



MATHER3D (new project)

Magnetic hyperthermia and hadron **T**HERapy applied to **3D** cellular scaffolds

Duration of the project: 3 yrs (2022-2024)

RN – Alessandro Lascialfari

INFN Units

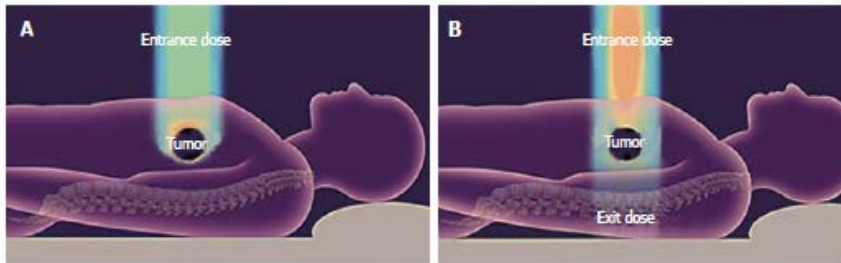
Pavia	-	RL Manuel Mariani
Milano	-	RL Ivan Veronese
Firenze	-	RL Claudio Sangregorio

External participants

Fondazione CNAO	- Pavia
IRCCS S. Matteo	- Pavia
Fondazione Maugeri	- Pavia

INTRODUCTION : the clinical techniques

Hadron Therapy (HT)



(A) targeted proton therapy deposits most energy on target;
(B) conventional radiation therapy deposits in a wider area



CNAO

Magnetic Fluid Hyperthermia (MFH)

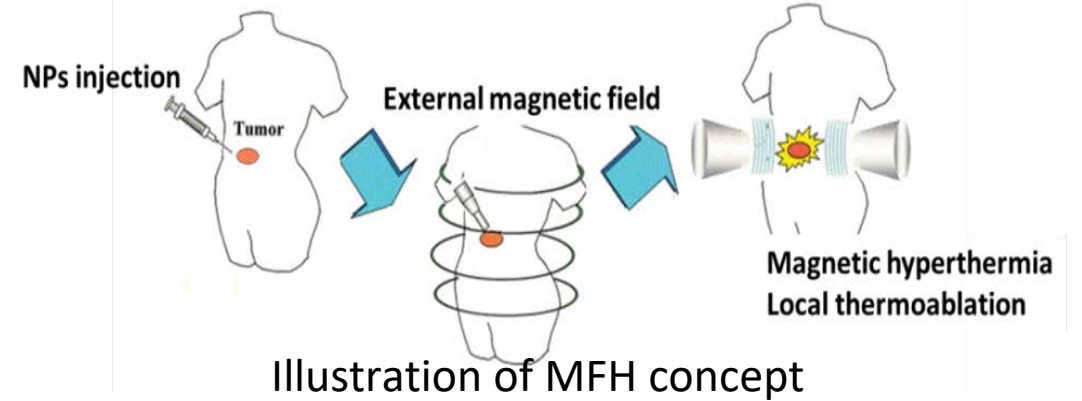


Illustration of MFH concept



Makes use of Magnetic NanoParticles (MNPS)

**Clinic (mainly glioblastoma) :
Germany, Poland, USA,
France, Spain, UK,....**

INTRODUCTION : old projects and the new one

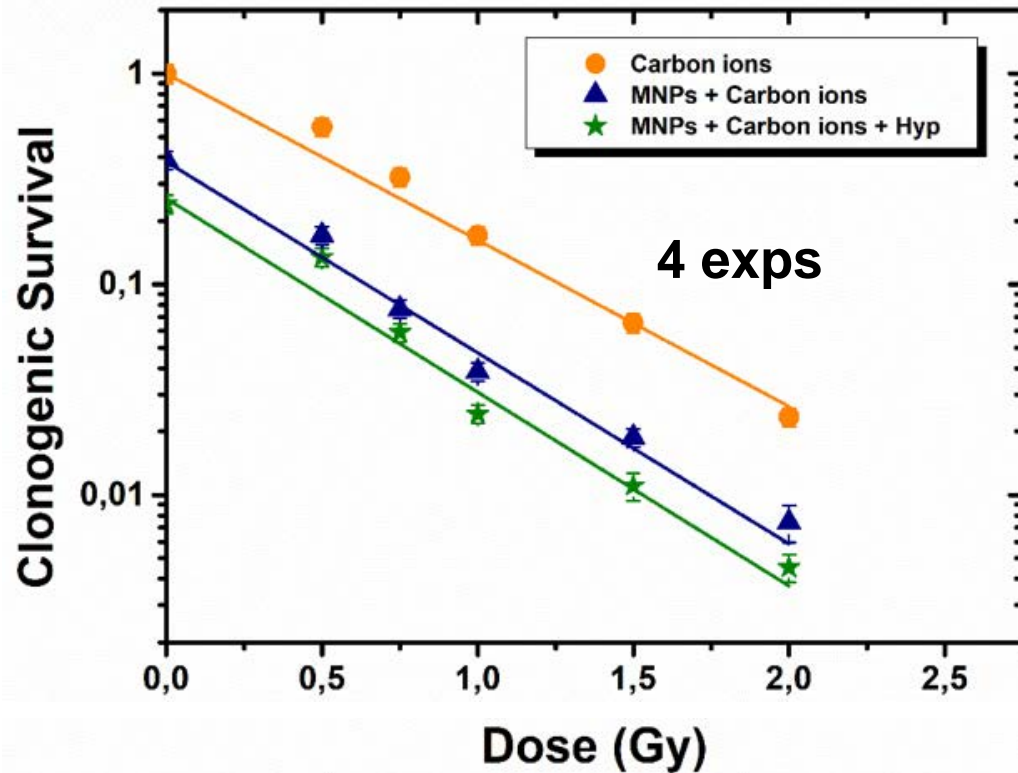
Hadron Therapy and Magnetic Fluid Hyperthermia:

treatments for cancers **where the "classical" therapies fail** - their combination is clinically un-explored

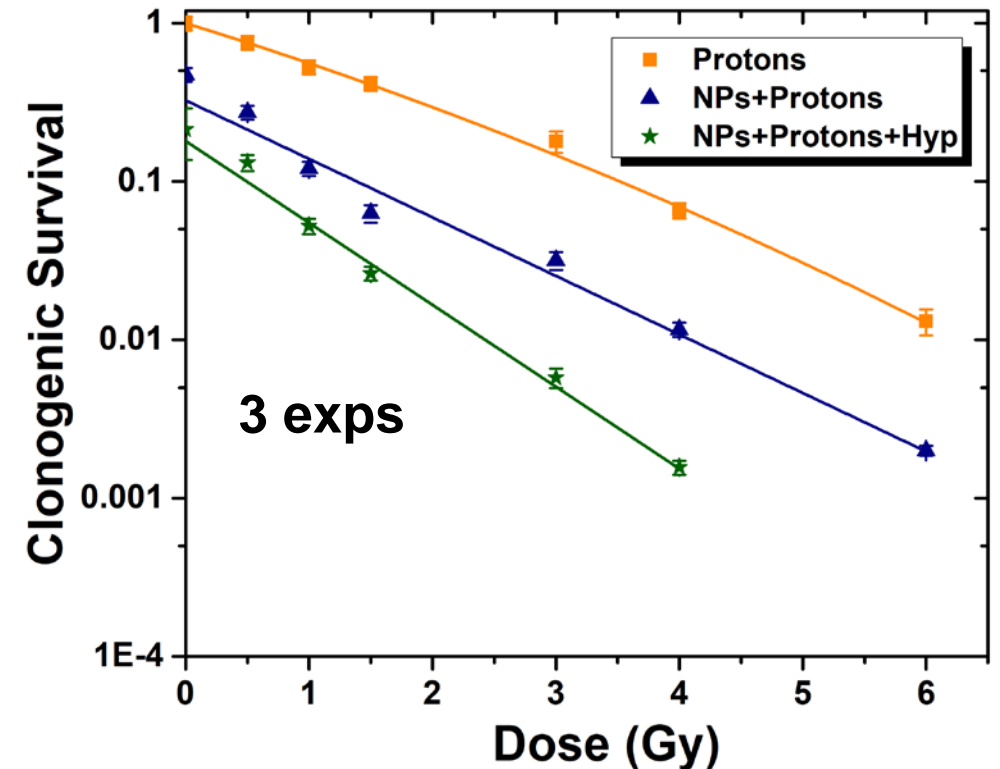
Previous INFN experiments on BxPC3 pancreatic tumor cells →

combined HT and hyperthermia work!

HADROCOMBI (carbons), HADROMAG (carbons)



PROTHYP (protons)



Currently proposed experiment : same combination on 3D scaffolds charged with BxPC3 cells containing MNPs

