(Intra)cellular therapies using magnetic and/or plasmonic nanoparticles: from thermal cancer treatments to tissue engineering and biotransformations
Remote activation (light, magnetism, radiation): Towards **temporal** and **spatial** control of the therapeutic action

**Nano-Magnetism & Nano-Plasmonics**

at the heart of **Nano-Bio-Medicine**

"on-demand" & "at a distance" therapies

**Thank you!**

PHENIX, Paris 6, Christine Ménager, Ali Abou-Hassan

IIT Genova, Teresa Pellegrino

biomaGUNE, Javier Reguera, Luis Liz-Marzán
1. **Thermal therapies**

*In situ* measurements of therapeutic efficiency

2. **Thermal therapies**

Combined (synergistic) nano-therapies

3. **Tissue Engineering**

Magnetic approaches to tissue mechanics, stimulation & engineering

4. **Nano-Bio-Degradation in tissues**

Multiscale nanometrologies to track the nano-bio-fate
THERMAL NANO-THERAPIES:
CURRENT RESEARCH = to optimize heating efficiency, thanks to innovative designs

SIZE, MAGNETISATION
and ANISOTROPY
of magnetic nanoparticles
govern their heating capacities

SIZE, DESIGN and
PLASMON BAND
of gold nanoparticles
govern their heating capacities

MEASURE of heating efficiency: in AQUEOUS DISPERSION

<table>
<thead>
<tr>
<th>Size (nm)</th>
<th>Heating Power (W/g)</th>
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<tbody>
<tr>
<td>50</td>
<td>7500</td>
</tr>
<tr>
<td>100</td>
<td>8080</td>
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<tr>
<td>150</td>
<td>15000</td>
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808 nm
BUT THERAPEUTIC TARGET = CANCER CELL
& NANOPARTICLES ARE INTERNALIZED BY CANCER CELLS AND DELIVERED TO ENDOSOMES

MEASURE of heating efficiency : in AQUEOUS DISPERSION
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MAGNETIC NANOCUBES

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cell membrane

nucleus

endosomes

---

1 µm

100 nm

100 nm
THERAPEUTIC TARGET = CANCER CELL
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MAGNETIC NANODIMERS

nucleus

endosomes

cell membrane

1 µm

100 nm

100 nm
THERAPEUTIC TARGET = CANCER CELL & NANOPARTICLES ARE INTERNALIZED BY CANCER CELLS AND DELIVERED TO **ENDOSOMES**

**MAGNETIC NANOFLOWERS**
THERAPEUTIC TARGET = CANCER CELL
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GOLD NANOSTARS (small)
THERAPEUTIC TARGET = CANCER CELL & NANOPARTICLES ARE INTERNALIZED BY CANCER CELLS AND DELIVERED TO ENDOSOMES
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GOLD NANOSTARS (large)
THERMAL THERAPIES EFFICIENCY INSIDE CANCER CELLS?
Magnetic hyperthermia efficiency in the cellular environment for different nanoparticle designs.


Biomaterials 24, 6400-6411 (2014)
PHOTOTHERMIA INSIDE CANCER CELLS?

1. Measurements in aqueous dispersion

PHOTOTHERMIA INSIDE CANCER CELLS?

2. Measurements on internalized nanostars

PHOTOTHERMIA INSIDE CANCER CELLS?

3. Measurements in vivo inside tumors

3. Measurements in vivo inside tumors

In situ measurements in the biological target environment: physical (thermal) fingerprints of therapeutic efficacy

Nanoparticles internalization by cancer cells impact their heating efficiency

MAGNETIC HYPERTHERMIA with iron oxide nanoparticles:
Systematic decrease after cell internalization; more pronounced for Brown relaxation.

PHOTOTHERMIA with gold nanoparticles:
Cell internalization can either increase or decrease photothermal efficiency depending on size and laser excitation.

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<th>1064 nm</th>
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<tr>
<td>900 kHz aqueous dispersion</td>
<td>inside cells</td>
<td></td>
</tr>
<tr>
<td>0</td>
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<tr>
<td>400</td>
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1. In situ measurements of therapeutic efficiency

2. Combined nano-therapies

3. Magnetic tissue engineering

4. Nano-Bio-Degradation in tissues
Can magneto-plasmonic nanohybrids efficiently combine photothermia with magnetic hyperthermia?

