



Society



Companies



Schools



Researchers



Journalists



Personnel

- Biomedical sciences
- Chemistry and materials technology
- Earth and environment
- Engineering, ICT, energy and transportation
- Physics and matter
- Human sciences and cultural heritage
- Bio and agri-food



- 102 Research Institutes
- 8.000 Employees

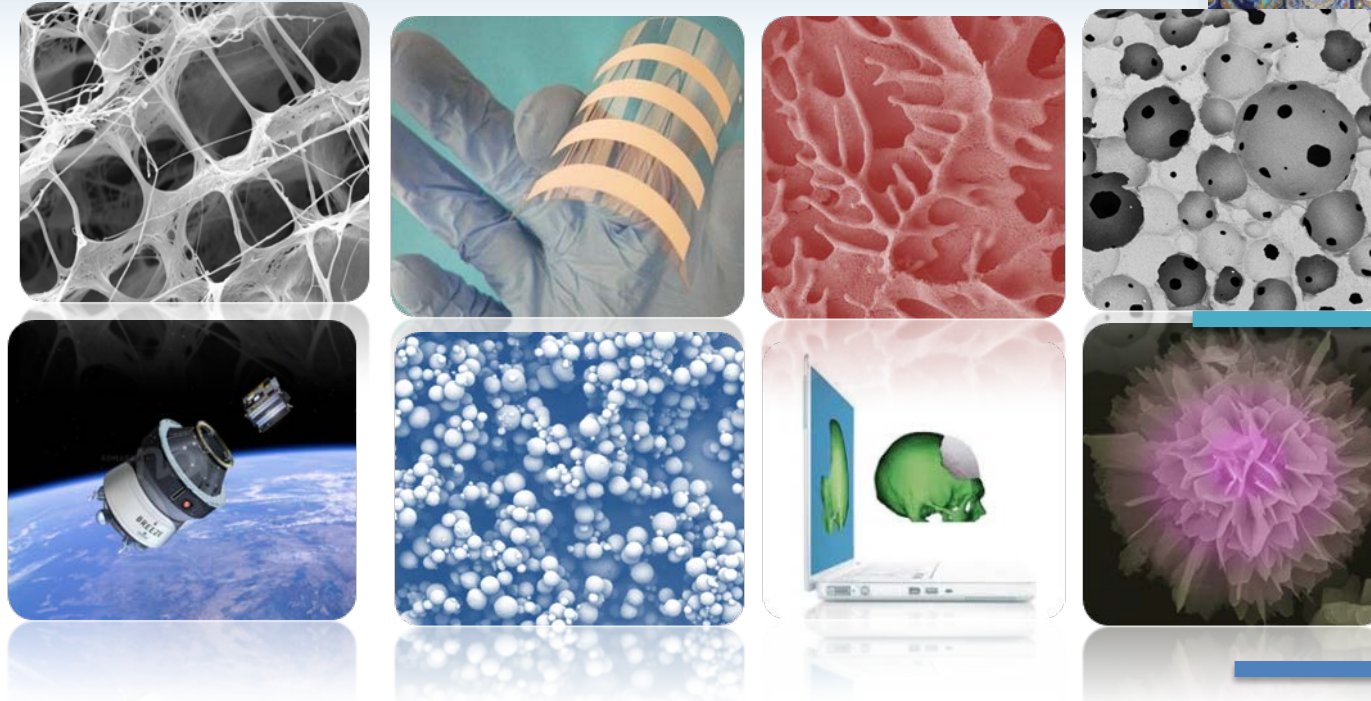
Scienze del sistema terra e tecn.per l'ambiente  
Scienze bio-agroalimentari  
Scienze biomediche  
Scienze chimiche e tecnologie dei materiali  
Scienze fisiche e tecnologie della materia  
Ingegneria, ICT e tecn. per l'energia e i trasporti  
Scienze umane e sociali, patrimonio culturale



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- **ELECTROCERAMICS**
- **TRADITIONAL CERAMICS & CULTURAL HERITAGE**





# Fe-doping-induced magnetism in nano-apatite: application in regenerative & nanomedicine

*Anna Tampieri, A. Adamiano, S.Sprio, M.Iafisco, S.Panseri*

 National Research Council of Italy  
Istec Institute of Science and Technology for Ceramics  
**Faenza -ITALY**



