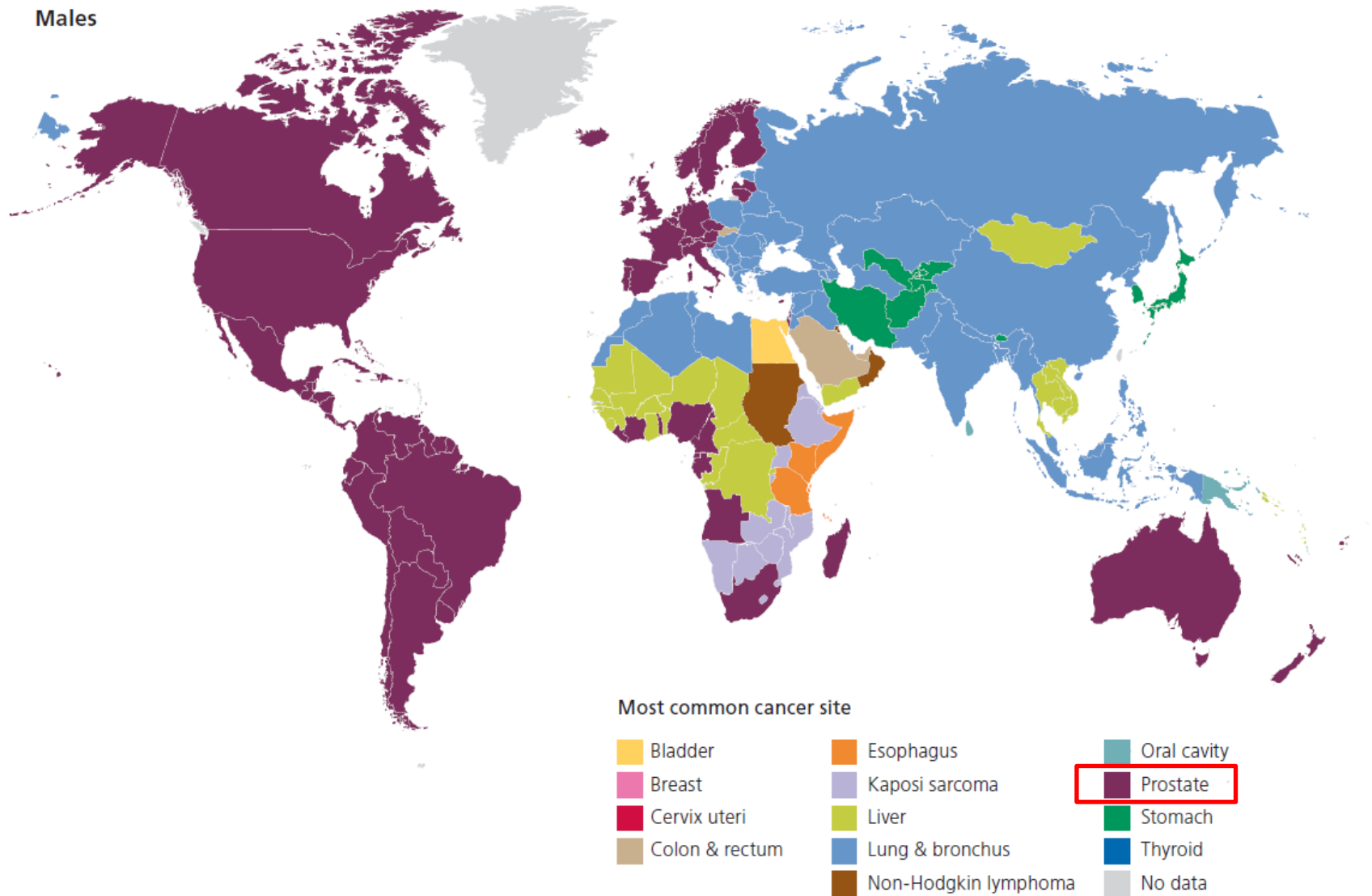
Les nanotubes pour radiosensibiliser des tumeurs (rechutes de cancer, tumeurs radiorésistantes)



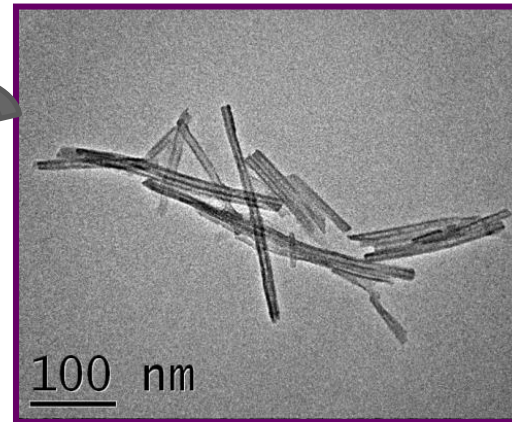
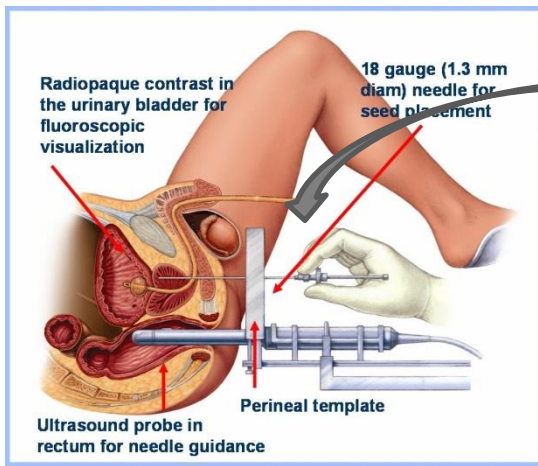
Concentrer
un radiosensibilisant
dans la tumeur

Most Common Cancer Sites Worldwide by Sex, 2008

Males



Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012, J. Ferlay, E. Steliarova-Foucher, J. Lortet-Tieulent, S. Rosso, J. W. W. Coebergh, H. Comber, D. Forman, F. Bray, *Eur. J. Cancer* **2013**, 49, 1374-1403. <http://dx.doi.org/10.1016/j.ejca.2012.12.027>



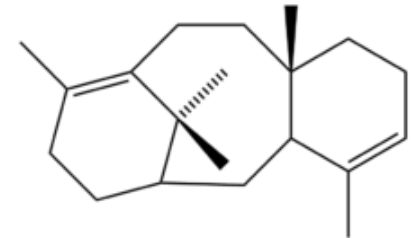
Curiethérapie :

- patients atteints d'un cancer de la prostate
- implantation intraprostatique de grains radioactifs via un ensemble d'aiguilles
- dose importante de radiothérapie délivrée au niveau de la tumeur

Jusqu'à 50% des patients présentent une rechute locale

↳ Augmenter l'efficacité du traitement en radiosensibilisant les tumeurs par des agents de chimiothérapie de type taxanes

Nanotechnologies



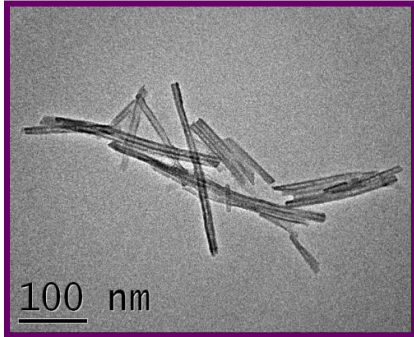
Toxicité des taxanes :

	Groupe 1 (n=332)	Groupe 2 (n=330)
Anémie	75,5%	78,4%
Neutropénie (grade 3-4)	32%	1,8%
Neuropathies (sensorielles)	32,5%	25,2%
Neuropathies (grade 3-4)	2,7%	2,1%
Symptômes gastro-intestinaux (nausées et vomissements)	72,6%	66,1%
Symptômes gastro-intestinaux (diarrhées)	12,3%	10,9%
Toxicité cardiaque	16,4%	26,5%
Rétention d'eau	14,4%	16,1%
Toxicité pulmonaire	26,5%	24,5%



