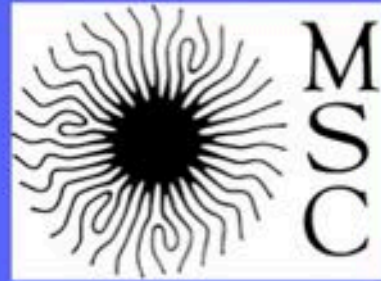




Université de Paris



# A Soft Matter Approach of Nanomedicine: Prospects and Challenges

Jean-François Berret



Université Paris-Diderot

Matière et Systèmes Complexes, Université de Paris, France



**Pierre-Gilles de Gennes**  
Nobel prize in physics (1991)

## Soft Matter (Nobel Lecture) \*\*

By **Pierre-Gilles de Gennes** \*

What do we mean by soft matter?

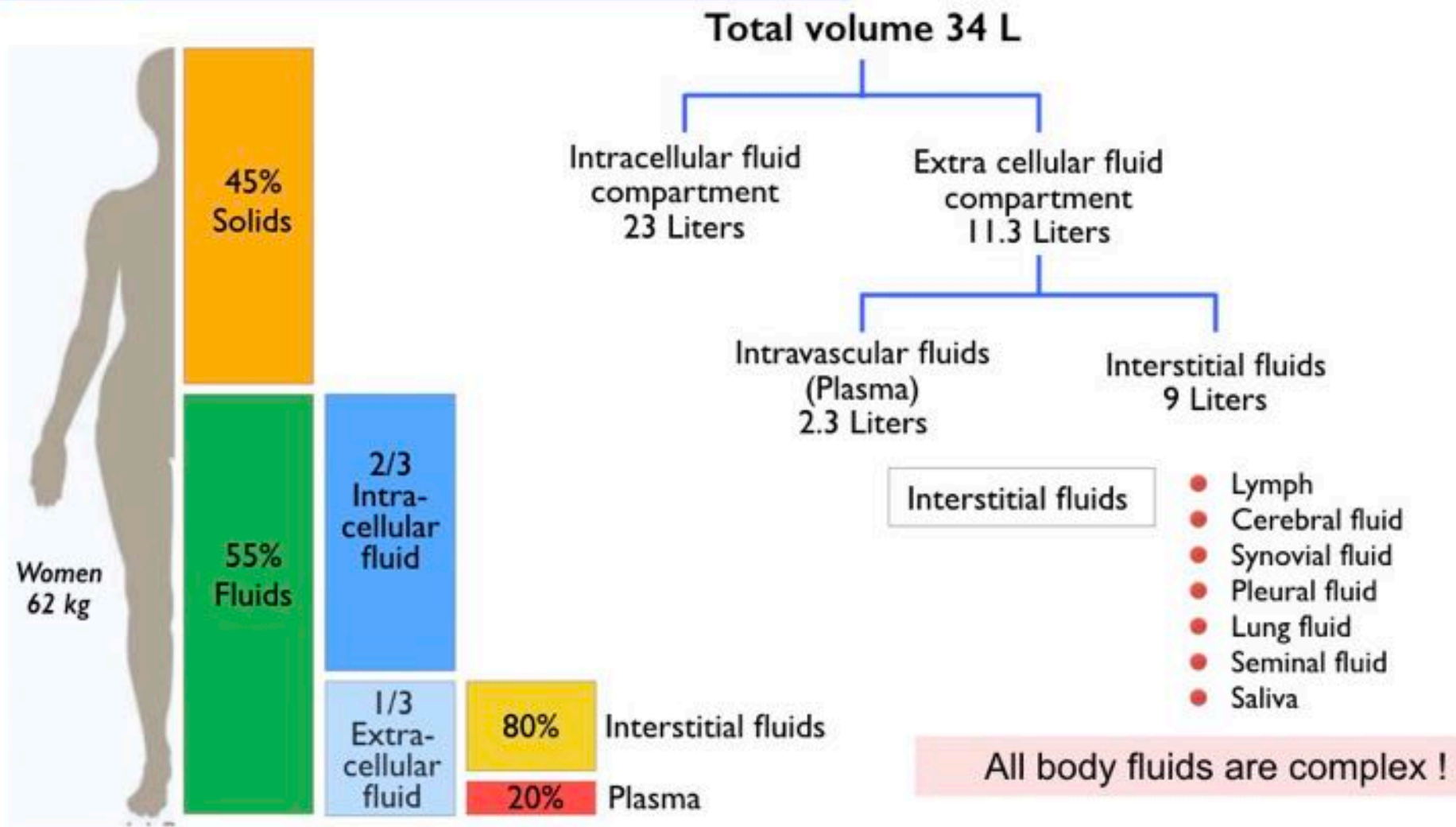
*“Soft matter is based on polymers, surfactants, liquid crystals and colloid grains”*  
*“Some researchers also call it Complex Fluids”*

- Surfactants/lipids
- Colloids
- Polymers
- Foams
- Gels
- Liquid crystals
- Granular materials
- Biological fluids

### Daily life examples

- Dairies, food items
- Ink, gels, paints, foams
- Soap solutions, shampoo, cosmetics
- Molten plastic, glassy materials

Soft matter denotes materials between simple liquids and hard solids.

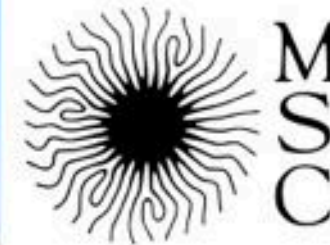


Portals of entry of nanomaterials in the body are by contact (skin), inhalation (lungs), injection (blood) and ingestion (gastric fluid)



# Outline

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Matière et Systèmes Complexes

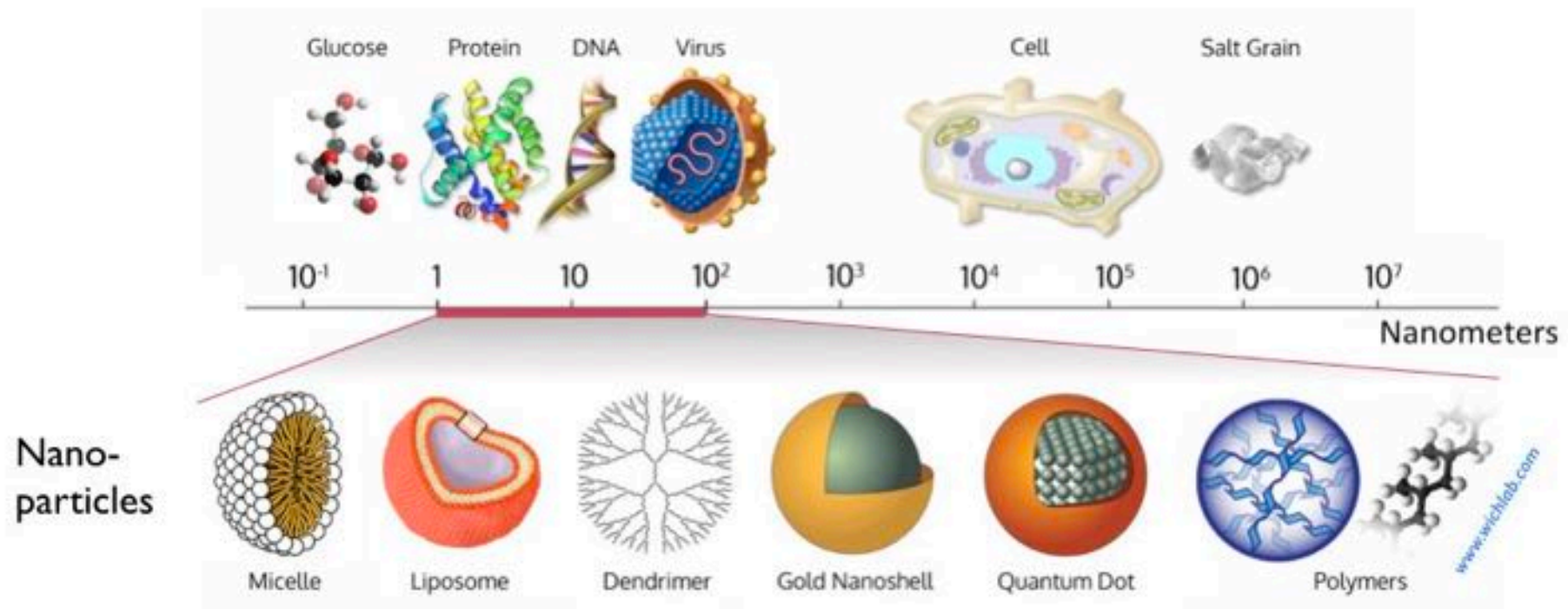
I - Nanomedicine

II - Ischemic stroke

III - Cell biomechanics

IV - Lung fluids

Nanomedicine is the medical application of nanotechnology



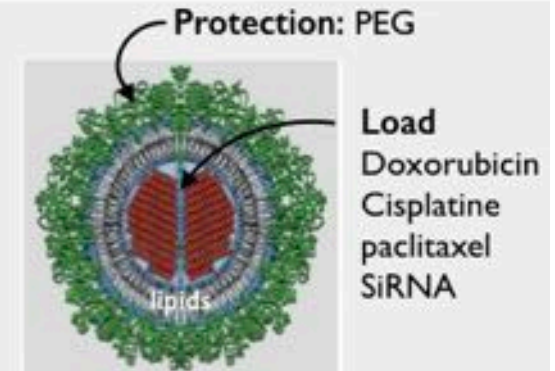
- A nanoparticle is a particle of matter with at least one dimension comprised **between 1 and 100 nm**
- Nanoparticles are the elementary building blocks of **vectors** developed in nanomedicine