ALMA MATER STUDIORUM  
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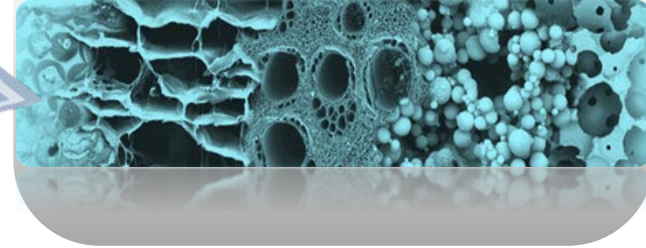
# ***TOOLS OF REGENERATIVE MEDICINE***

***NANOMEDICINE***

***Scaffolds***

## **Material Science**

- Scaffolds
- Nanomaterials
- Delivery system



***Biologics***

***Cells***

**GOAL  
Cell/Tissue/  
Organ  
Regeneration**

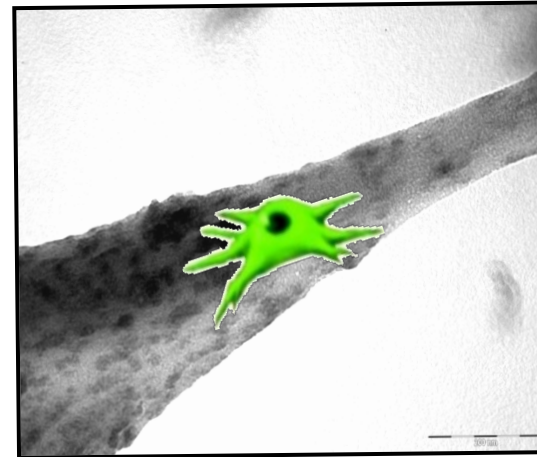
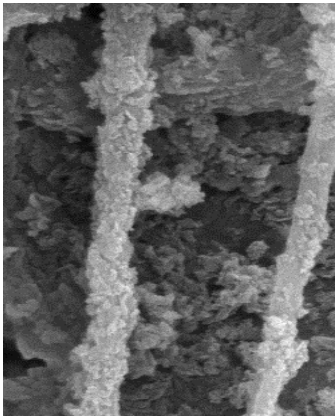
...today the frontier are

# BIOMIMICRY

Biomimetics generally reproduce both chemical composition and architecture of native tissues