OBJECTIVES

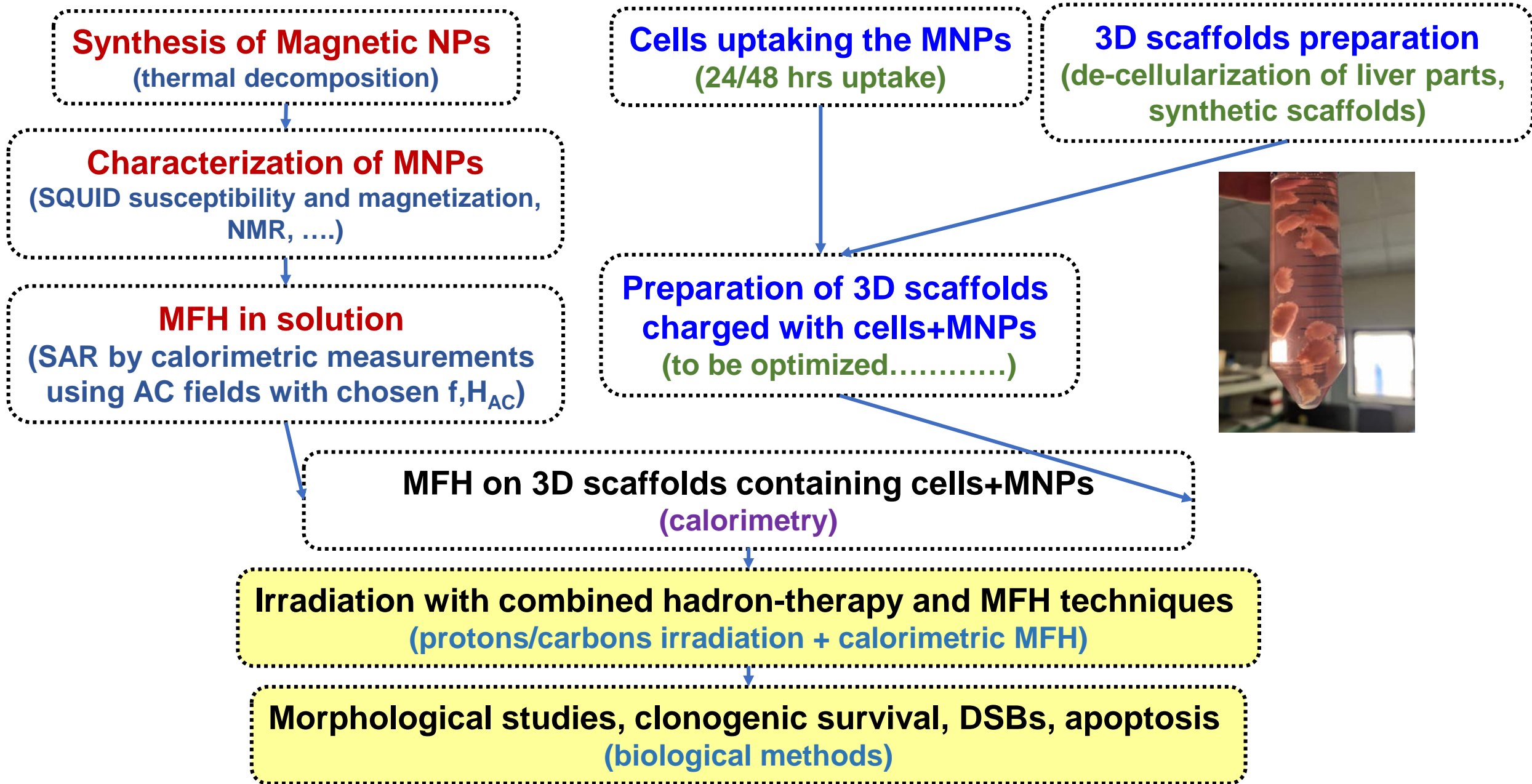
Combined action of HT and MFH techniques
on 3D scaffolds containing pancreatic BxPC3 tumor cells.

To translate to clinic : IN-VIVO PRECLINICAL MODELS ARE NECESSARY
but CNAO has not still the beam available for this.

Other translational aspect: HOSPITALS ARE GOING TO INSTALL PROTON THERAPY

- 1) *Synthesis and optimization of magnetic nanoparticles and their SAR optimization*
- 2) *3D Scaffolds preparation (natural and, contingency plan, artificial)*
- 3) *Inclusion of Cells + MNPs in 3D scaffolds*
- 4) *Combined therapies on 3D scaffolds containing cells+MNPs*
- 5) *Effects of therapies on 3D scaffolds : morphology, DBSs, clonogenic survival*

METHODS : schematic workflow (feedbacks not marked)



Budget (tentative) and FTE-Pavia

Budget Pavia

Total	43-50 kEuro
Consumables	40-46 kEuro
6-8 scaffolds; 21-23 plast/reagents/suppl.;	
6-8 immunoist., etc; 4 liquid helium + lab spares chemicals, electronics, ... ; 3 MRI consumables;	
Missions	2-3 kEuro
Laptop for MFH	1 kEuro

Other Units Budget

Milano 14-16 Keuro
(6-7 reagenti/kit bio; 6-7 ICP/imaging scaffold; 2 AFM/ipertermia; 2 missioni)

Firenze 14-16 keuro
(5 elio liq+reagenti chimici; 8 gene expression, kit reagents for RNA extraction, primary monoclonal and polyclonal antibodies, etc; 2 missioni)

Anagrafica di Pavia 2023 – 2.4 FTE

Alessandro Lascialfari (RN) – PO – UNIPV	0.3
Manuel Mariani (RL) - RU - UNIPV	0.3
Francesca Brero - postdoc – INFN	0.2
Marta Filibian – technician - UNIPV	0.2
Margherita Porru – PhD	0.5
Ilaria Villa – MD (ass.ric.) – UNIPV	0.2
Angelica Facchetti - CNAO-INFN	0.4
Marco Pullia – CNAO-INFN	0.3