L'objectif de ce projet est d'éviter ou de limiter la toxicité des taxanes en concentrant leur administration au niveau de la tumeur et non par voie systémique

A new nanomedicine

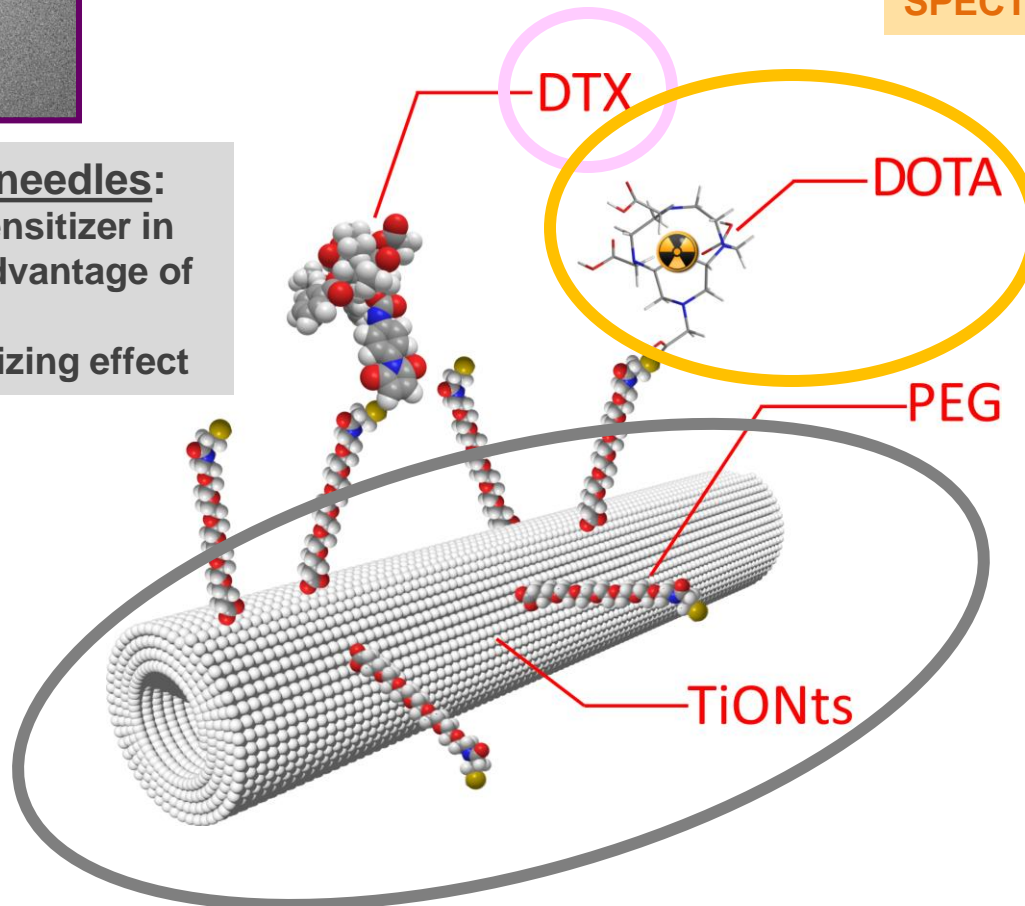


Nanotubes = nano-needles:
To focus the radiosensitizer in the tumor by taking advantage of their morphology
+ intrinsic radiosensitizing effect

Docetaxel (taxane):
Radiosensitizer focused and maintained in the tumor

Radioelement	Half time (h)
^{99m}Tc	6
^{123}I	13
^{111}In	67

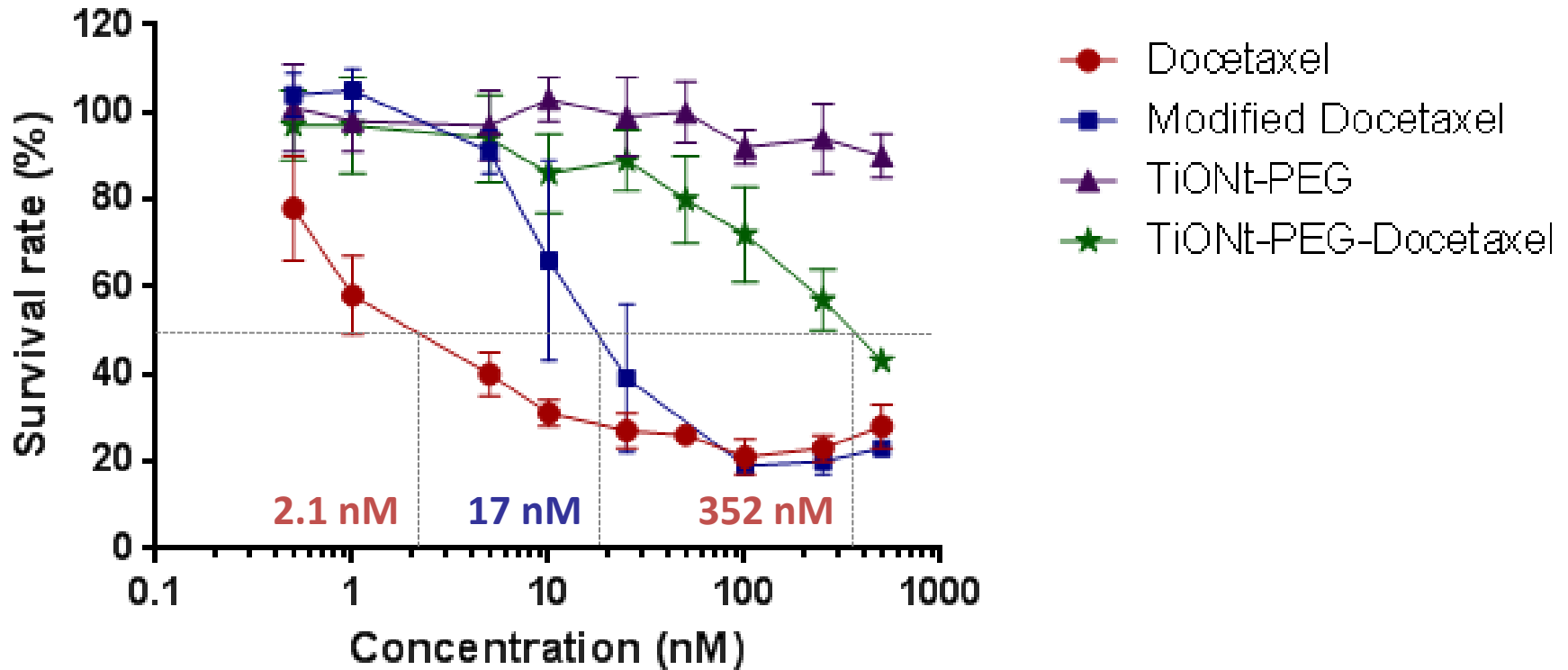
Chelating agent
SPECT/CT via ^{111}In labelling