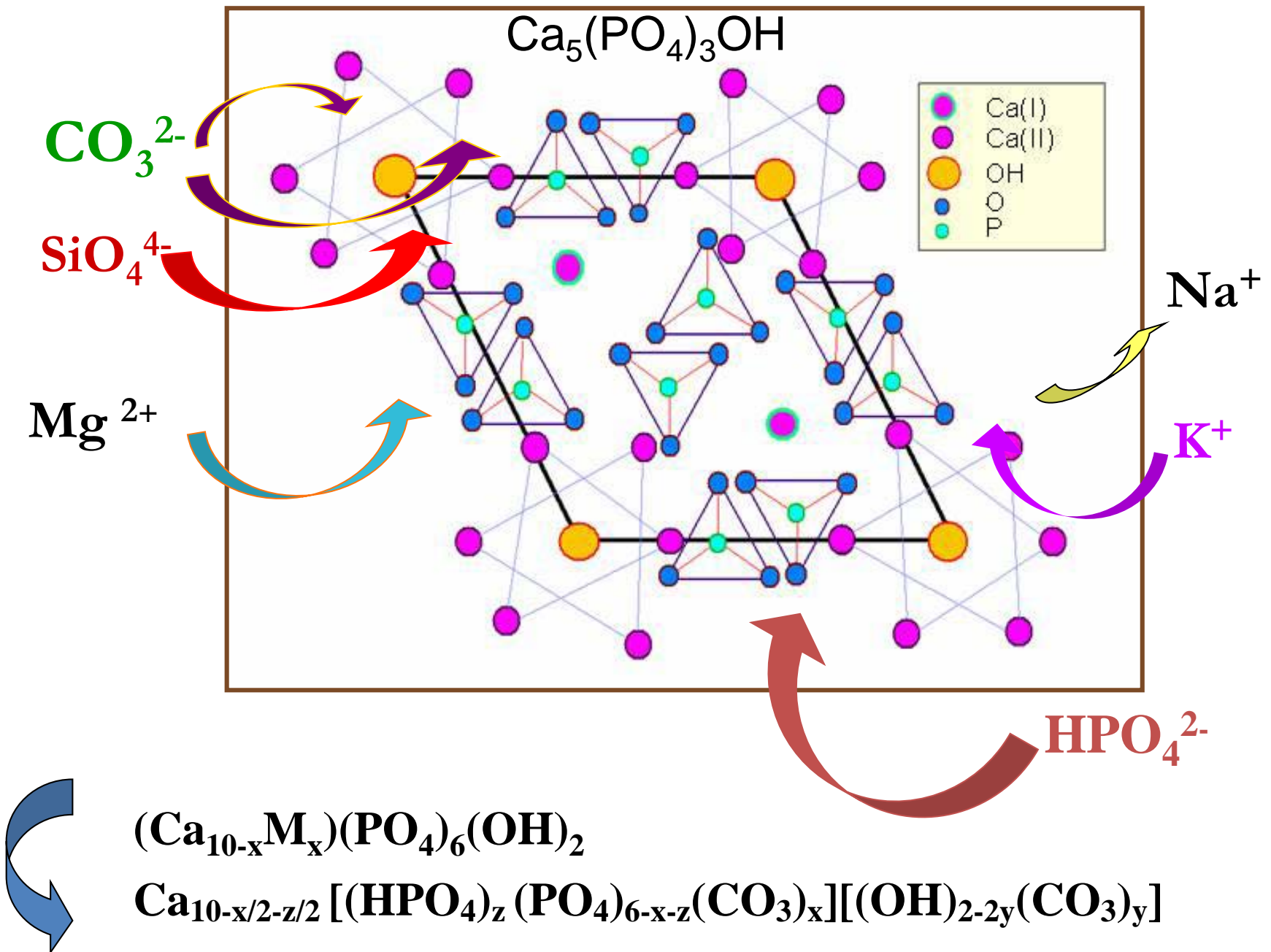
Once implanted, the chemical and structural biomimetism of the scaffold can stimulate cell chemotaxis and colonization by autologous cells.



..... and then the human body can be used as a natural bioreactor and guide a proper tissue regeneration



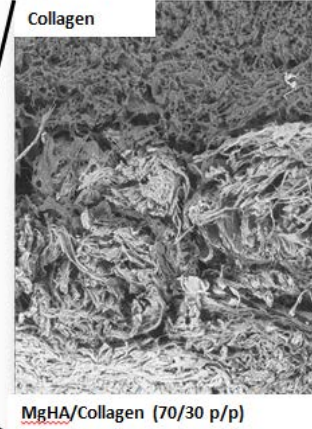
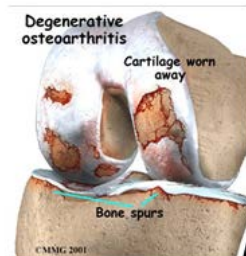
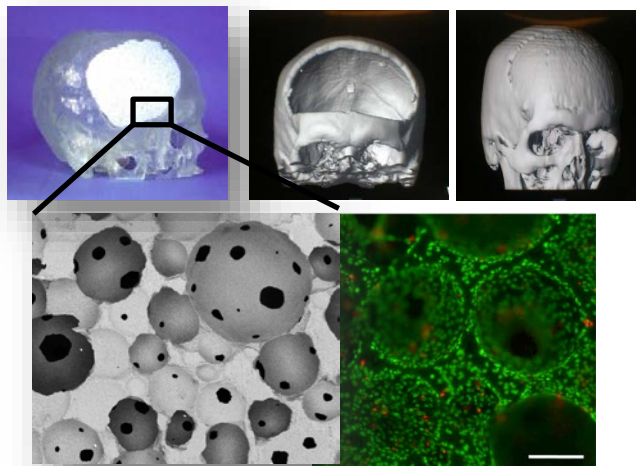
# CHEMICAL BIOMIMETISM