The end

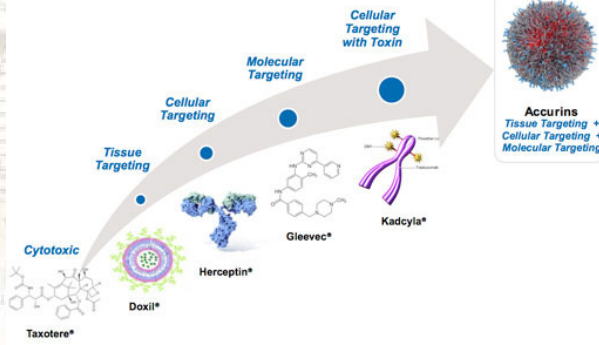
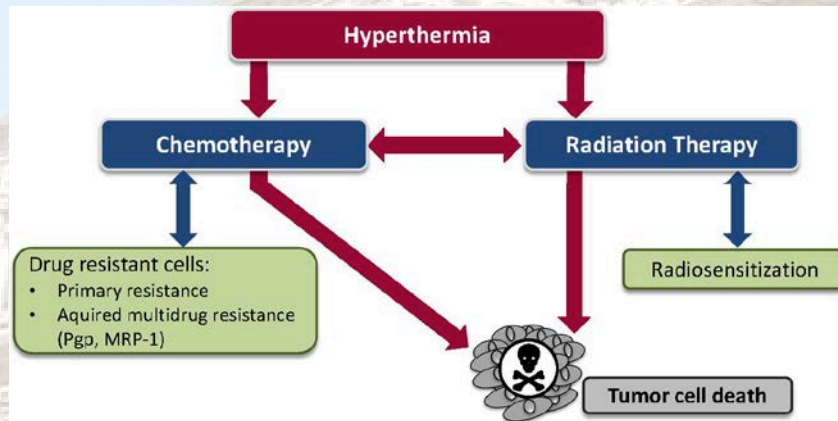
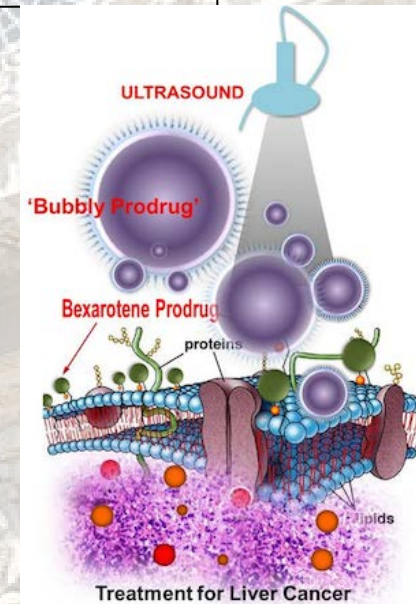
INTERNATIONAL FRAMEWORK AND ORIGINALITY

FRAMEWORK OF OUR PROJECT : recent advances in therapies.....

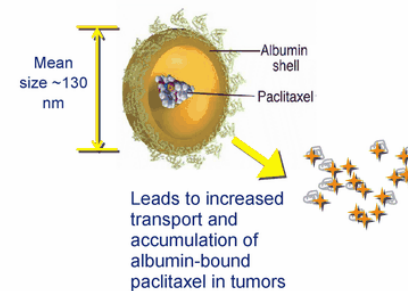


Mutidisciplinary importance of :

- **combined therapies** (e.g. chemotherapy and radiation therapy)
- **Nanomedicine and nanotechnology**



ABRAXANE®: Lead Compound Utilizing nab® Technology



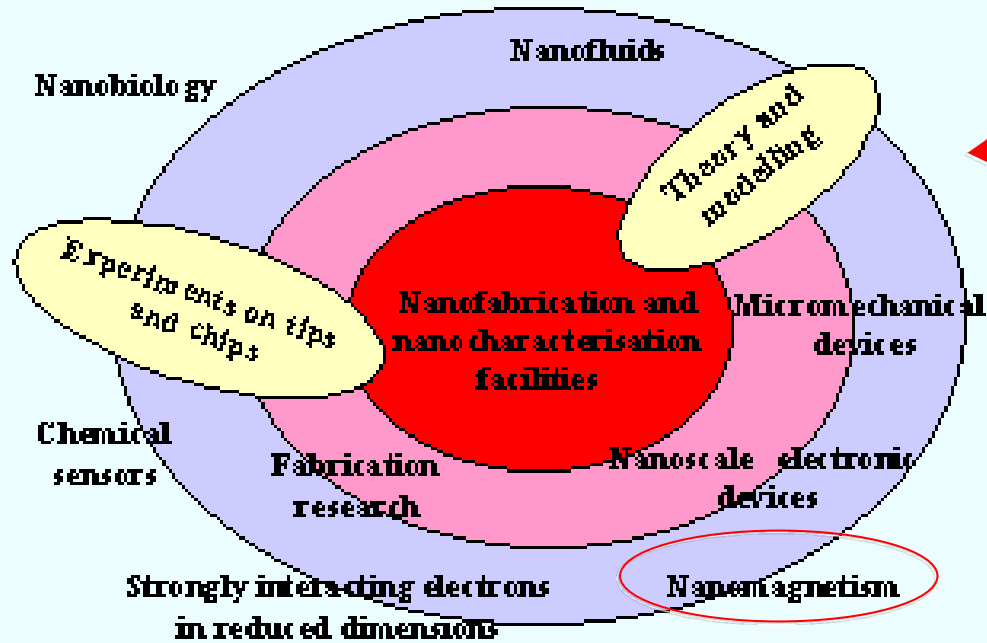
Leads to increased transport and accumulation of albumin-bound paclitaxel in tumors

ABRAXANE Value Proposition

- Improved clinical outcomes in metastatic breast cancer and lung cancer vs. paclitaxel
- Emerging, unprecedented data in pancreatic cancer
- Comprehensive, ongoing clinical program with recognized KOLs ensuring a steady flow of data in additional solid tumor cancers
- Leveraging our combined expertise to improve patient care