Vectorization concerns the transport of biologically active molecules (drug, peptide, protein, nucleic acids) to their targets (cells, tissues, organs)

## Main goals

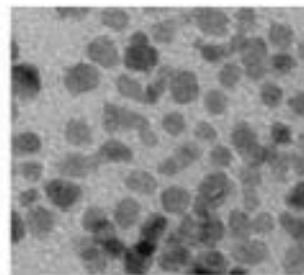
- Increased drug stability
- Bypass the physiological barriers
- Increase the circulation time in blood
- Decrease toxicity

## PEGylated liposomes (anti-cancer, 1990's)



## Inorganic nanoparticles

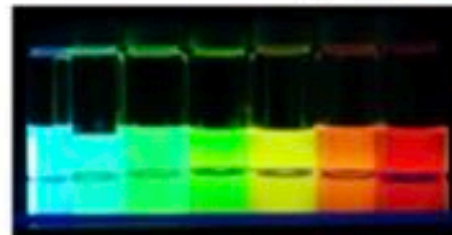
National Nanotechnology Initiative (2000, USA)  
→ Nanosciences



Iron oxide



gold



quantum dots

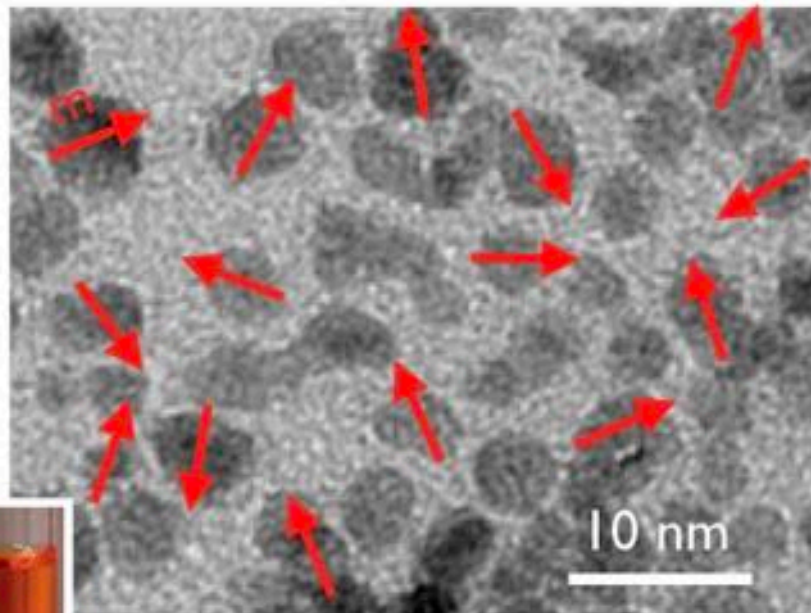
**New paradigm**  
from chemistry to physics

## Applications

- Magnetic NPs → Imaging  
Hyperthermia
- Gold → Photothermal therapy
- Silver → Antimicrobial
- Cerium oxide → Antioxydant

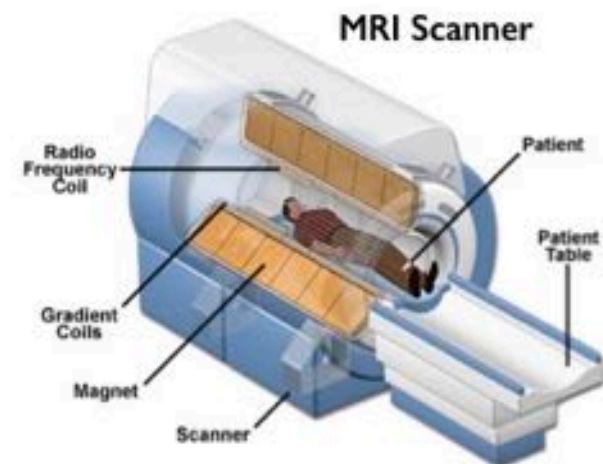
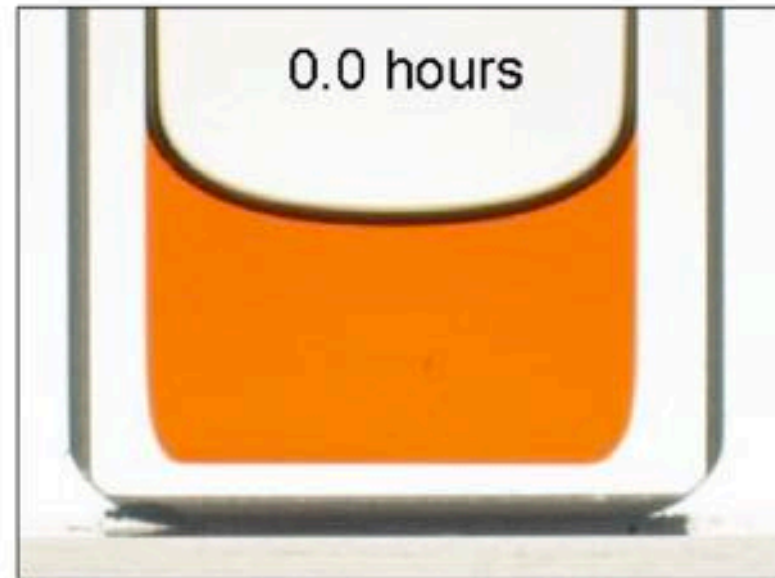
Iron oxide nanoparticles  $\gamma\text{-Fe}_2\text{O}_3$

TEM



Iron oxide nanoparticles are superparamagnetic

- Magnetic Resonance Imaging (Guerbet, Bayer)
- Hyperthermia (MagForce)



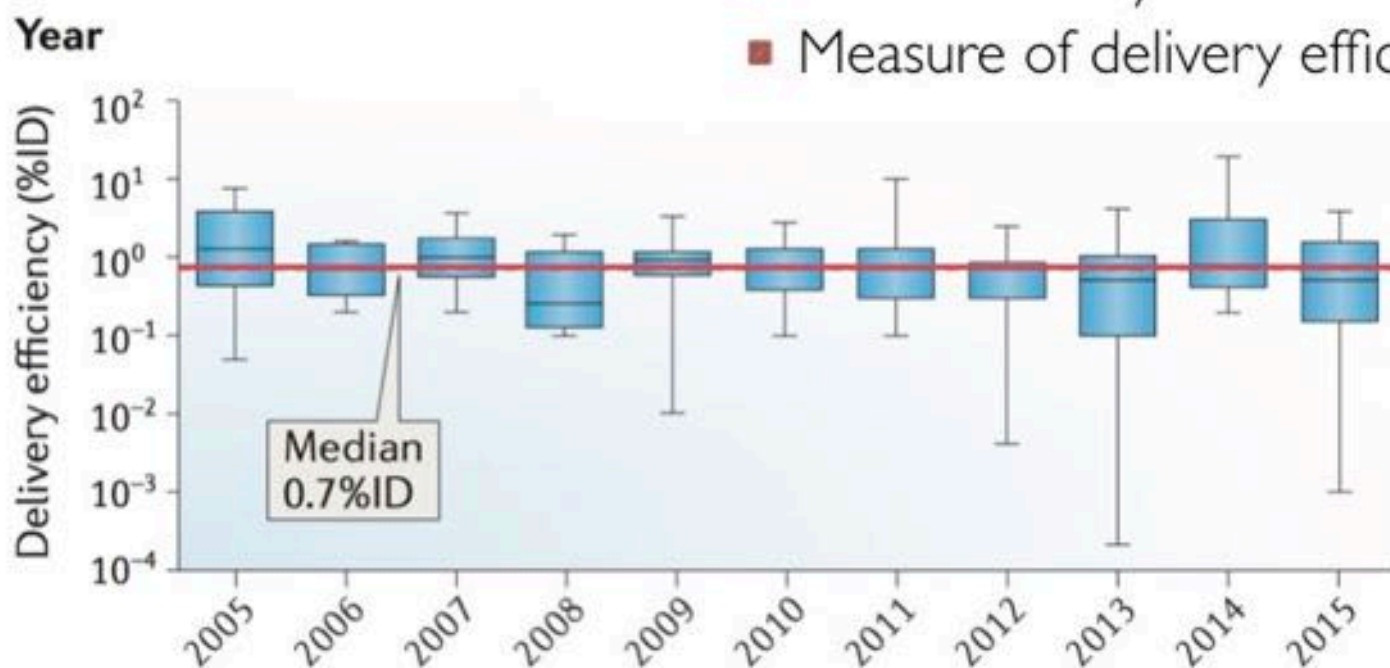


# Analysis of nanoparticle delivery to tumours

Stefan Wilhelm, Anthony J. Tavares, Qin Dai, Seichi Ohta, Julie Audet, Harold F. Dvorak and Warren C. W. Chan