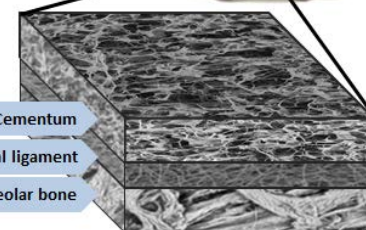
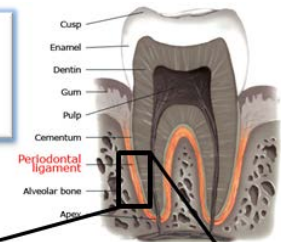
# Regenerative medicine

**CUSTOM BONE® Integra (USA)**

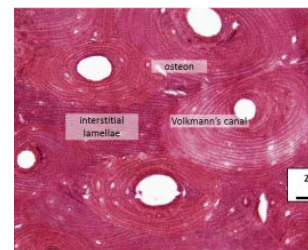
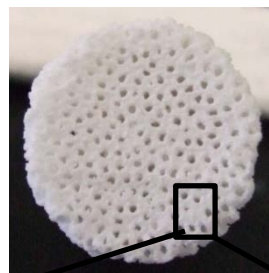
**MAIOREGEN® J&Johnson (USA)**



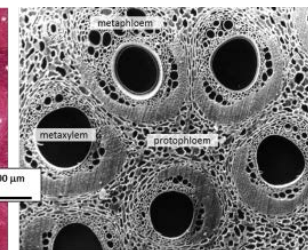
Multi-layer graded scaffold for periodontal regeneration



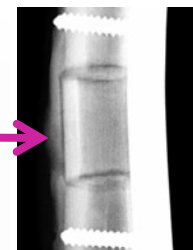
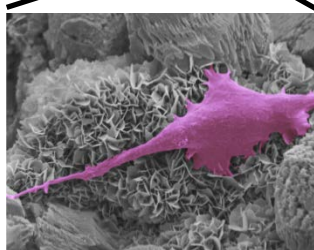
**GREEN BONE® 13 ml Eurs**