ABRAXANE extended market exclusivity from proprietary nab technology

Nowadays : NPs, **interdisciplinarity** and world interest



UCL Nanotechnology center



Track 4: Advances in Nanomedicine

- » Track 4-1 ☒ Drug delivery
- » Track 4-2 ☒ Tissue engineering
- » Track 4-3 ☒ DNA technology
- » Track 4-4 ☒ Nanobiotechnology
- » Track 4-5 ☒ BLOOD Purification
- » Track 4-6 ☒ Cancer
- » Track 4-7 ☒ Photodynamic therapy
- » Track 4-8 ☒ Medical devices

6th Global Experts Meeting & Expo on Nanomaterials and Nanotechnology, "Advances in Nanomaterials & Nanotechnology", April 21-23, 2016 Dubai, UAE



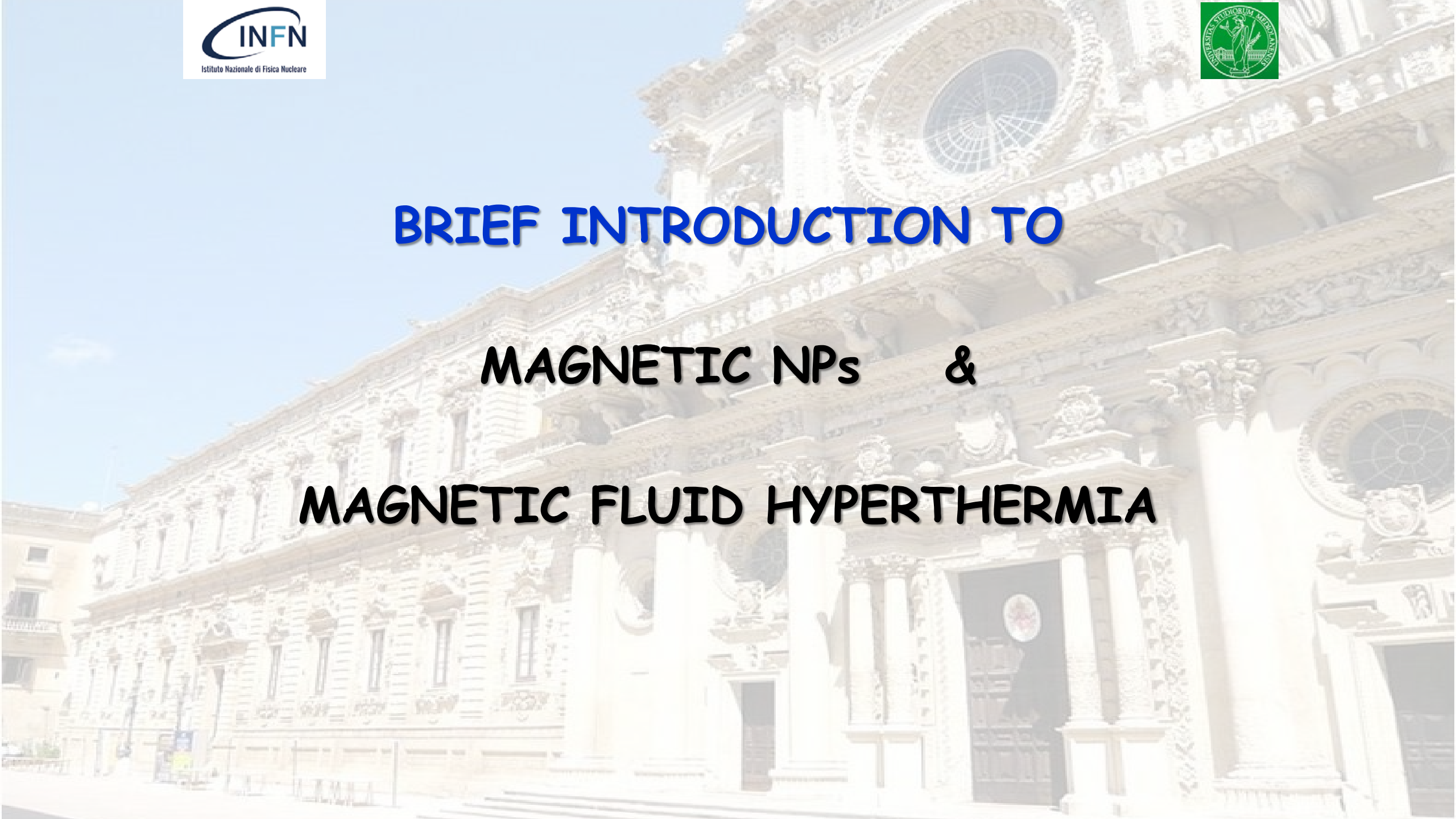
OUR PROJECT



It's **the first time (to our knowledge)** that
**Magnetic Fluid Hyperthermia and Proton
Therapy** are **combined**

The INFN group: a **combination of skills/expertise** on :
Magnetism and nanoscale, Nanotechnology
Radiobiology, Irradiation therapies, Imaging,....