TiONts: Coupling with activated DTX

In vitro evaluation

PC3 cell lines

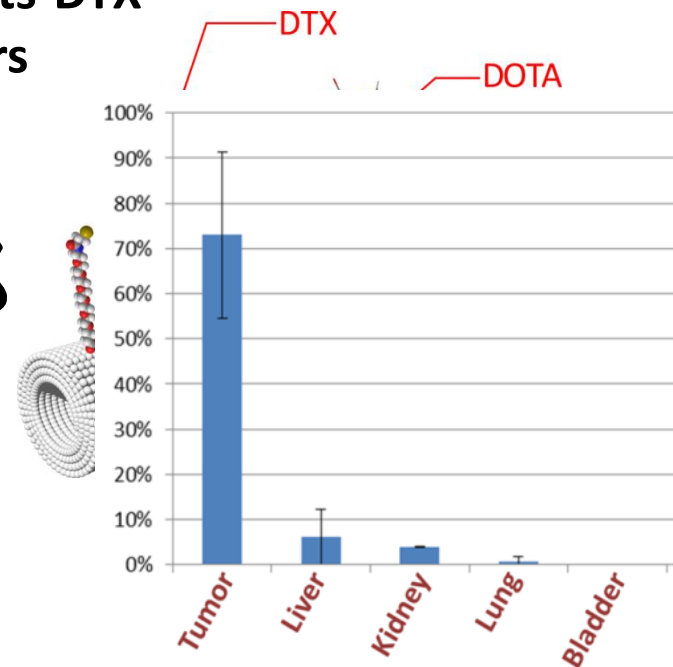
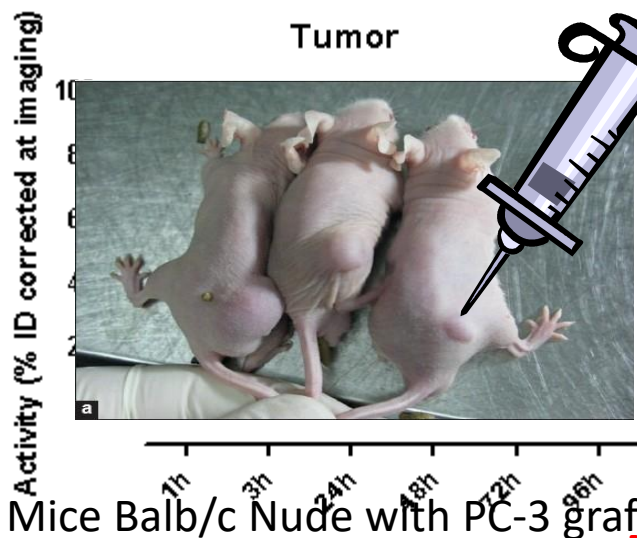


Determination of half-maximum inhibitory concentration (IC50)

In vivo evaluation of TiONts/DTX/DOXA



Injection of **radiolabeled** TiONts-DTX nanohybrid into grafted tumors
 → **SPECT/CT** monitoring

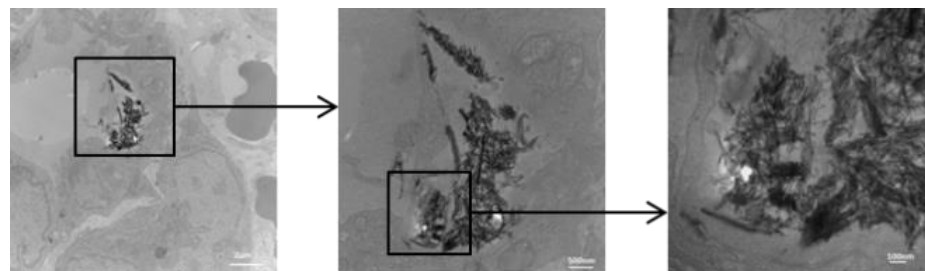


Mice Balb/c Nude with PC-3 grafted prostate tumors

- DOTA-In111
- ▨ TiONts-DOXA-In111

Nanotubes remain in the tumor even four days after intratumoral injection

24h post-injection

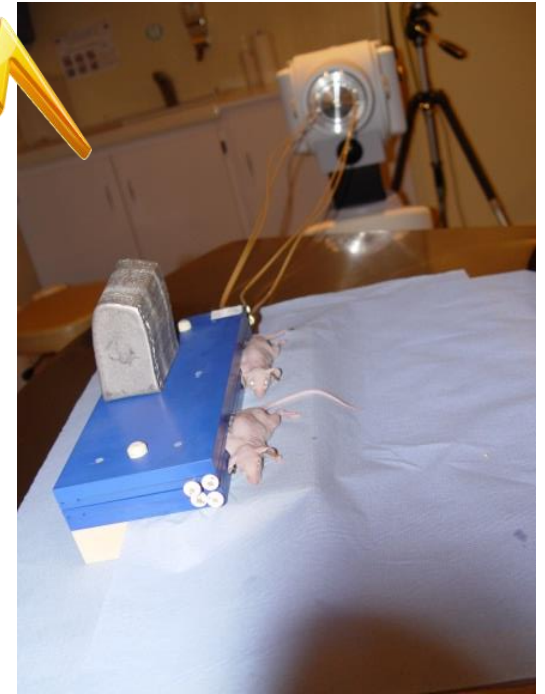


TEM tumor histology

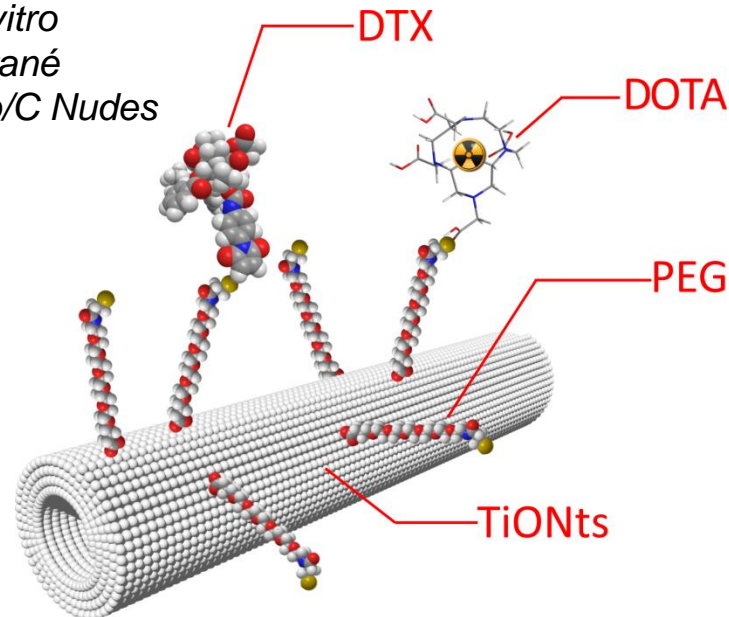
Etudes précliniques et imagerie médicale