- Delivery through blood circulation
- Statistical analysis on 117 studies
- Measure of delivery efficiency



A delivery efficiency of 0.7% means that 7 nanoparticles over 1000 reach their targets



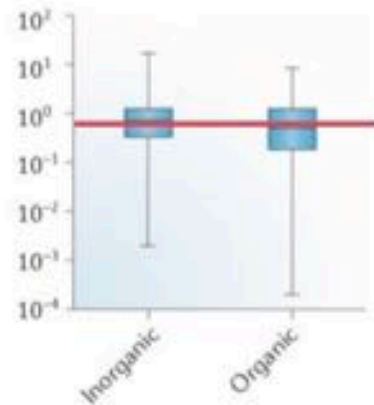


# More puzzling results!

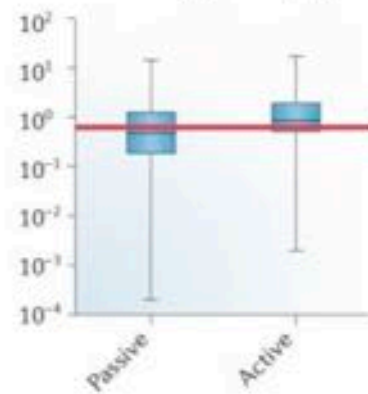
## Analysis of nanoparticle delivery to tumours

Stefan Wilhelm, Anthony J. Tavares, Qin Dai, Seiichi Ohta, Julie Audet, Harold F. Dvorak and Warren C. W. Chan

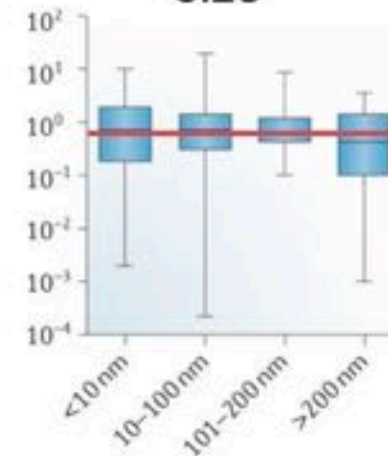
### Organic vs inorganic



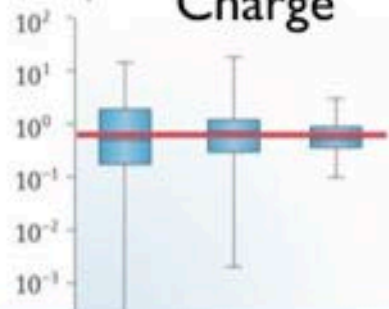
### Targeting



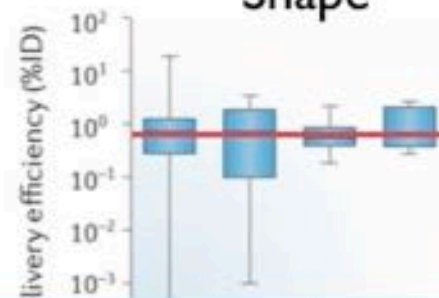
### Size



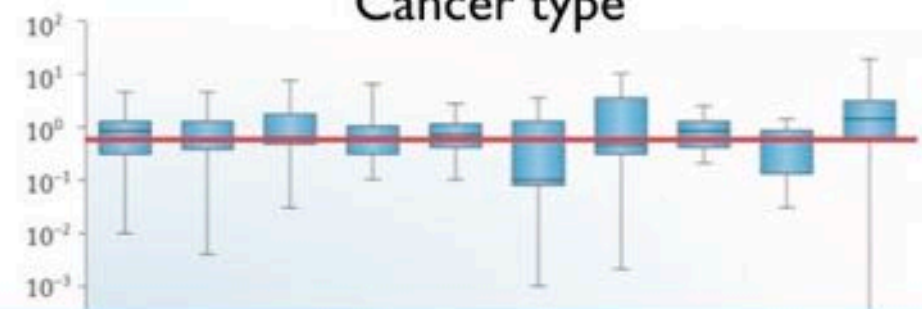
### Charge



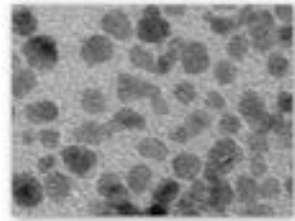
### Shape



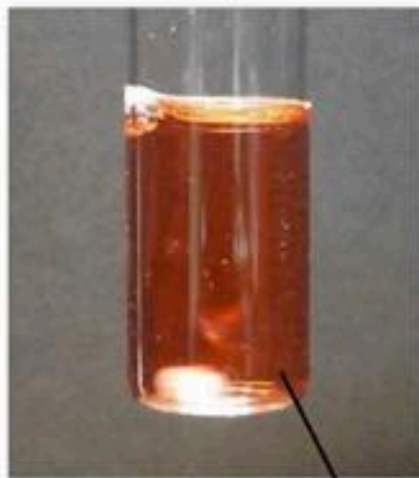
### Cancer type



Translation of inorganic nanovectors to the clinic during the last decades did not live up to the initial expectations



10 nm iron oxide nanoparticles



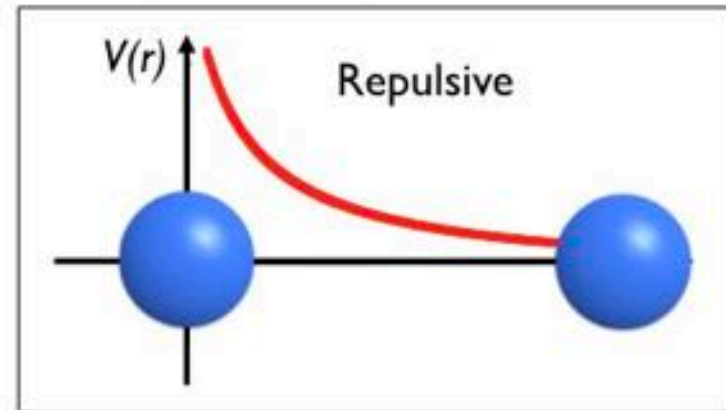
Cell culture medium

- pH 7.4
- Ionic strength (salt) 160 mM
- Biomolecules

The combined effect of collision and attractive potential leads to the aggregation of nanoparticles into large chunks on materials

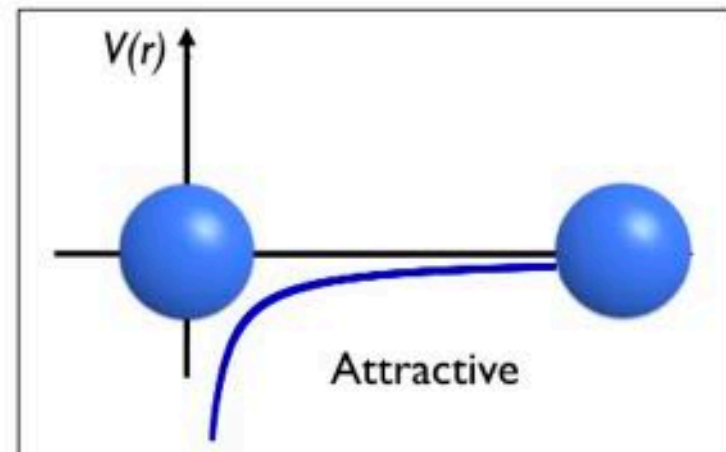
## DLVO theory for colloids Derjaguin, Landau, Verwey, Overbeek (1950)

In the as-synthesized dispersion

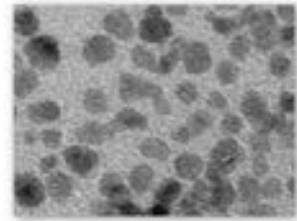


Electrostatic

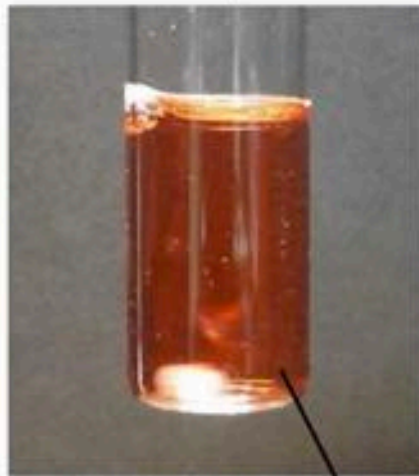
In physiological cell medium/plasma



van der Waals



10 nm iron oxide nanoparticles



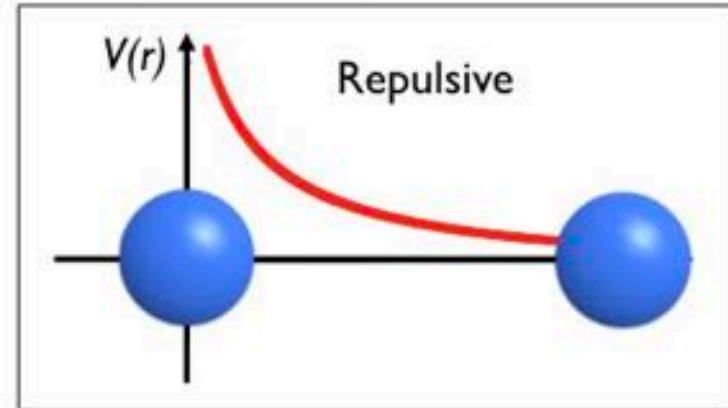
pH 7.4  
Ionic strength (salt) 160 mM  
Biomolecules