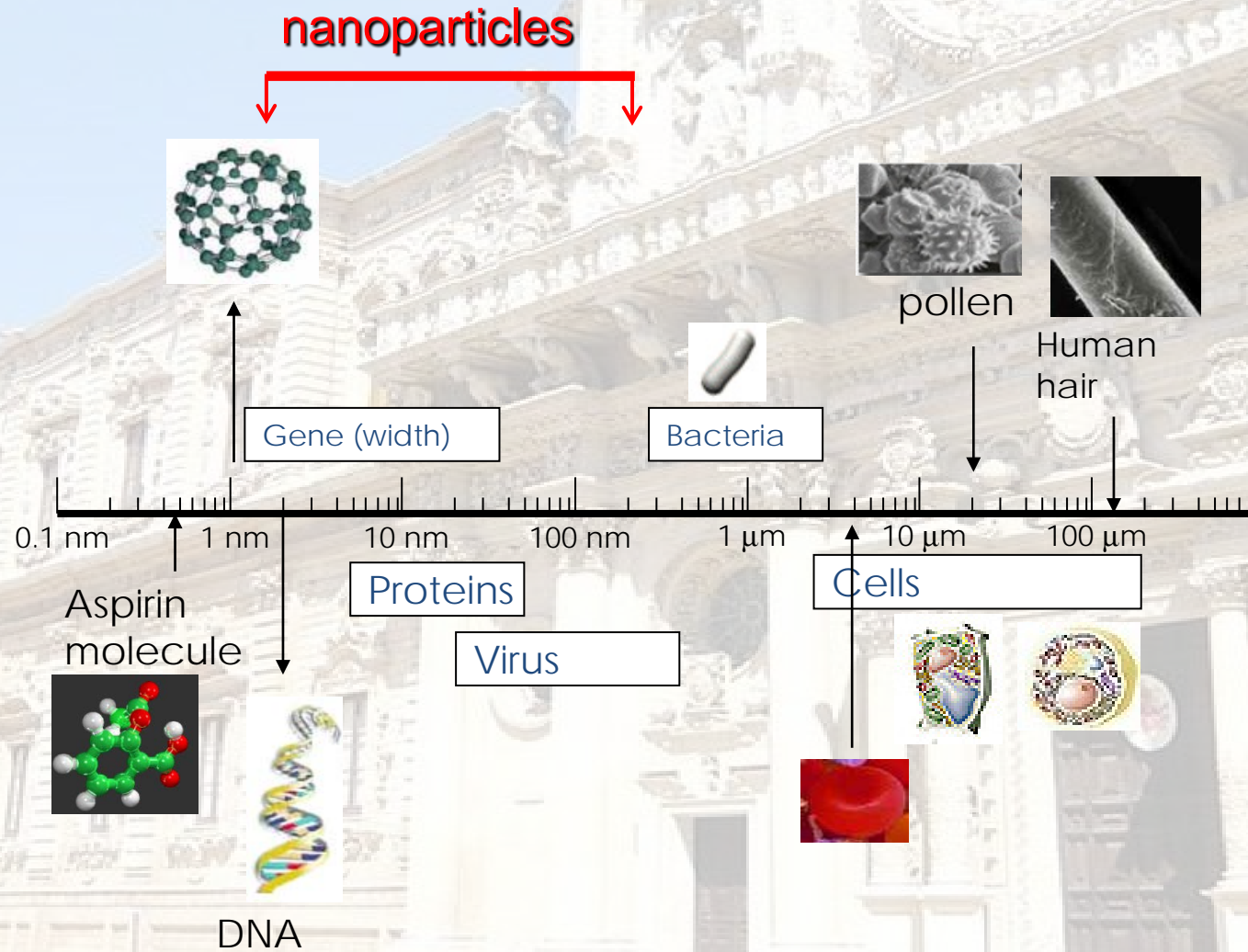
Old projects' experience : EU-FP7 (Nanother), COST-
Radiomag, FIRB-Riname, AIRC, INFN, Cariplo, FBML, etc.



BRIEF INTRODUCTION TO
MAGNETIC NPs &
MAGNETIC FLUID HYPERTHERMIA

Magnetic Nanoparticles

Why NPs in biomedicine (I)



Why **Magnetic** NPs in biomedicine (II)

Sensing

(MRI, Sentimag, MEG-SQUID,...)



SENSING



MOVING

Moving
(navigation)

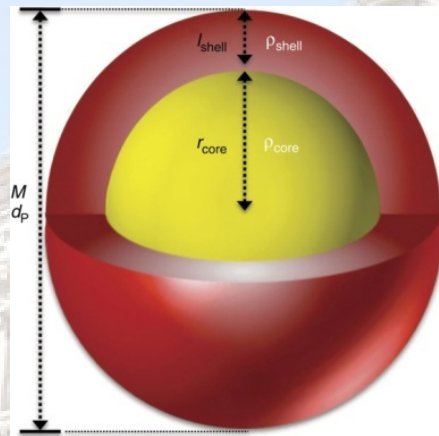


HEATING

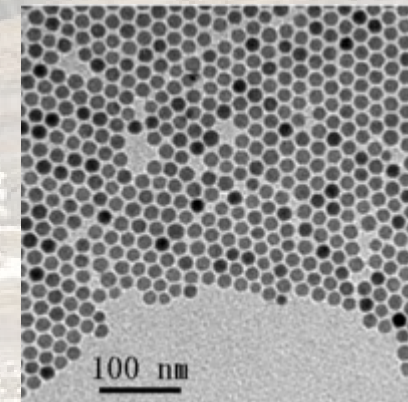
Heating
(Magnetic
Hyperthermia)

What are magnetic nanoparticles ?