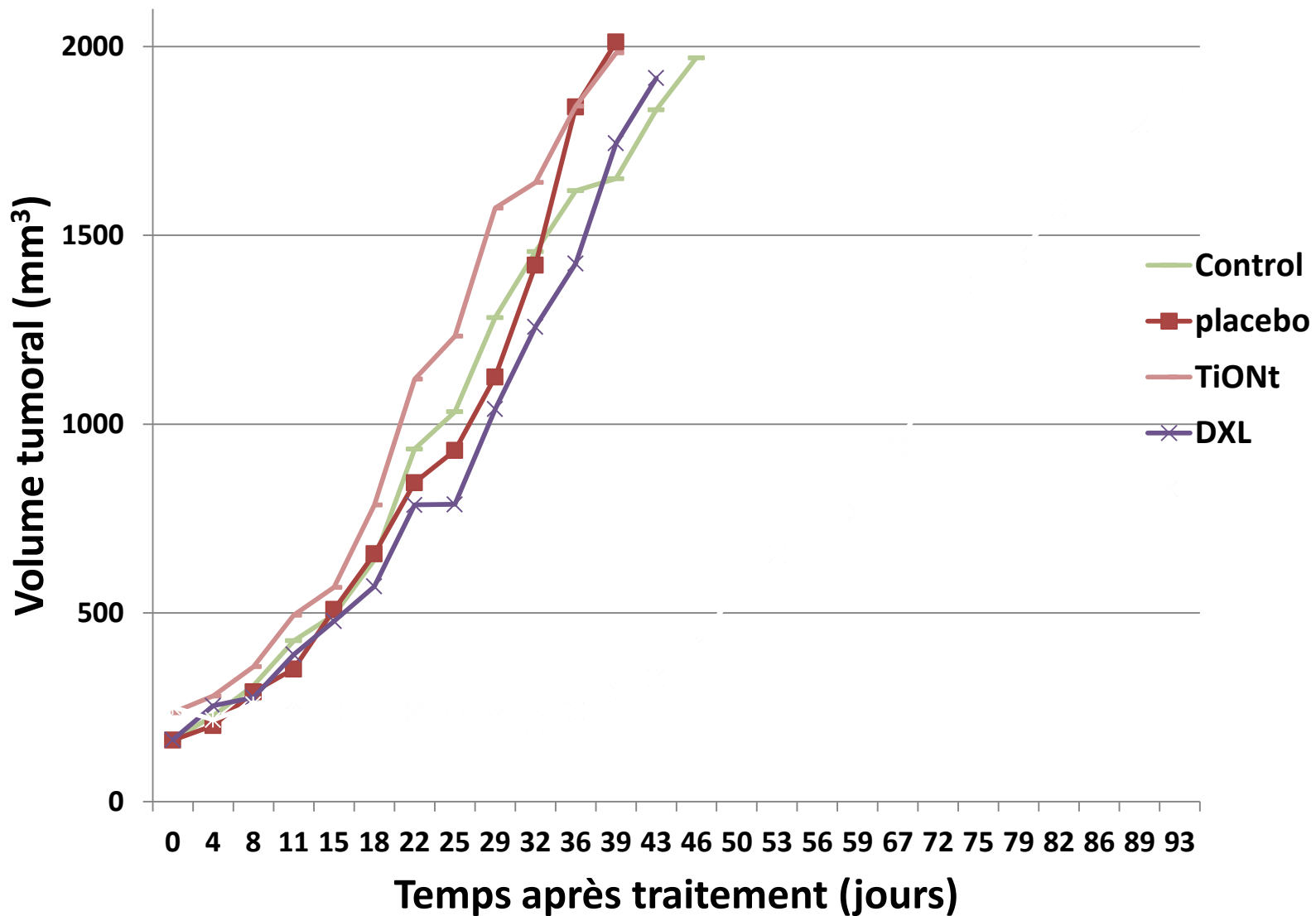
Irradiation à 3 X 4Gy
Courbes de croissance tumorale



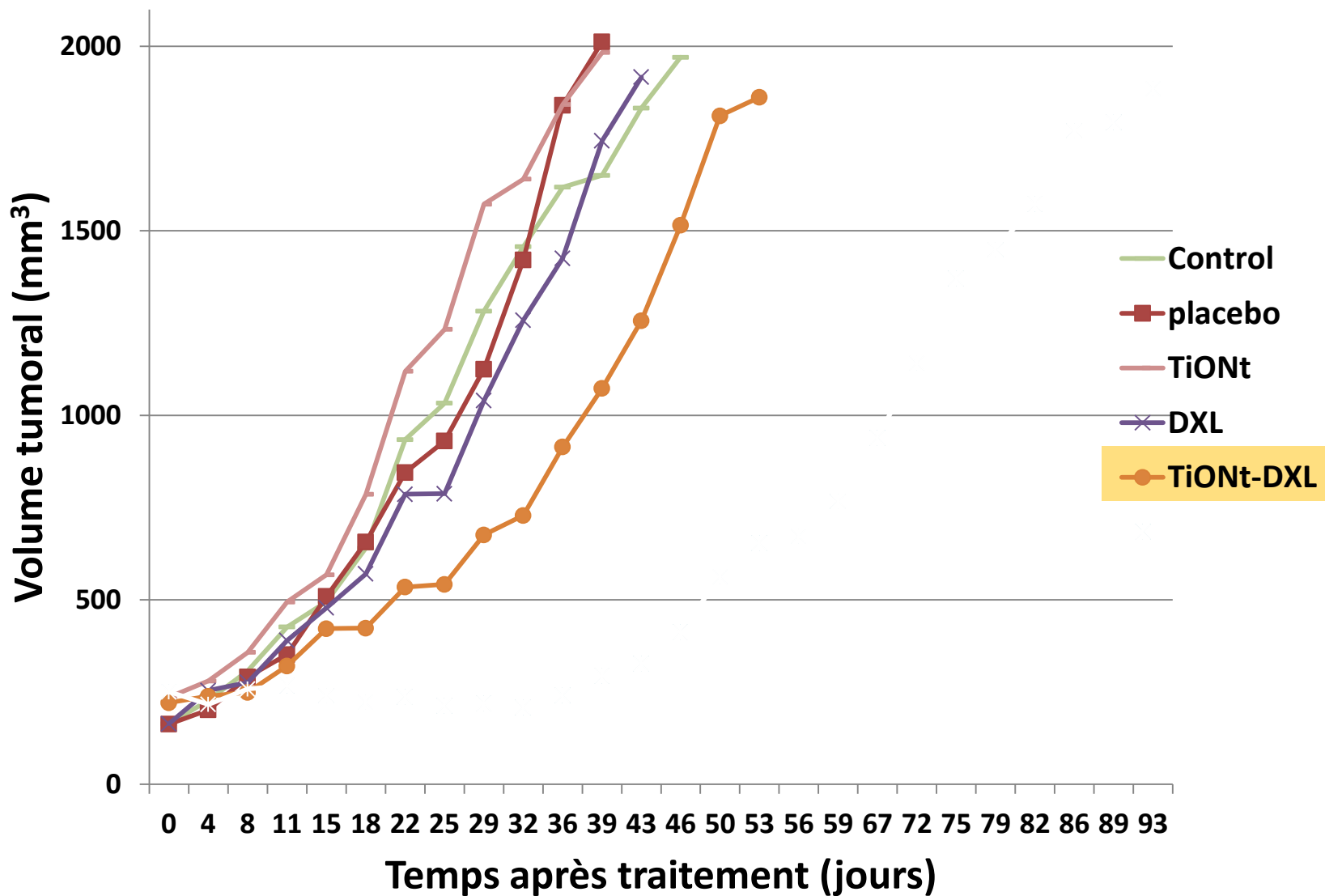
Cellules de tumeurs de prostate humaines
(PC-3) amplifiées *in vitro*
injectées en sous-cutané
flancs de souris mâles Balb/C Nudes