Cell culture medium

The combined effect of collision and attractive potential leads to the aggregation of nanoparticles into large chunks on materials

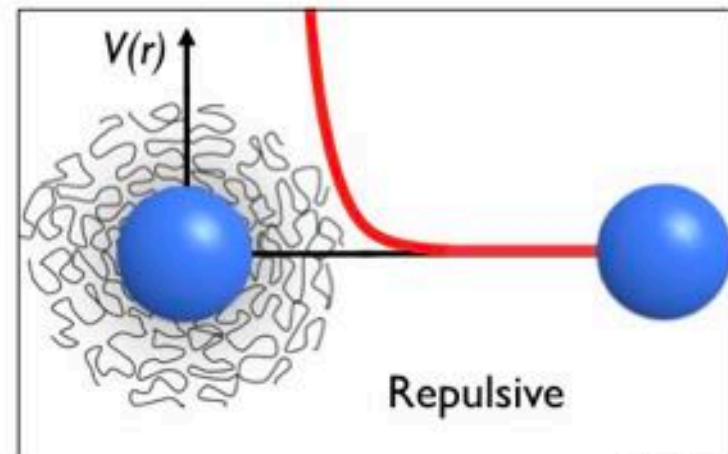
## DLVO theory for colloids *Derjaguin, Landau, Verwey, Overbeek (1950)*

In the as-synthesized dispersion



Electrostatic

In physiological cell medium/plasma



Steric



## Collaborations

**University Paris 5**

**Nathalie Mignet**

Grégory Ramniceanu

Bich-Thuy Doan

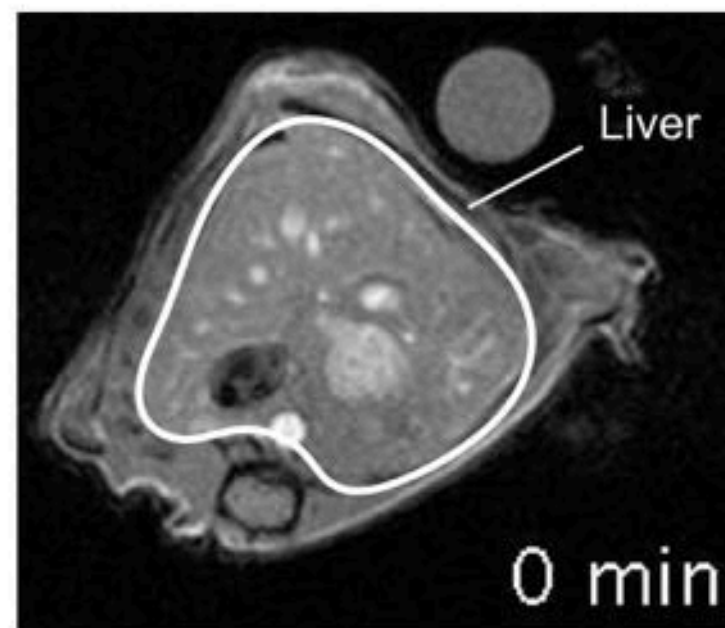
Isabelle Margail



Nathalie Mignet

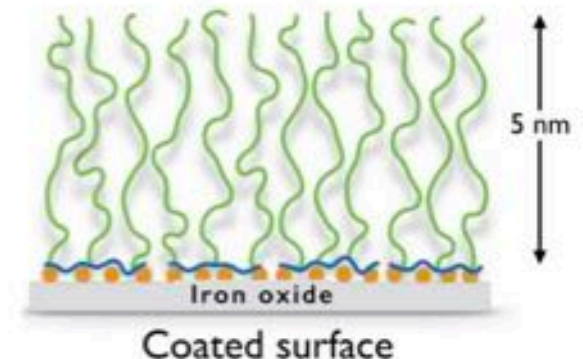
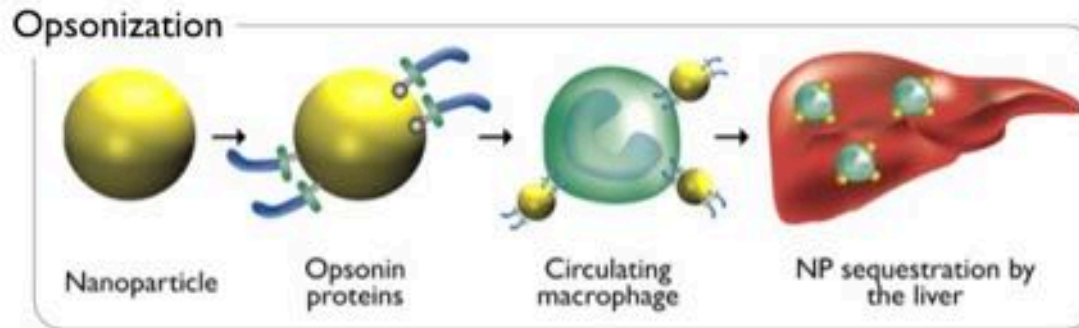


Grégory Ramniceanu



10 nm iron oxide

- *In Vivo*, make the nanoparticles stealth to the immune system and allows the long-term (> hours) circulation in the blood (targeting)



- At the microscopic level, build robust bio-interfaces between nanomaterials and living environment: prevent **protein adsorption** and (NP) aggregation

- Make the nanomaterials biocompatible and non-toxic

Soft matter allows to tackle fundamental issues related to nanomedicine

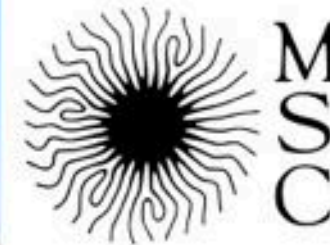


- Bio-interfaces
- Protein adsorption
- Quantitative approaches
- Development of new tools



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Matière et Systèmes Complexes

I - Nanomedicine

II - Ischemic stroke

III - Cell biomechanics

IV - Lung fluids

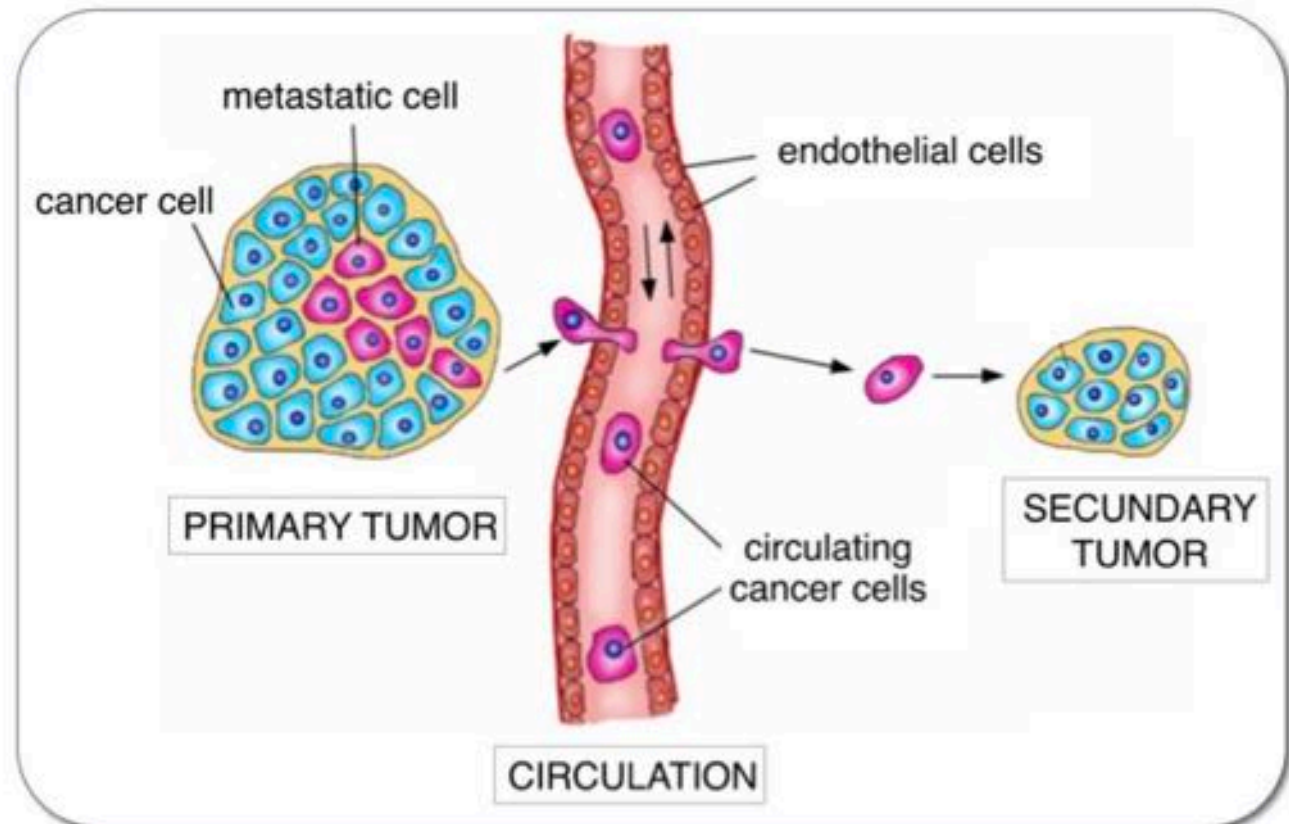
Body fluid  
Intracellular medium  
(cytosol)