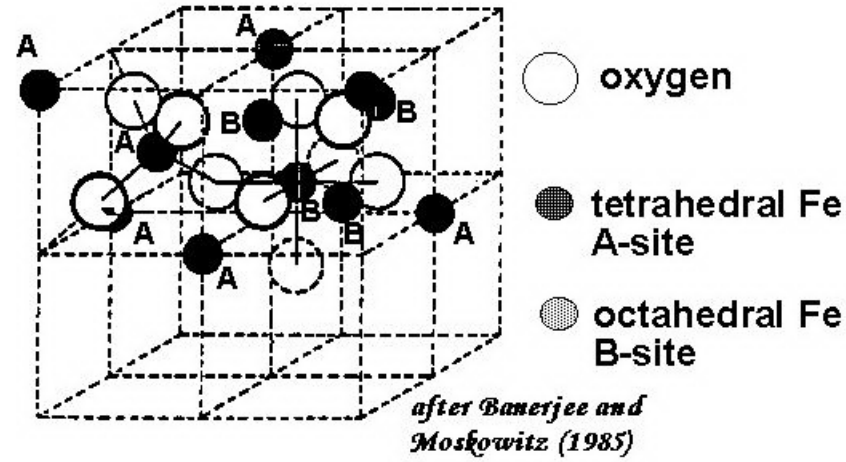
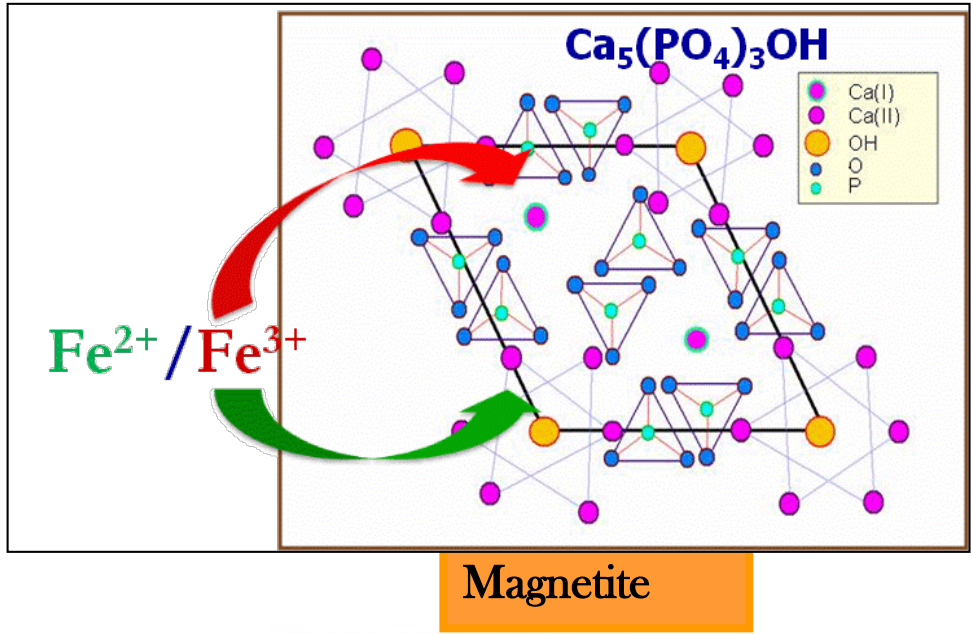
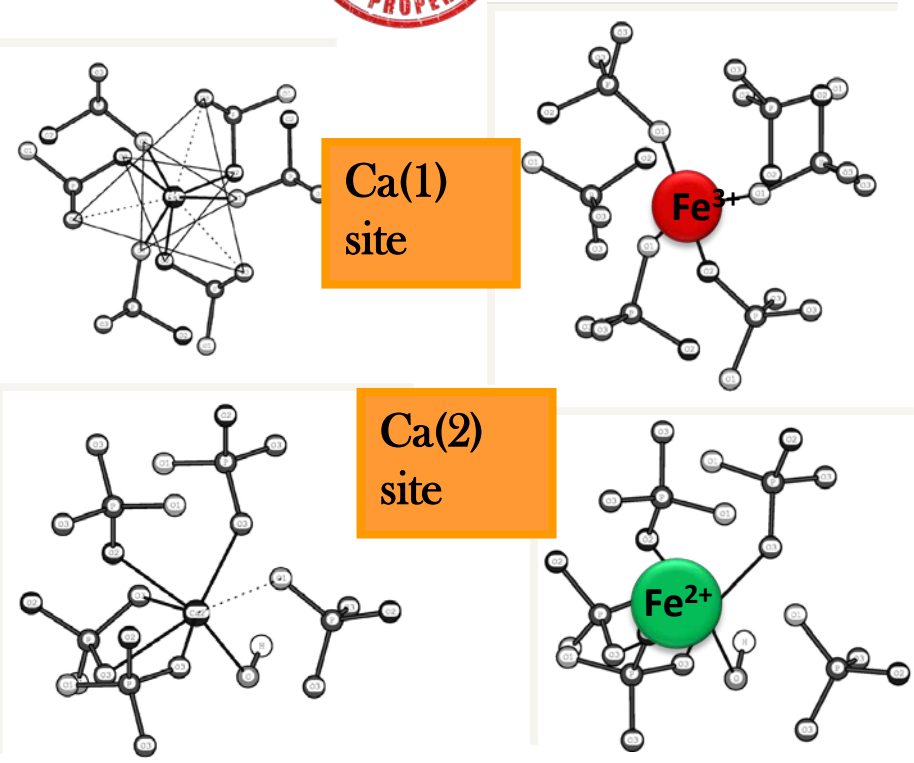