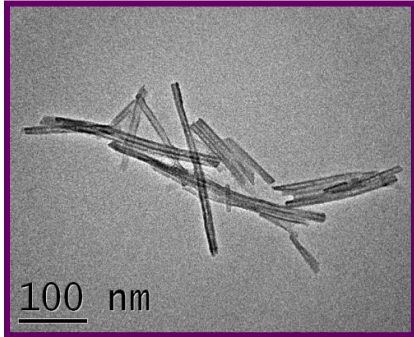
Courbes de croissance tumorale



Courbes de croissance tumorale

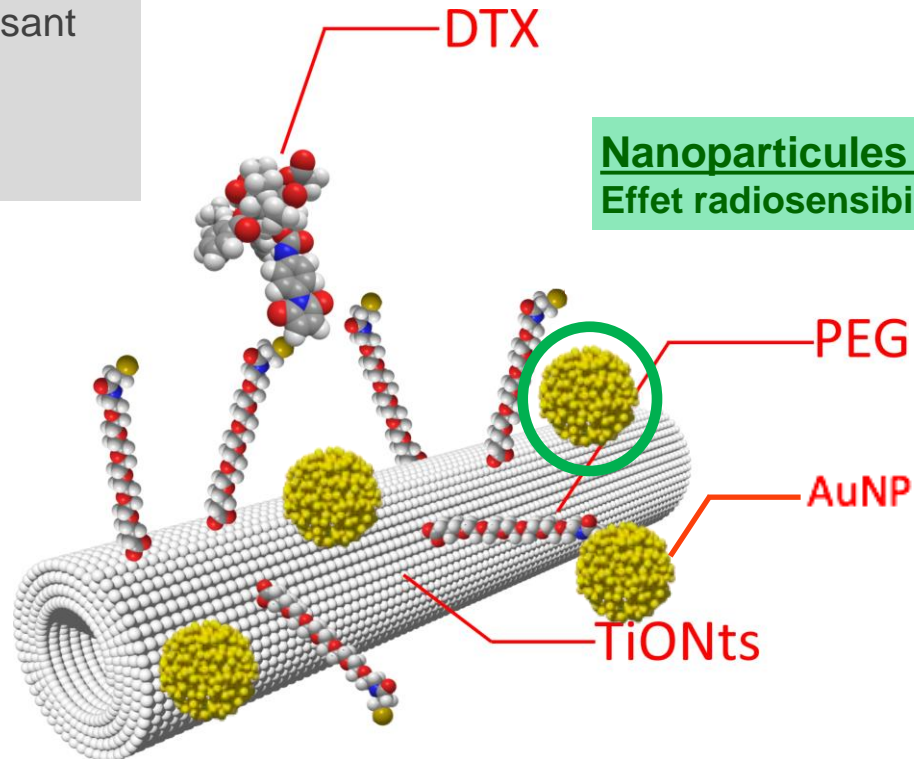


Un nouveau nanomédicament... deuxième génération

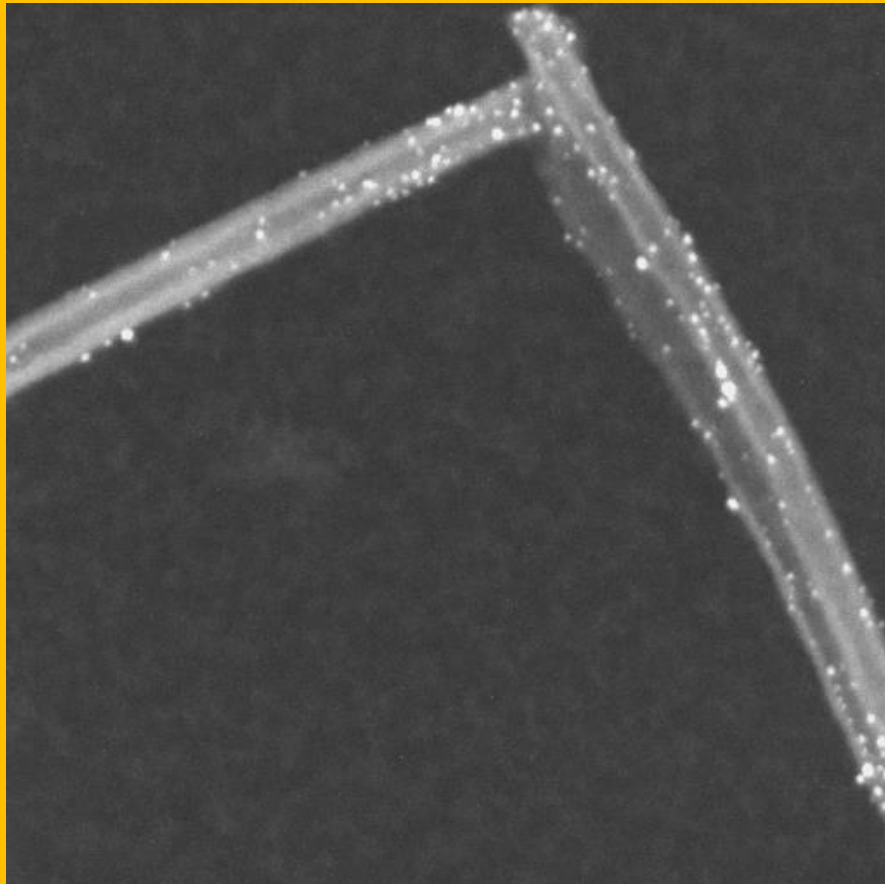


Nanotubes = nano-aiguilles :

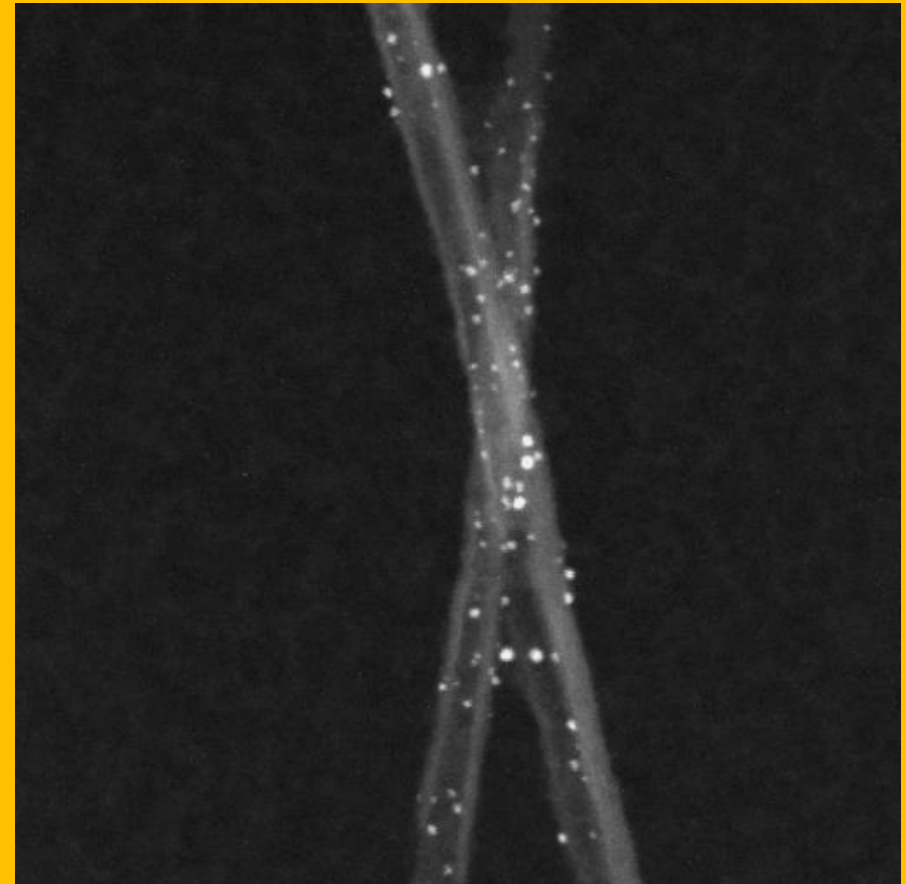
Concentrer le radiosensibilisant
dans la tumeur
+ Effet radiosensibilisant
intrinsèque



Des nanotubes dorés

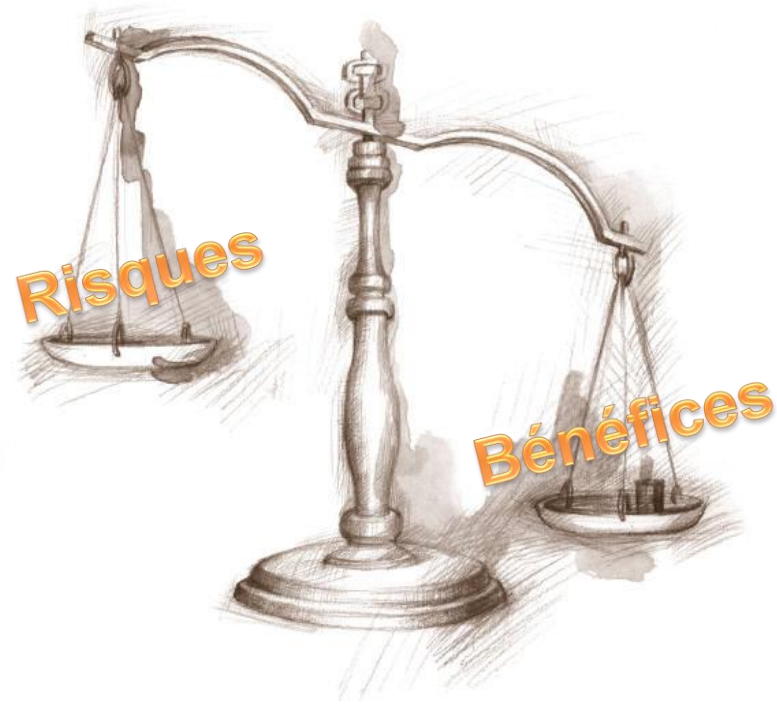


Specimen [STEM DF]
JEOL-TEM 200kV x800k 100%
Comment:
5/4/2016 15:33:52
Operator:



Specimen [STEM DF]
JEOL-TEM 200kV x1.0M 100%
Comment:
5/4/2016 15:43:22
Operator:

Conclusion



Thanks



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Research Associate



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Dr. JérémY Paris



Dr. Guillaume Thomas



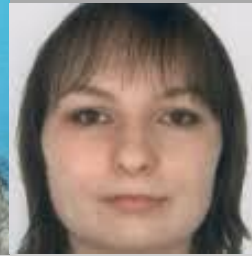
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Dr. Fadoua Sallem



Dr. Sruthi Sudhakaran



Annette Luce

PhD Students



Dr. Harender Bisht



Dr. Renée Mayap Talom



Dr. Thomas Courant

Post-doctoral researchers

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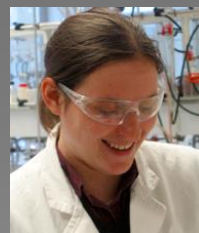
Dr. David VANDROUX



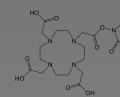
Dr. Laure DUMONT



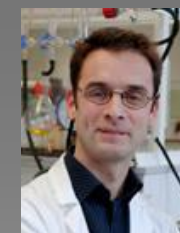
Prof. Franck DENAT



Dr. Claire BERNHARD



DOTA



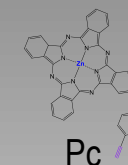
Dr. Frédéric BOSCHETTI



Dr. Mathieu MOREAU



Dr. Richard DECREAU



Pc



Yann BERNHARD



Dr. Paul WALKER



Prof. François BRUNOTTE



Prof. Marie-Christine
CHAGNON



Dr. Isabelle SEVERIN



Prof. Johanna CHLUBA



Dr. Bertrand COLLIN



Dr. Alexandra OUDOT



Prof. Philippe MIGNON



Prof. Gilles CREHANGES



Dr. Céline MIRJOLET



Merci
pour votre attention

Happysome 😊



Risque Nano : Boîte de Pandore ?

❖ Identification des étapes d'exposition potentielle

Un air chargé

Plus de 10 000 nanoparticules dans 1 cm³ d'air

☞ Nanoparticules produites par l'homme = 10 % des nanoparticules dans l'atmosphère (90% = érosion, biomasse, sels marins, poussières volcaniques, cosmiques etc.)

☞ Nanoparticules produites non intentionnellement (émissions de moteurs, suies de procédés thermiques, abrasion mécanique...)

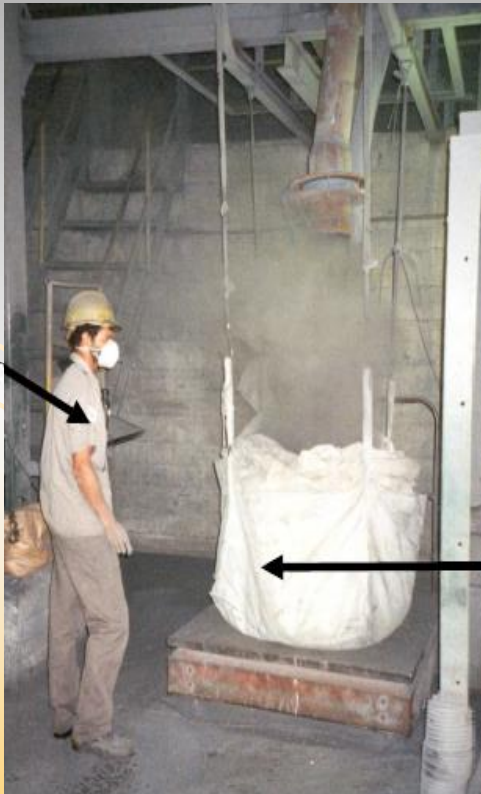
L'industrialisation des nanotechnologies pourrait changer la donne



❖ Modes de contamination

Deux types de contamination :

- Contamination aiguë (forte concentration d'exposition pendant un temps court)
- Contamination chronique



❖ Modes de contamination



Trois modes de contamination :

- Inhalation, exposition des poumons

Distribution des nanomatériaux dans les différentes régions de l'arbre respiratoire

Devenir des nanomatériaux après exposition pulmonaire

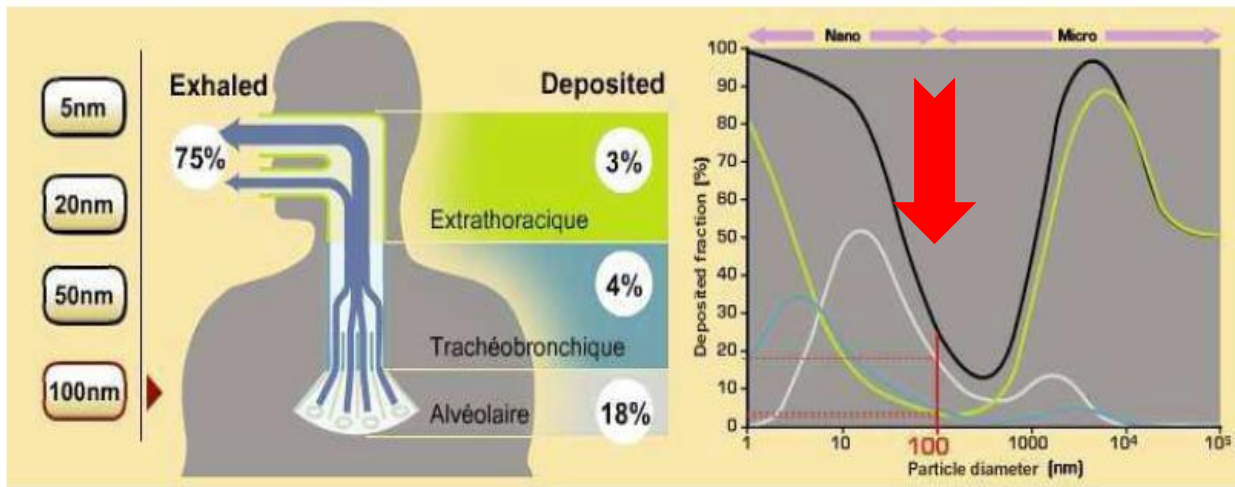
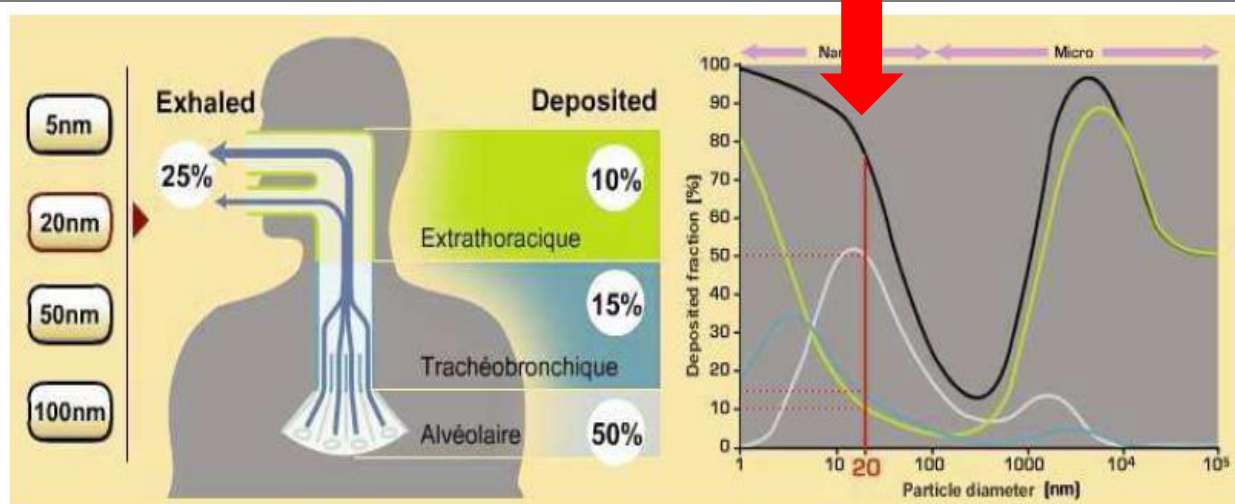
- Exposition cutanée