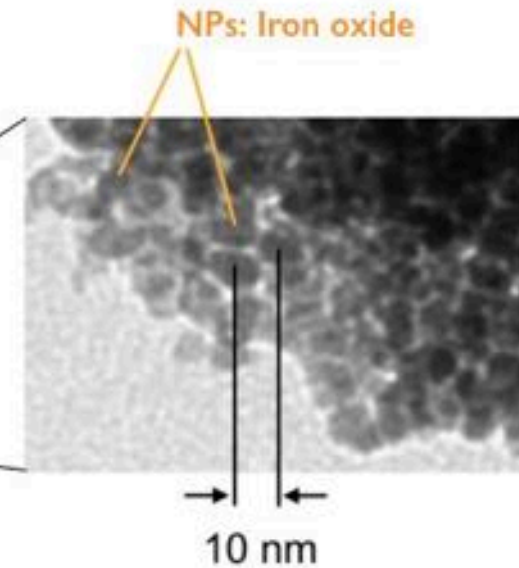
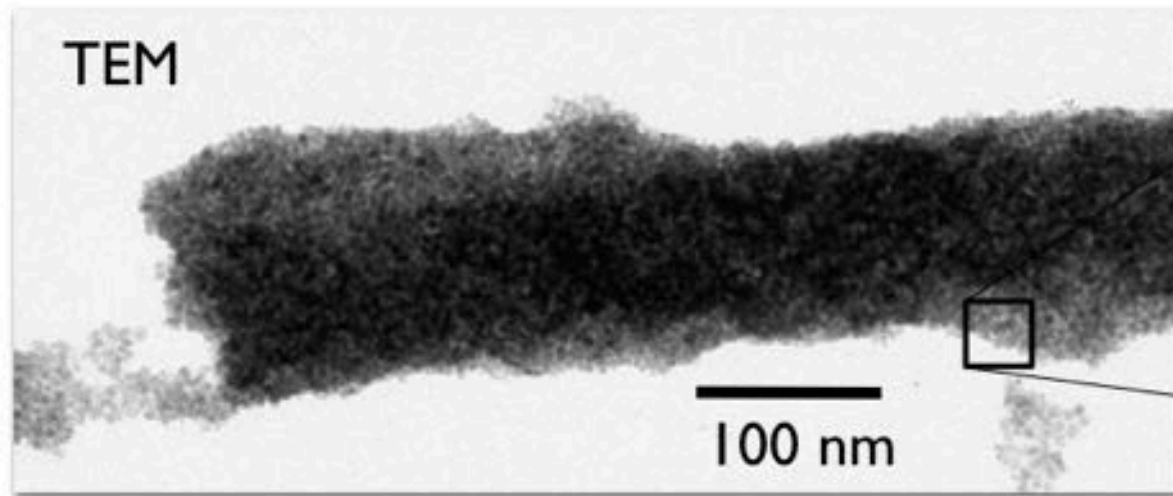
Are cancer cells really softer than normal cells?

Biology  
of the *Cell*

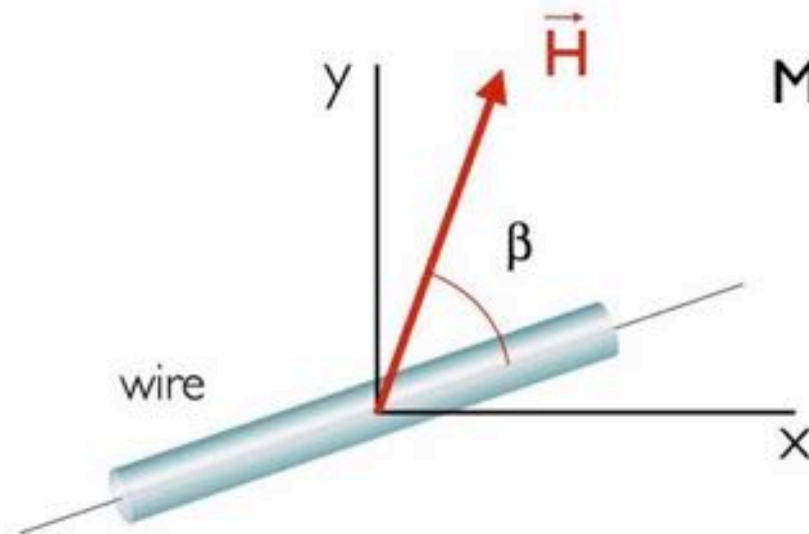
Charlotte Alibert\*†, Bruno Goud\*† and Jean-Baptiste Manneville