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MAGNETO-PHOTO-THERMIA AS AN EFFICIENT BIOMODAL CANCER THERAPY?

strategy 2 = Iron oxide nanoparticles only

TREATMENT in TUMORS: CUMULATIVE HEATING


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TREATMENT in TUMORS: TUMOR REGRESSION / ABLATION

CONTROL (no injection, no hyperthermia)

DUAL

complete tumor eradication

MAGNETO-PHOTO-THERMIA AS AN EFFICIENT BIOMODAL CANCER THERAPY?
strategy 2 = Iron oxide nanoparticles only

TREATMENT in TUMORS: MASSIVE DAMAGES TO THE EXTRACELLULAR MATRIX

organized collagen fibers

INTRACELLULAR NANOPARTICLES:
- Import inside the cells their (multiple) functions = COMBINED THERAPIES
- BUT internalization can impact their thermal efficiency = IN SITU MEASUREMENTS
INTRACELLULAR NANOPARTICLES:

→ Provide the cells with sufficient magnetization to manipulate single cells
1. **In situ** measurements of therapeutic efficiency

2. Combined nano-therapies

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MAGNETIC CELLS MANIPULATION FOR TISSUE ENGINEERING

Magnetic cells aggregation

Various shapes and sizes

MICRO-MAGNET

200 µm

500 µm

to build TISSUES

MAGNETIC TISSUE ENGINEERING

Advanced Materials 00342 (2013)

Magnetic forces promote stem cell differentiation, aggregates fusion and tissue building.
Magnetic forces promote stem cell differentiation, aggregates fusion and tissue building.

Magnetic engineering of stable rod-shaped stem cell aggregates: circumventing the pitfall of self-bending.

MAGNETIC CARTILAGE TISSUE ENGINEERING

Sequential formation of 3D thick cartilage tissues


*Magnetic forces promote stem cell differentiation, aggregates fusion and tissue building.*
Magnetic flattening of stem-cell spheroids indicates a size-dependent elastocapillary transition.

MAGNETIC approaches to tissue engineering and manipulation, in which magnetic forces are created intracellularly on internalized magnetic nanoparticles and used to manipulate single cells within a 3D construct, allow producing 3D organized artificial tissues with an inherent capacity for further physical stimulation.
1. In situ measurements of therapeutic efficiency

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REMAINING ISSUE: WHAT IS THE TISSULAR FATE OF THE NANOPARTICLES?

Quantitative, multiscale nanometrologies to track the transformation – degradation of nanoparticles in tissue environments

SPHEROIDS: A tissue model composed of stem cells harboring nanoparticles

collagen fibers
Multicellular spheroids to monitor (intra)cellular nano-transformations during tissue maturation

Multicellular spheroids to monitor (intra)cellular nano-transformations during tissue maturation

Magnetic quantitative signature of (intra)cellular nano-transformations at the tissue scale

Nanoscale signature of (intra)cellular nano-transformations

Biological monitoring of iron homeostasis

Only Ferritin Light chain (iron binding and nucleation of the iron core) and Ferroportin (iron transport from the inside to the outside) are slightly overexpressed.

A model to be used with any magnetic nanoparticles

Nanocubes or Nanodimers as shape or composition probes to monitor their degradation at the nanoscale within the tissue

A model to be used with any magnetic nanoparticles

Gold can serve as a shield to prevent iron degradation

A model to be used with any magnetic nanoparticles

→ Gold can serve as a shield to prevent iron degradation

A model to be used with any magnetic nanoparticles
→ Gold can serve as a shield to prevent iron degradation

→ Magneto-Thermal Metrics to monitor biodegradation in situ

Nanomaterials import inside the cells their (multiple) functions: \textit{COMBINED THERAPY / MAGNETIC TISSUE ENGINEERING}

BUT internalization can impact their (thermal) therapeutic efficiency: \textit{IN SITU MEASUREMENTS}

AND they can experience massive \textit{INTRACELLULAR LYSOSOMAL DEGRADATION}
Nathalie Luciani, Myriam Reffay, Amanda Silva
Ana Espinosa, Riccardo Di Corato, Alberto Curcio, Sophie Richard, Aurore Van de Walle; postdocs; Anouchka Plan, Gaetan Mary, PhD students; François Mazuel, PhD 2016; Vicard Du, PhD 2015; Kelly Aubertin, PhD 2014; Delphine Fayol, PhD 2012; Michael Levy, PhD 2011; Guillaume Frasca, PhD 2010, Damien Robert, PhD 2010;

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