Bone



Rattan wood

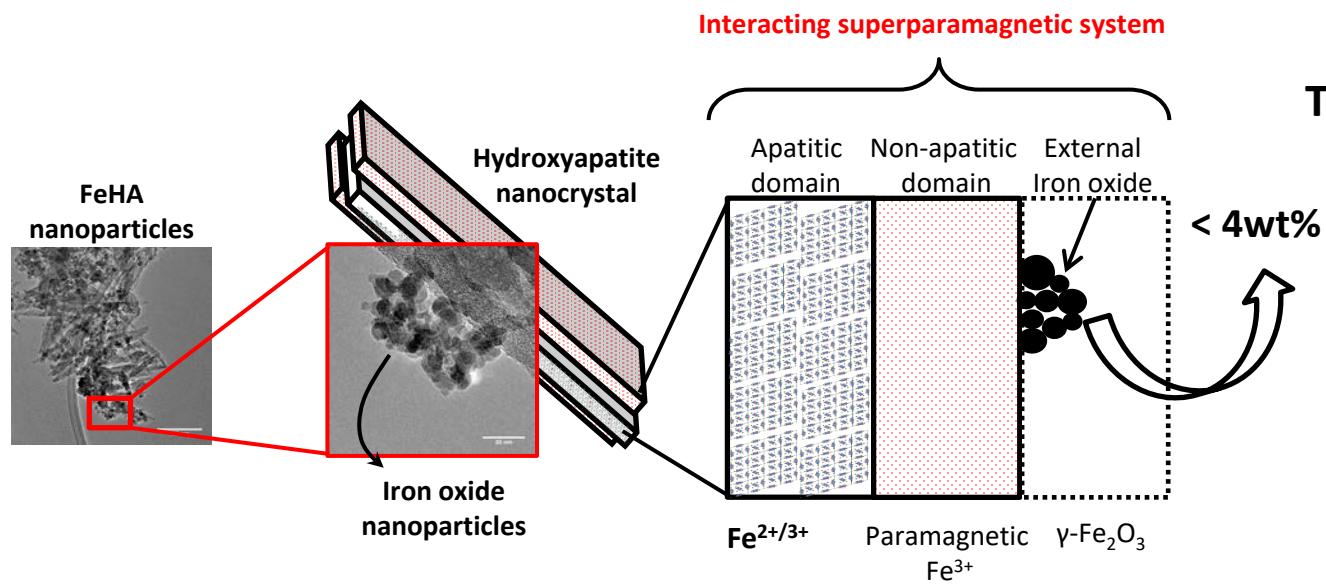




At the bulk level : -  $\text{Fe}^{2+}$  is distributed on both Ca(1) and Ca(2) with a preferential occupation of **Ca(2)** with sixfold coordination  
-  $\text{Fe}^{3+}$  is distributed on both Ca(1) and Ca(2) with a preferential occupation of **Ca(1)** with fourfold coordination.



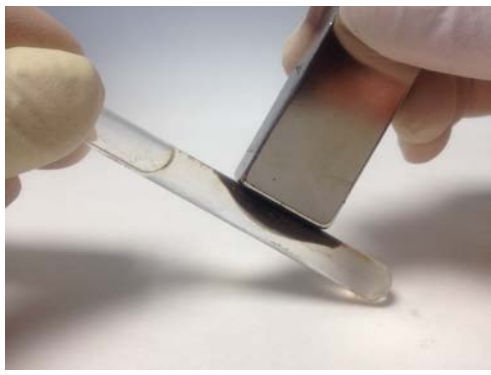
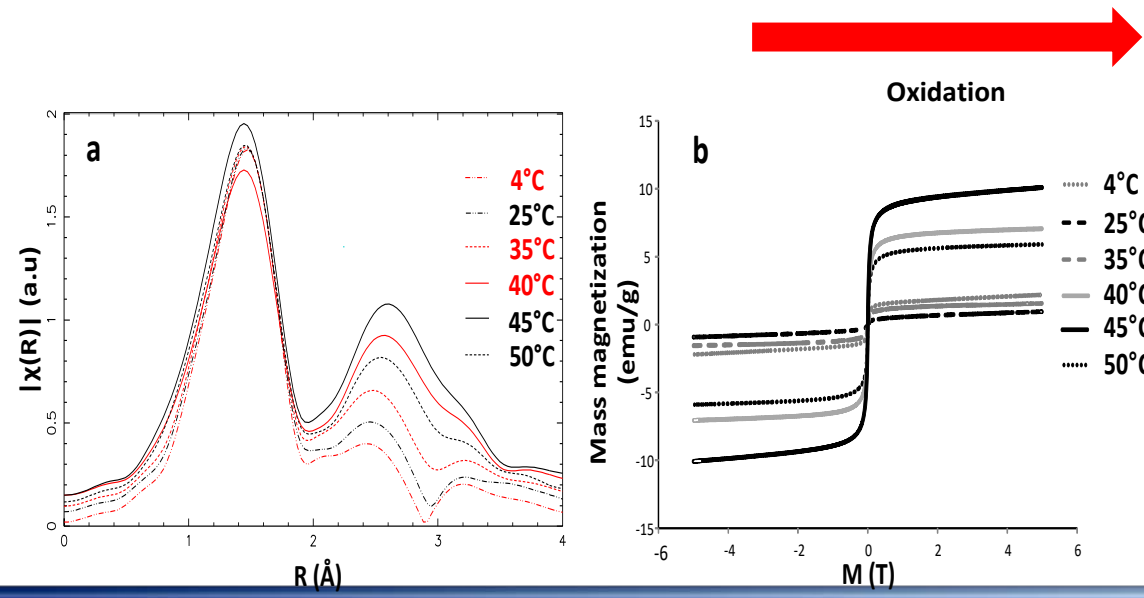
FeHA ---> 40°C and  $Fe^{2+} / Fe^{3+} = 1.0$