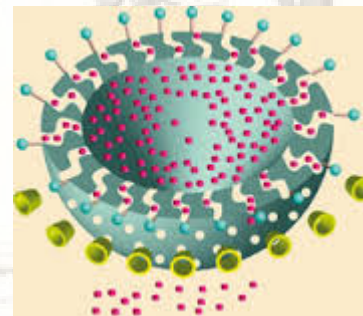
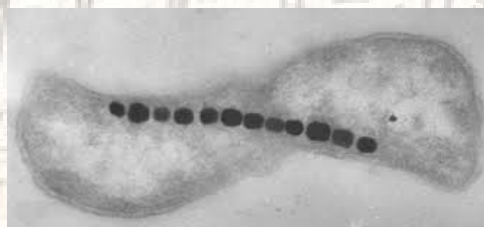
Simplest form : magnetic core (often simple ferrites) + organic coating



TEM



- * Natural NPs (magnetosomes)
- * Hollow / different shape



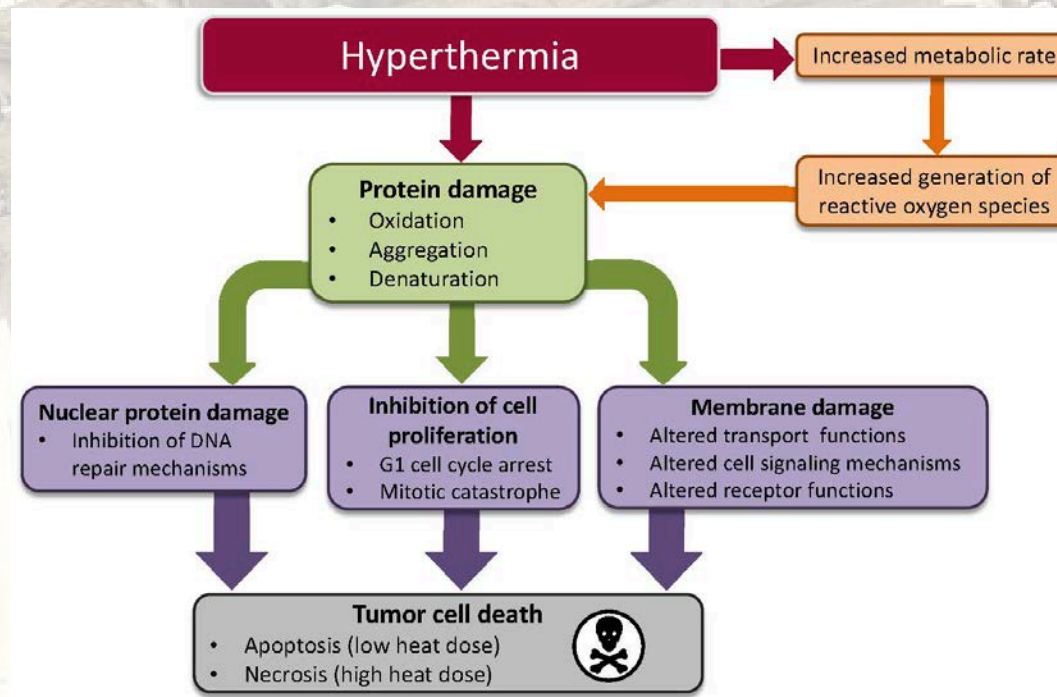
High monodispersity

Magnetic Fluid Hyperthermia

What is hyperthermia?