→ Measure of the viscosity and elasticity of living cells





Volume fraction of particles  
30 vol. %



Magnetic torque

$$\Gamma_{Mag} = \frac{1}{2} \mu_0 V \Delta\chi H^2 \sin(2\beta)$$

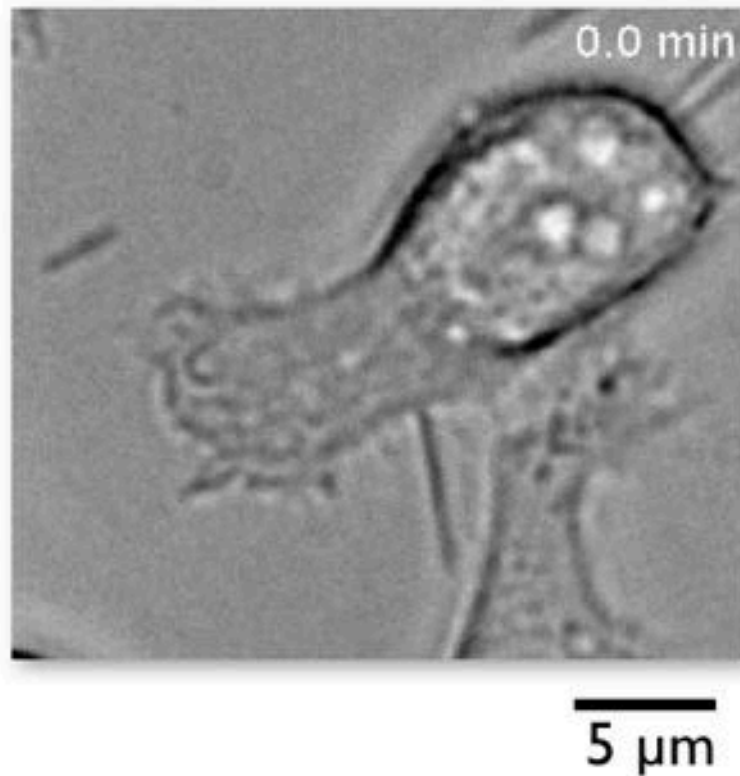
wire  
volume

susceptibility  
anisotropy

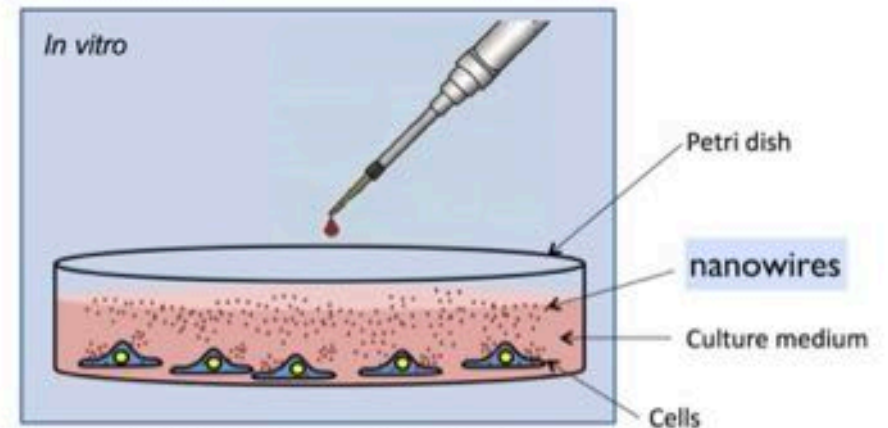
magnetic  
excitation



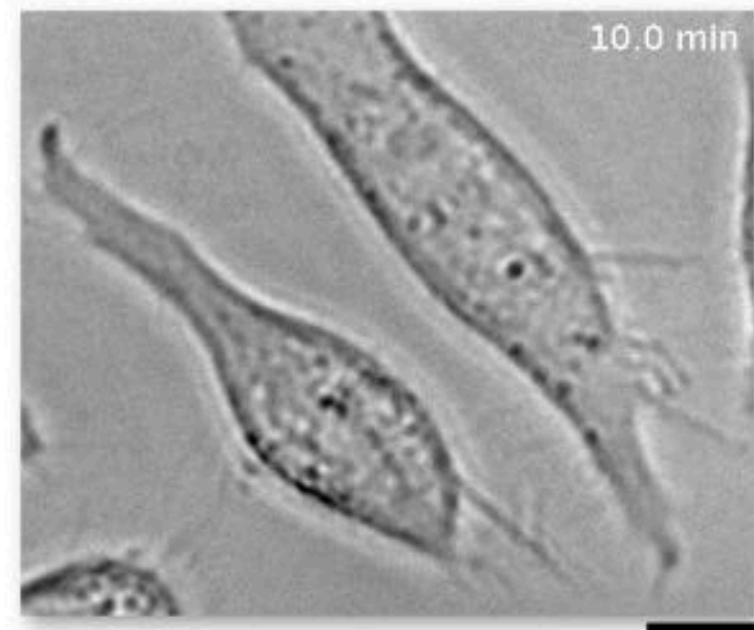
## 1 - Internalization from lamellipodia



## 2 - Internalization from the membrane

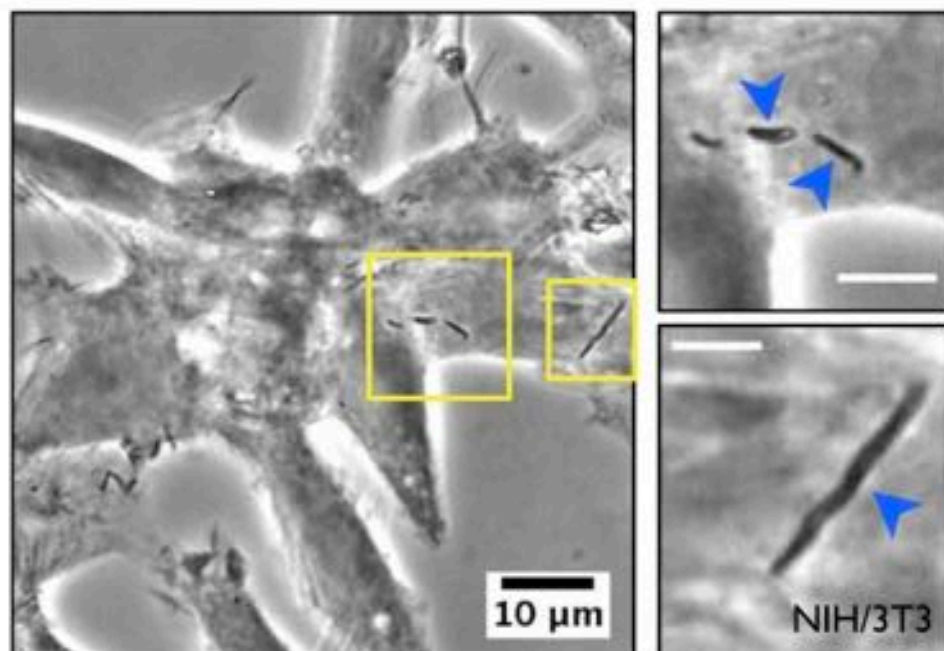


NIH/3T3 mouse fibroblasts  
(maintain integrity of tissues)

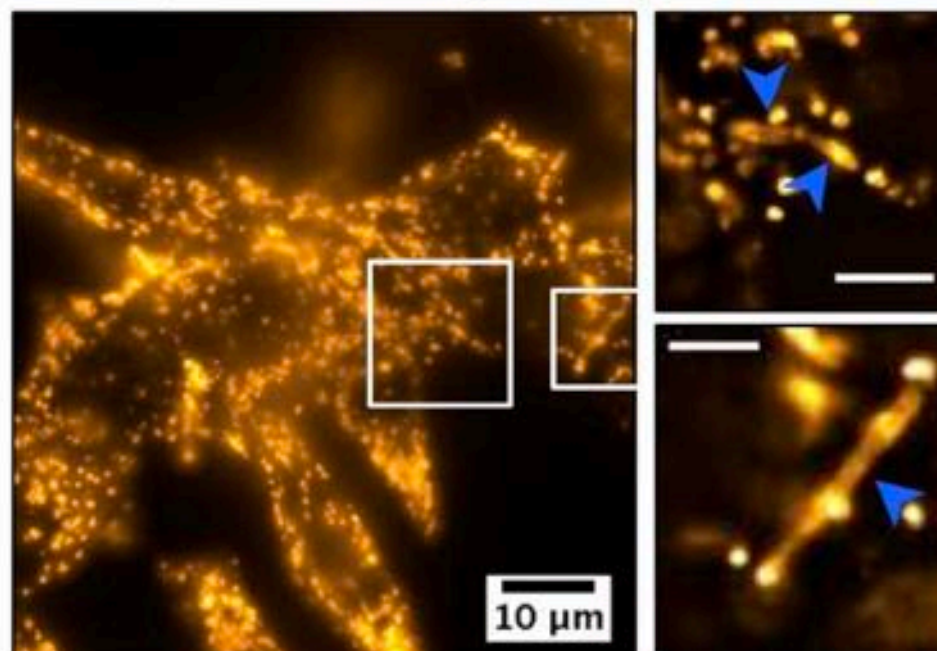


## TEM and immunofluorescence

Phase contrast



Immunofluorescence using LAMP1 proteins



F. Niedergang, Institut Cochin (Paris)

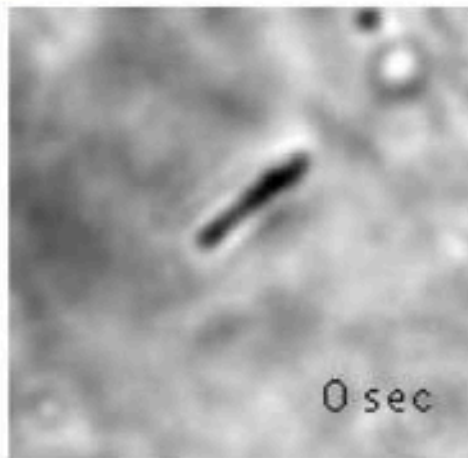
- 90% of the wires are dispersed in the cytosol  
(confirmed with TEM)
- No short time toxicity  
(membrane integrity, metabolic pathway cellular growth)



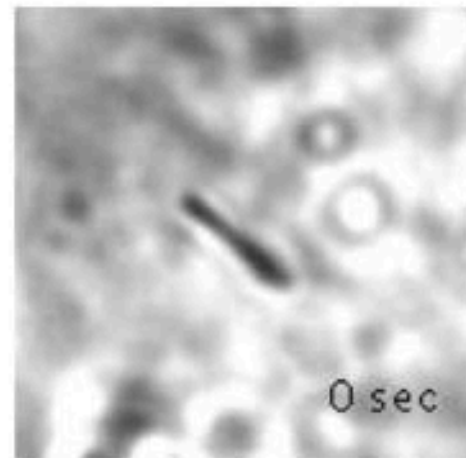
# Active $\mu$ -rheology in cells



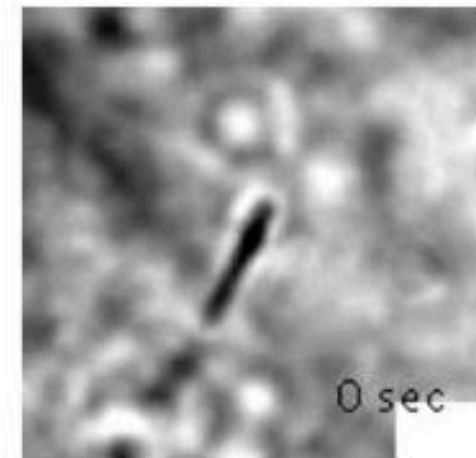
2.8  $\mu\text{m}$  wire



$\omega = 0.15 \text{ rad s}^{-1}$



$\omega = 1.2 \text{ rad s}^{-1}$



$\omega = 3.8 \text{ rad s}^{-1}$

synchronous rotation

$\omega_c$

hindered rotation

$\omega$

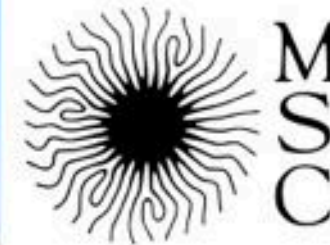
NIH/3T3 mouse fibroblasts  
HeLa cells  
A549 epithelial cells

First identification of the rheological signature of intracellular medium.  
Measure of the viscosity and elasticity of the cell interior



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Matière et Systèmes Complexes