Total mass magnetization  
9.0 emu/g

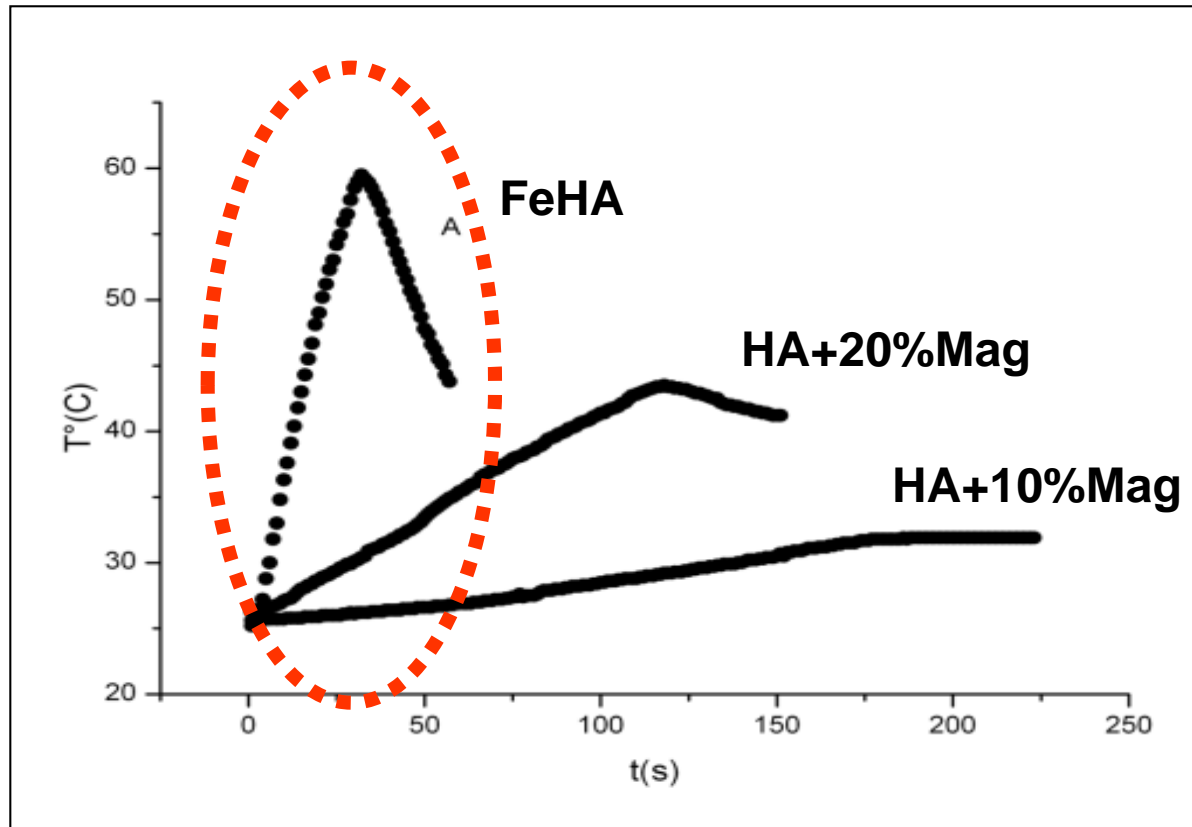


Normalized on Iron is  
130 emu/g !