Follicule pileux, Plaies
Flexion de la peau

- Exposition par ingestion

Aliments contenant des nanoparticules
Emballage alimentaire
Remontée mucociliaire



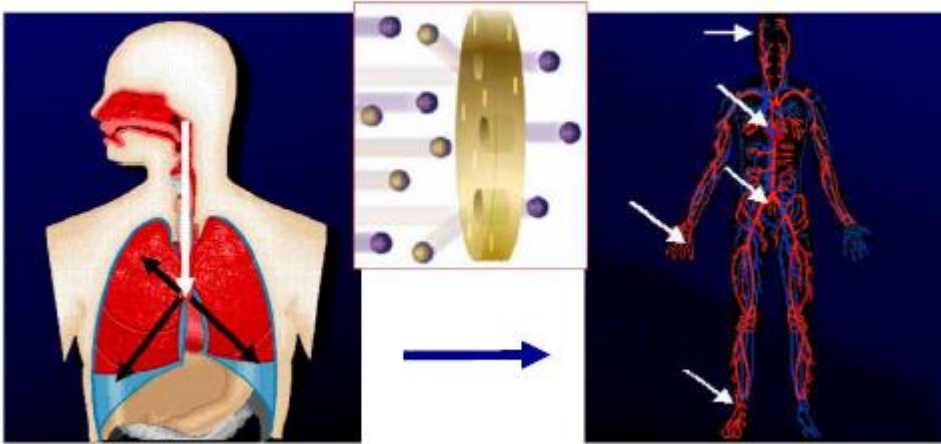


Impact du paramètre taille

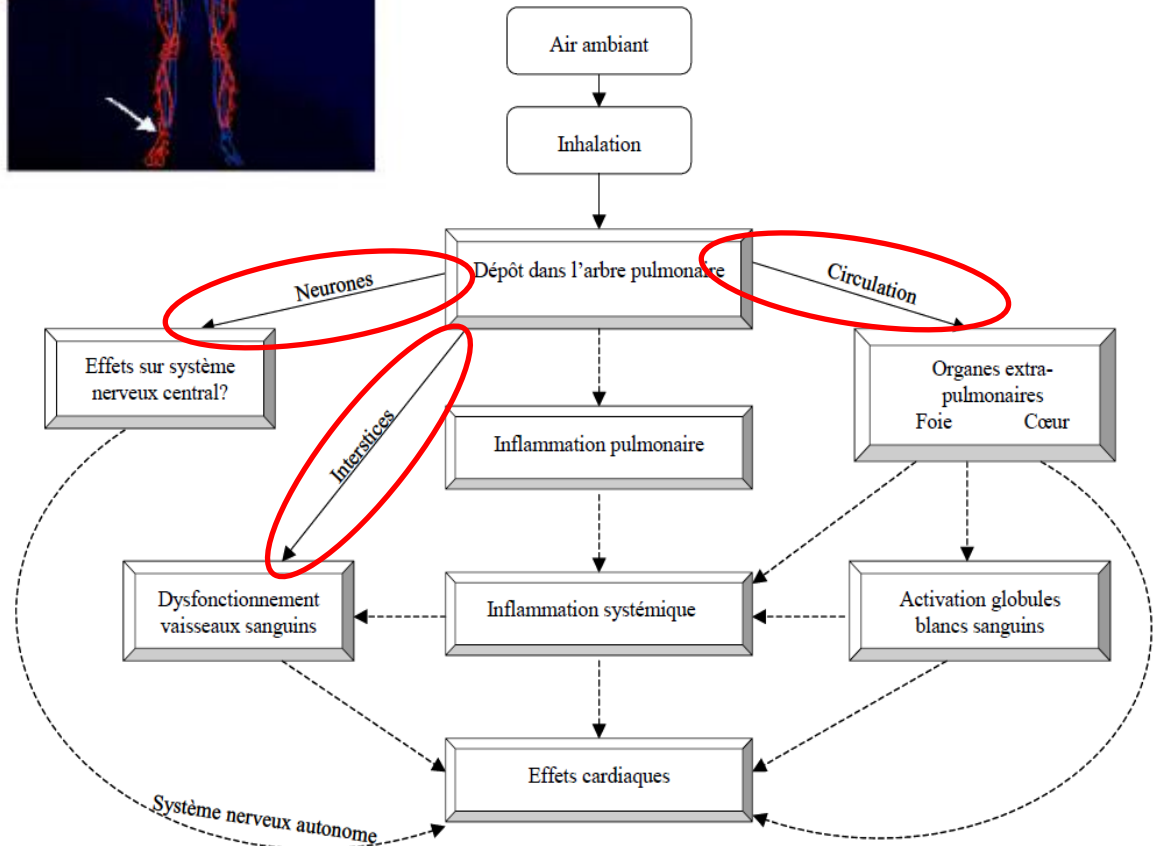
Modèle mathématique de prédiction de dépôt des particules dans l'appareil respiratoire (International Commission on Radiological Protection)