I - Nanomedicine

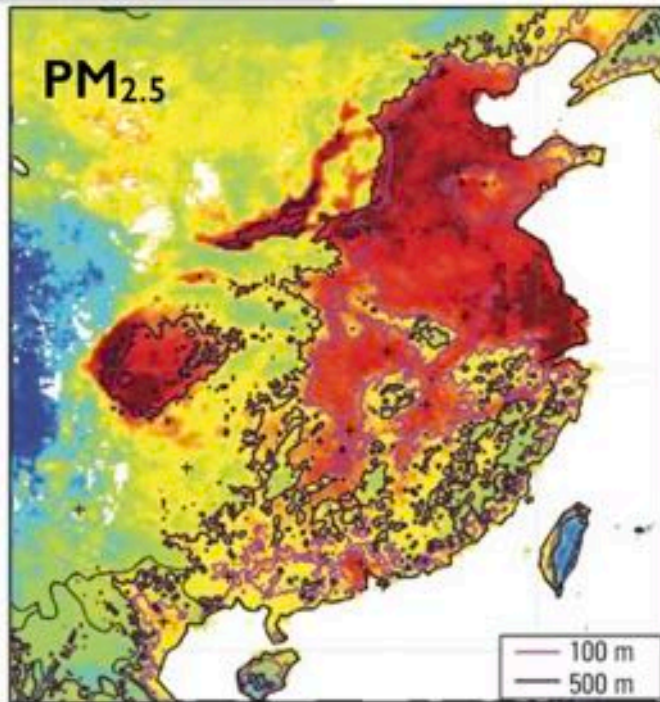
II - Ischemic stroke

III - Cell biomechanics

IV - Lung fluids

Body fluid  
Mucus and surfactant

## Air Quality Index (AQI)



Regional satellite-derived  $PM_{2.5}$  concentrations

$PM_{2.5}$  : Particulate Matter < 2.5  $\mu m$   
(measured by satellite)

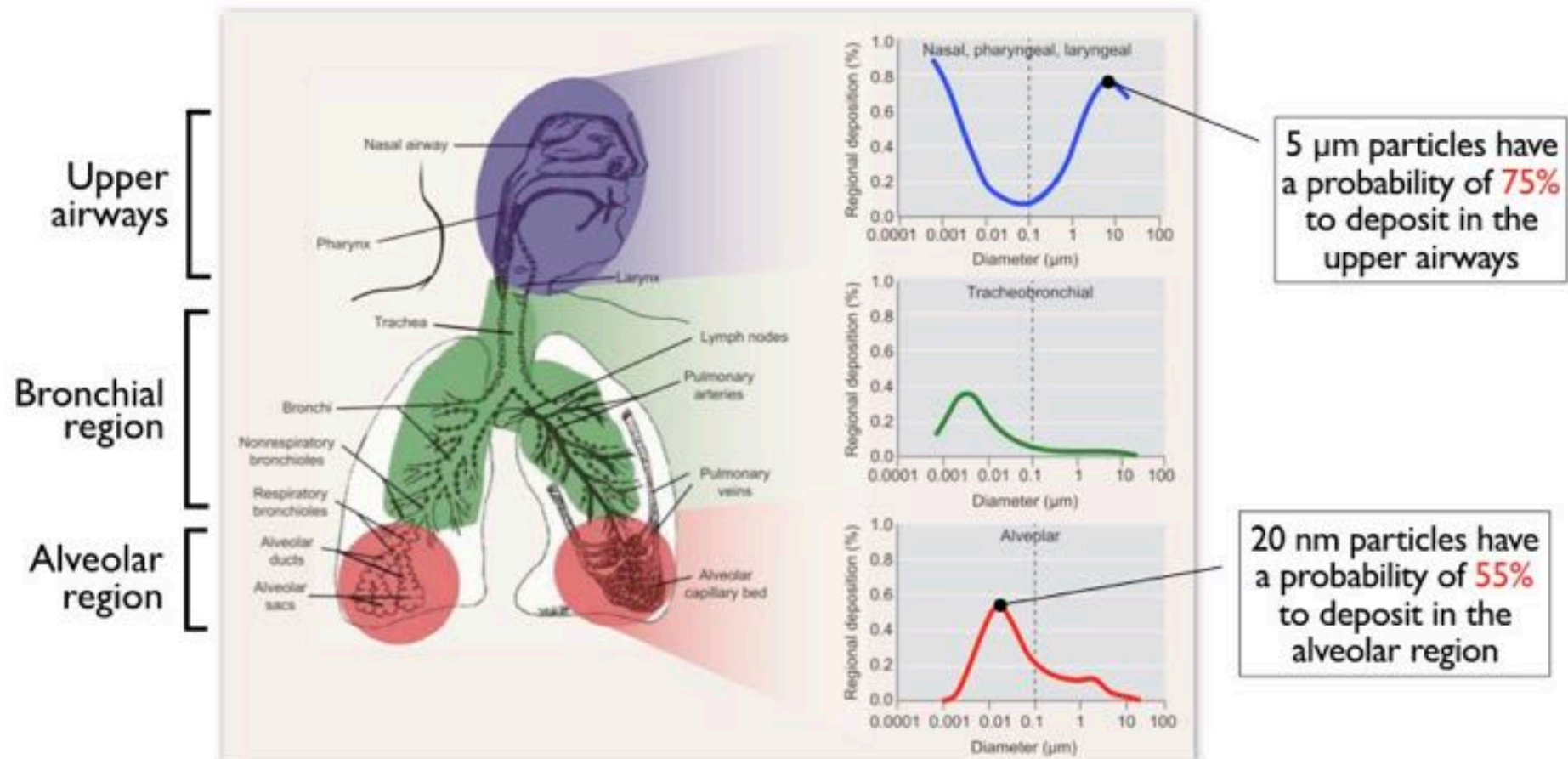
- A daily dose ( $PM_{2.5}$ ) of  $100 \mu g m^{-3}$  corresponds to a total deposition of  $50 \mu g$  in the deep lungs
- Excess mortality worldwide: 3.5 millions / year

- Residential energy (heating, cooking) has the largest impact on premature mortality
- Agricultural emissions are the largest contributions to  $PM_{2.5}$  in USA, Europe, Russia and East Asia



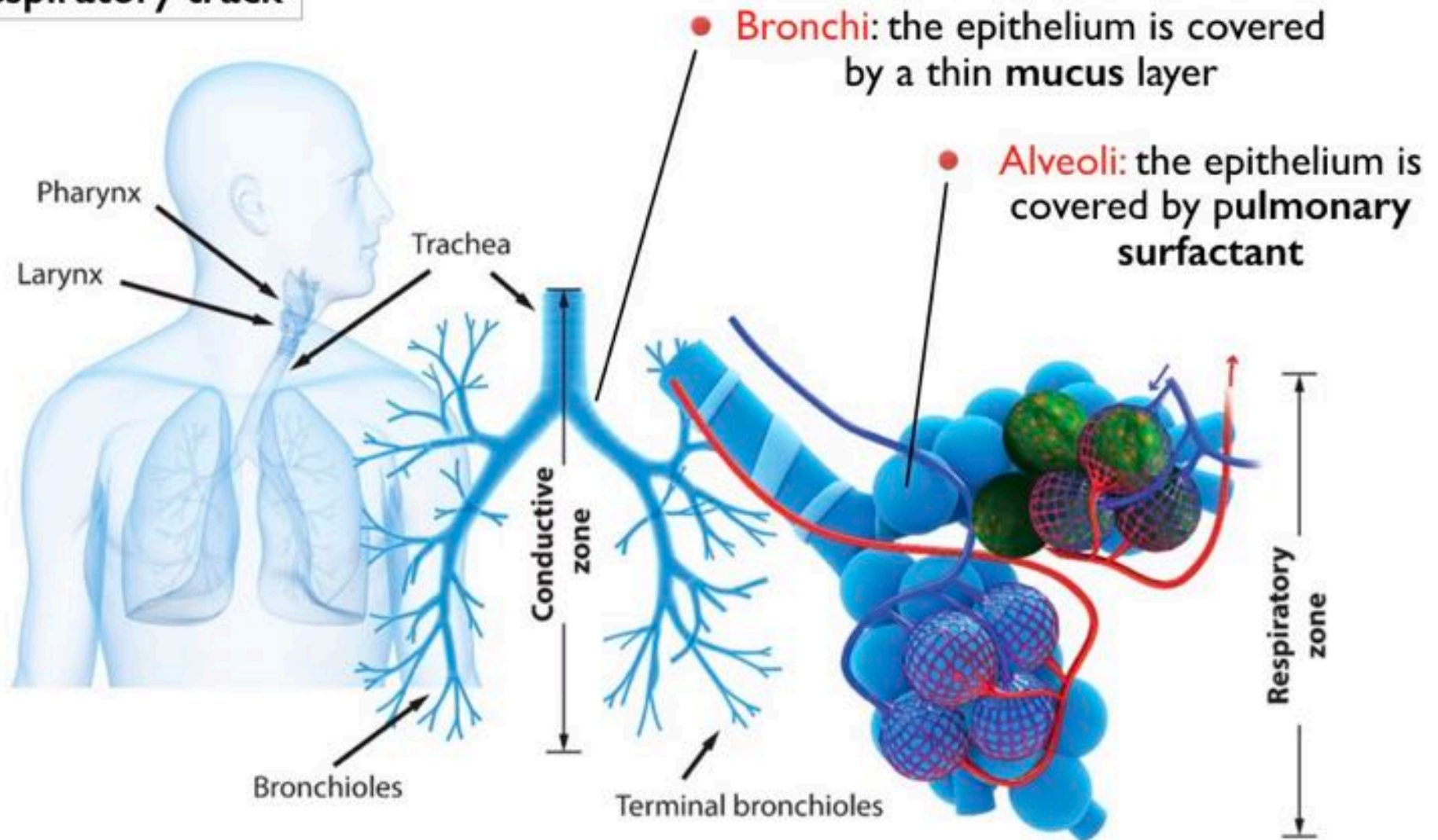
# Deposition profiles with respect to NP size