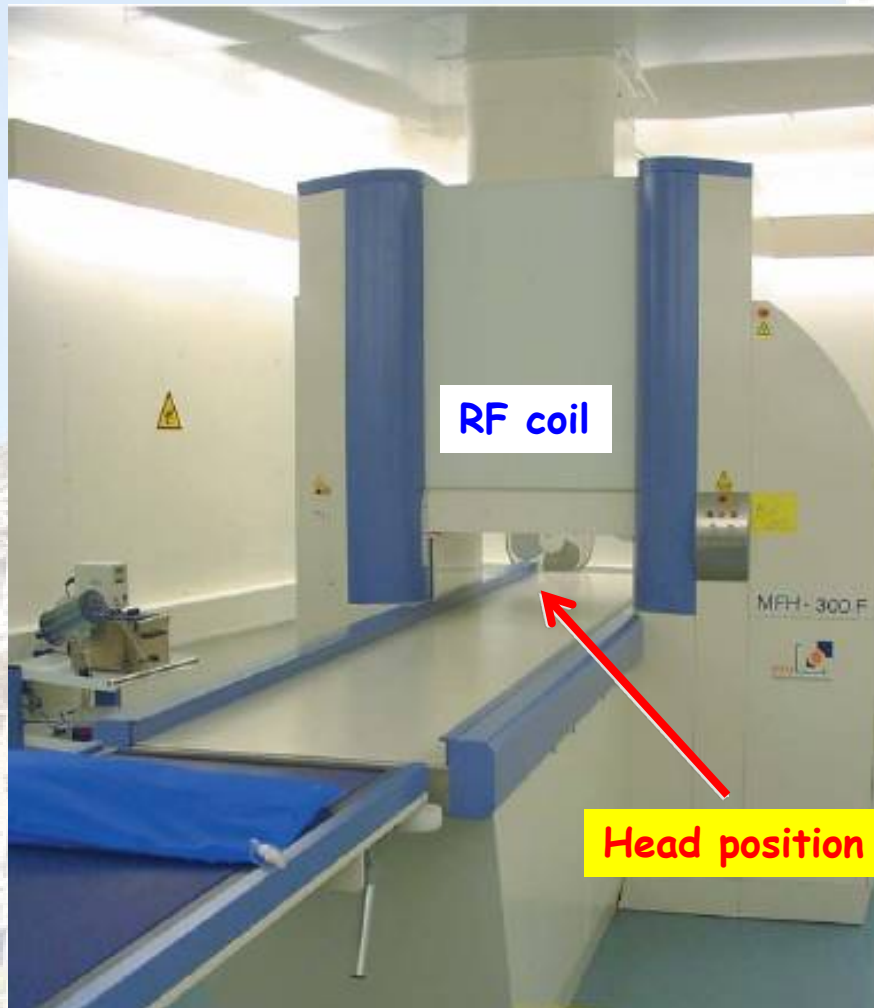
- **THERMOABLATION**: if **temperature is raised $> 50^{\circ}\text{C}$** high enough to **cause immediate cellular death**
- **HYPERTHERMIA**: it refers to **smaller temperature rises, usually to $40\text{--}45^{\circ}\text{C}$** , rendering the cells susceptible to various forms of damage including apoptosis, leading to subsequent cell death.



Magnetic Fluid Hyperthermia (MFH)



Magnetic Fluid Hyperthermia allows to **strictly controlling the region under treatment** by using **Magnetic Nanoparticles (MNPs)** as heating elements.



**Used in clinics (Germany, USA)
on glioblastoma and prostate**

Web-site : <http://www.magforce.de/en/home.html>

- **Heating** through application of **AC magnetic field** via activation of MNPs directly injected in the tumour mass at high doses (ca. 50 mg/cm³).
- Typically: $f \sim 100$ kHz, amplitude ~ 10 kA/m.
- Minor side-effects

To specify the **efficiency of MNPs in releasing heat**, the **Specific Absorption Rate (SAR)**

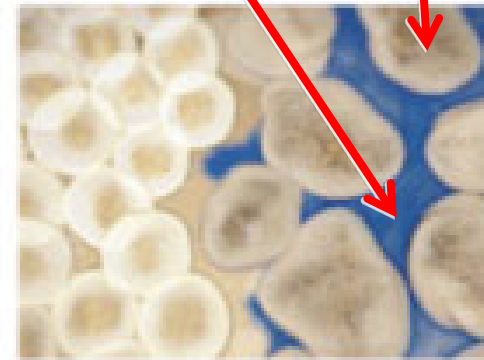
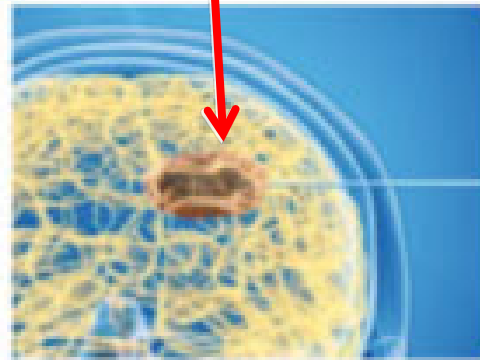
Magnetic Fluid Hyperthermia - Clinical applications



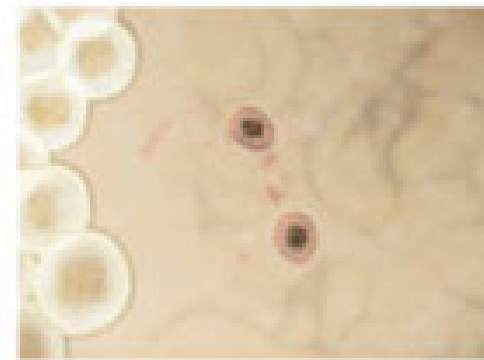
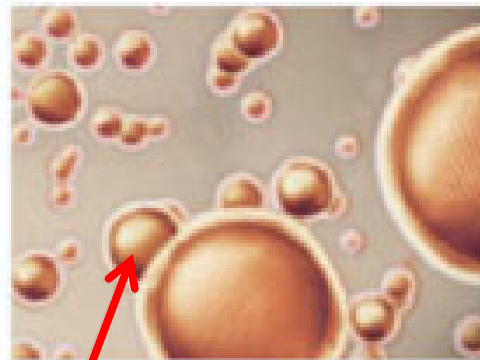
MNPs coated
With amminosilane

Direct injection in
the brain tumour

Tumour cells
ferrofluid



AMF



Heating - kill
tumour cells



The ideal task – novel systems: a single theranostic nano-object

Diagnostics : MRI CA, fluorescence
Therapy : Magnetothermia, drug release