Appareil respiratoire

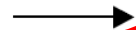
Courant circulatoire



Translocation

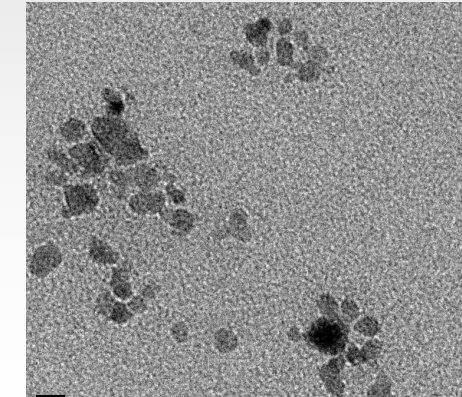
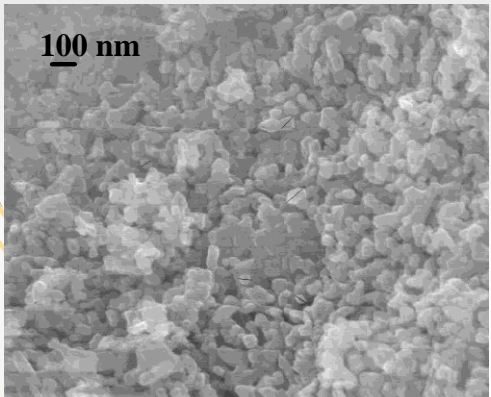
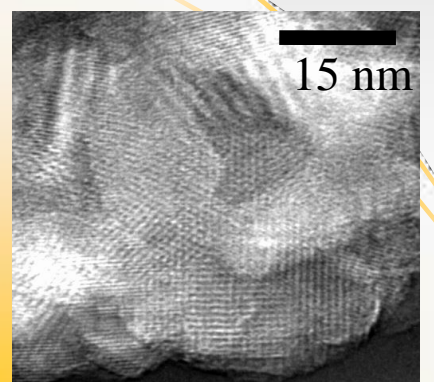
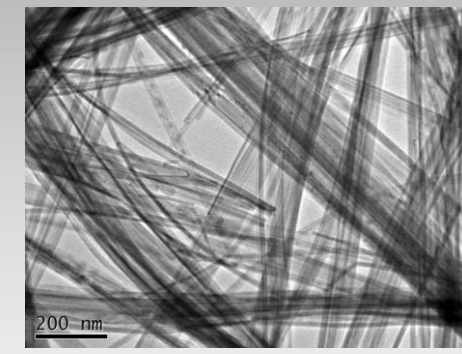
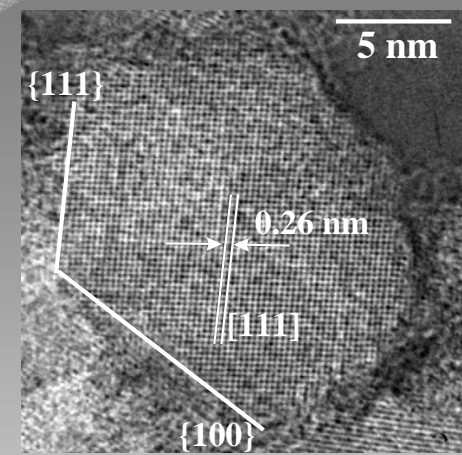
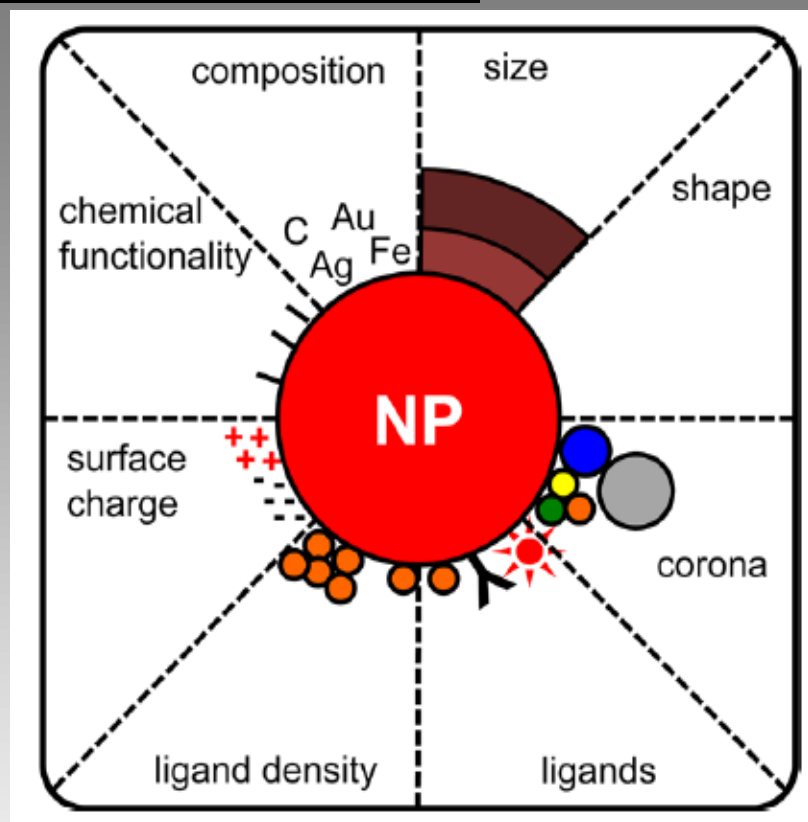
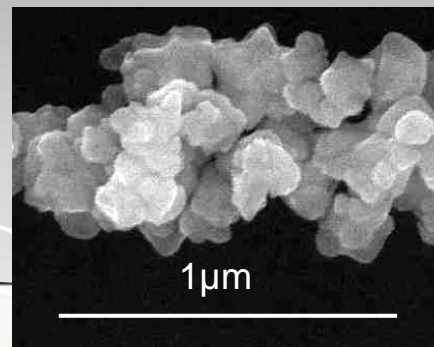
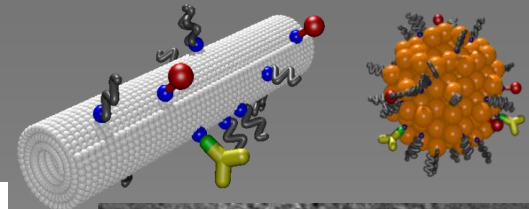
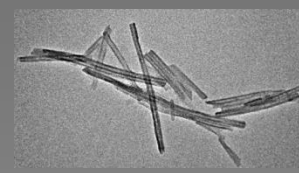
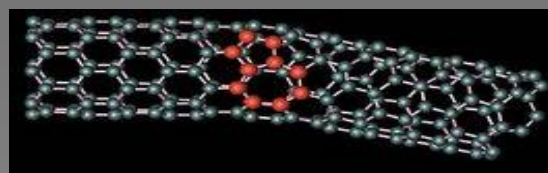
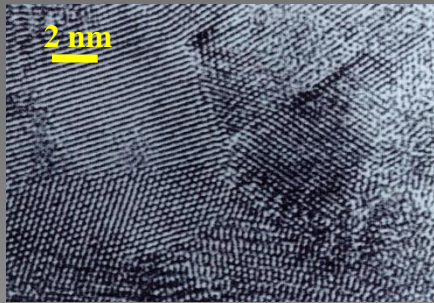


Translocation de particules :



Cerveau
Carrefour
aéro-digestif
Poumon
Foie
Tube digestif
Rein
Peau





❖ Identification des risques

$$\text{Risque} = \text{Danger} \times \text{Exposition}$$

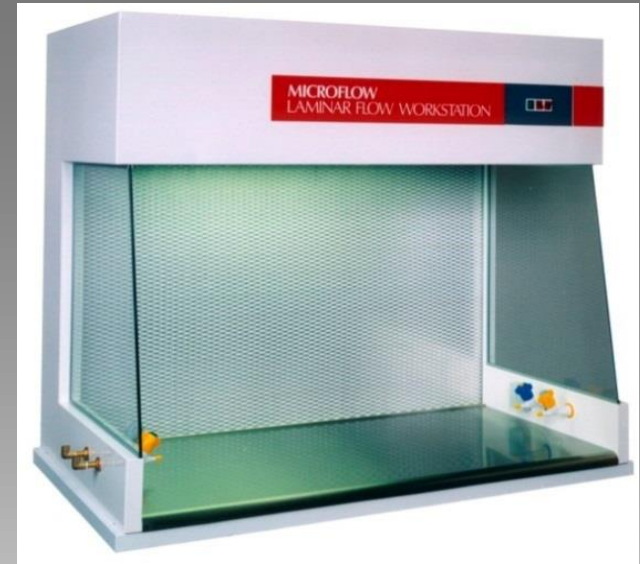
Risque de dissémination réduit si nanoparticules :

- **incluses dans une matrice solide (nanomatériaux)**
(risque demeure en cas de découpage, nettoyage, ponçage...)
- **en suspension dans une matrice liquide (nanofluide)**

Risque majoritaire :

nanopoudres = nanoparticules ou nanotubes "libres"

Protection des travailleurs



Hotte à flux laminaire



Masques FFP3

❖ Cadre réglementaire

La loi n° 2009-967 du **3 août 2009** de programmation relative à la mise en œuvre du Grenelle de l'environnement dite **Grenelle 1** (article 42) :

Le grand débat public



La loi n° 2010-788 du **12 juillet 2010** portant engagement national pour l'environnement dite **Grenelle 2** (article 185) :

Les nanomatériaux sont soumis à déclaration (1^{er} janvier 2013, > 100g)

Obligation européenne d'étiquetage (produits) à partir de décembre 2014

↪ **En suspens car remise en cause additifs déjà utilisés "depuis des décennies"**





Risques

Bénéfices