**Mechanisms** • Impaction • Sedimentation • Diffusion

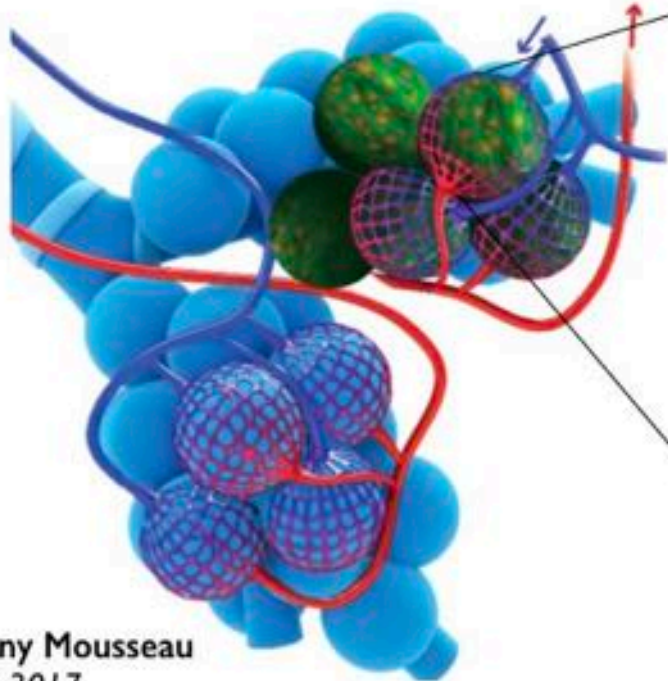


NP particles ( $< 100 \text{ nm}$ ) penetrate deeper into the alveolar region and deposit at high percentages

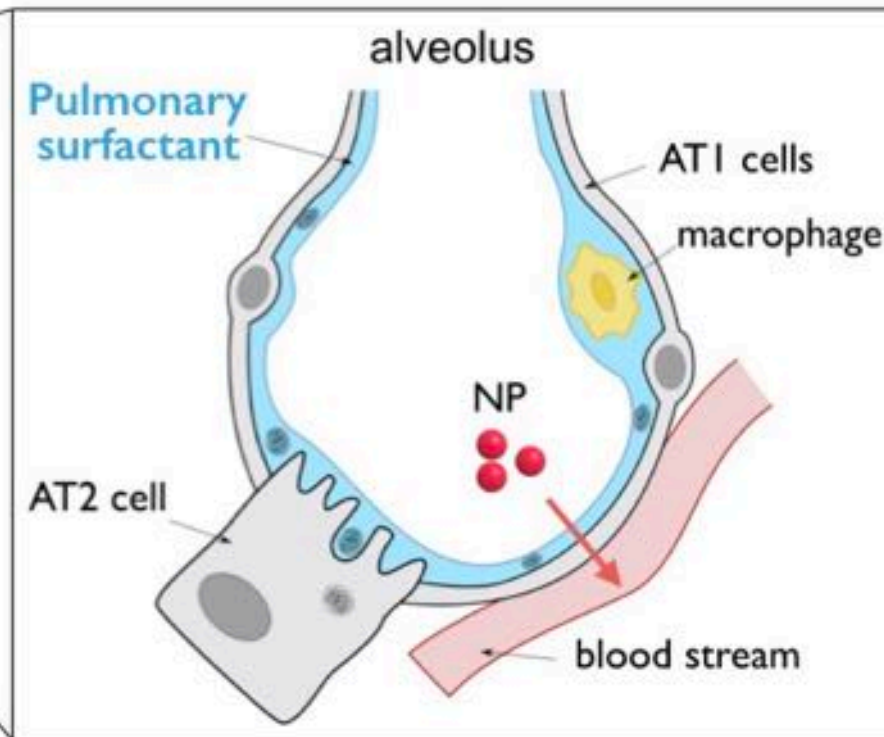
## Respiratory track



## Respiratory track



## Alveolus schematics



Fanny Mousseau  
PhD 2017

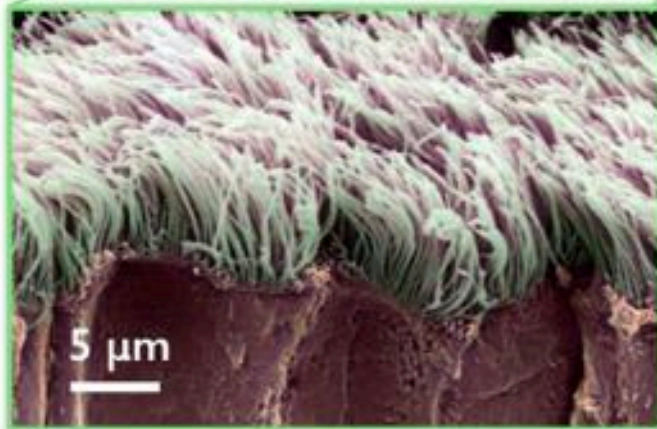
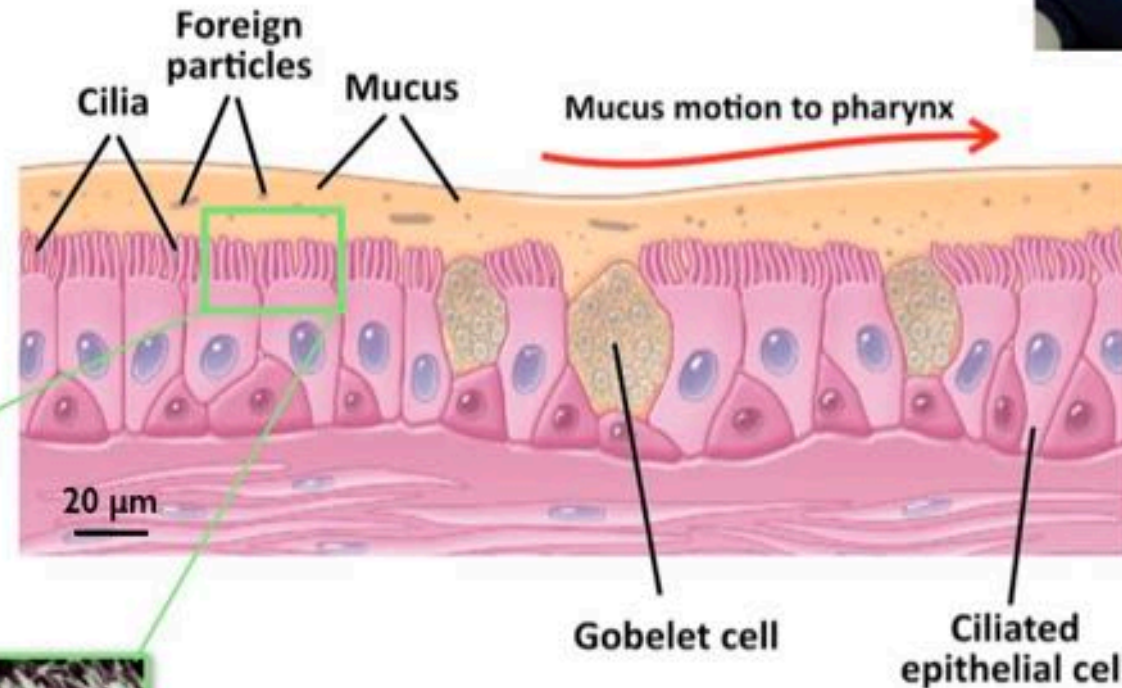


The pulmonary surfactant has a protective effect against nanoparticles through specific interactions with lipid vesicles





Bronchi and bronchioles



## Project

- Interaction studies of nanoparticles or drugs with mucus gel
- Construct a microfluidic device that reproduces the basic functions of cilia beating and bronchial environment



# Conclusions

Soft matter has a lot to do with nanomedicine

Is nanomedicine over?

Nanomedicine is interdisciplinary, so whatever field of science you studied, **OPEN YOUR MIND** and seek other horizons

If the 20th century was the century of physics, the 21st century will be the century of biology.





# Thank you for your attention

The lecture can be uploaded on the website  
<https://www.jean-francois-berret-website-pro.fr>