# Hyperthermia

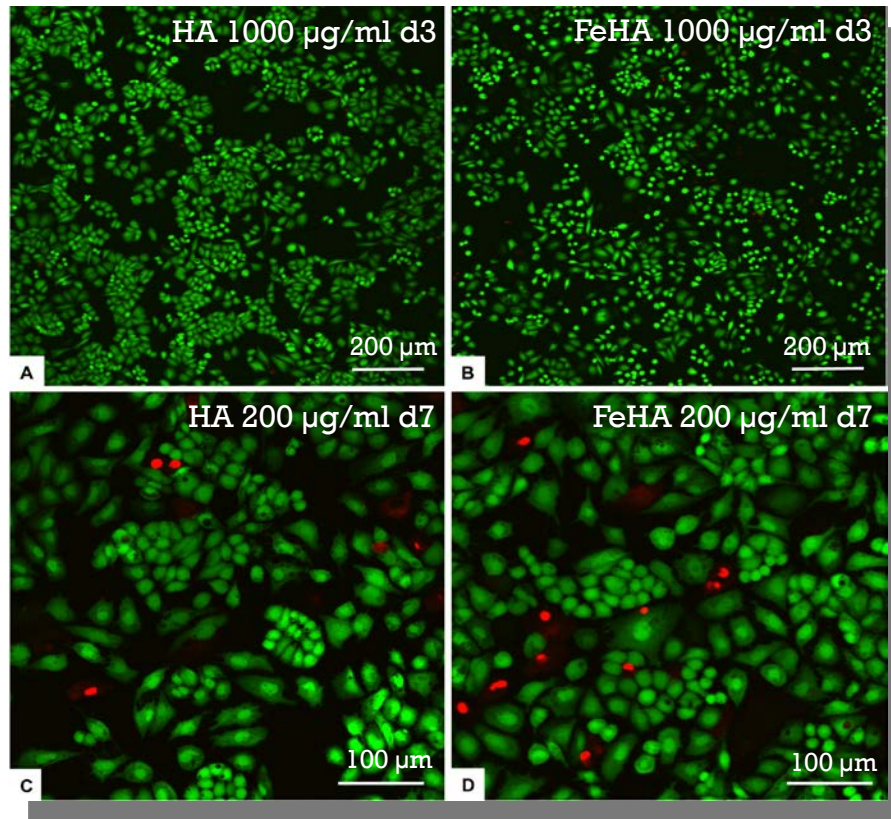
Alternate magnetic field of 30 mT at a frequency  $\nu = 293$  Hz.



A relevant Hyperthermia effect pointed up a bulk phenomenon that even more clearly confirms the intrinsic magnetism of this Fe-HA phase.

# *In vitro* evaluation of FeHA nanoparticles

Effect of novel FeHA NPs on cell culture compared to HA NPs already commercialized (bone filler or primary component of several bone substitutes)



**MSC**



**FeHA and HA NPs**

Concentrations:

- ✓ 2000 µg/ml
- ✓ 1000 µg/ml
- ✓ 500 µg/ml
- ✓ 200 µg/ml

(Live/Dead assay)

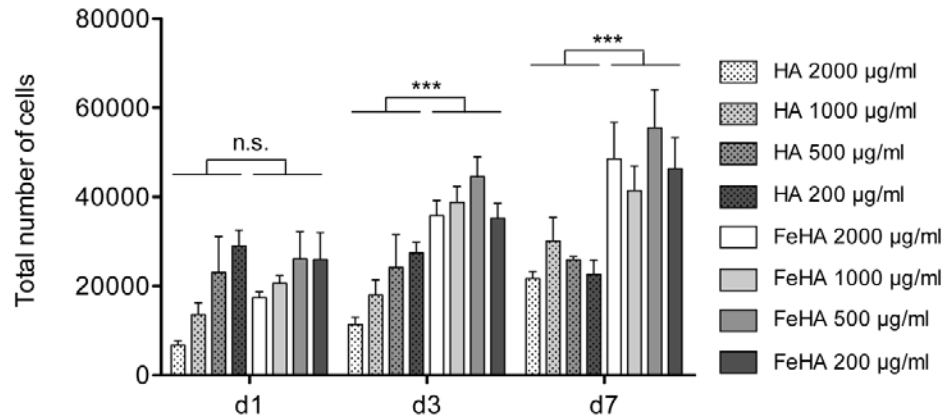
Panseri et al.  
2012  
J Nanobiotech

CELL VIABILITY: very high ratio of viable cells at each time point with no significant differences between the FeHA and HA groups

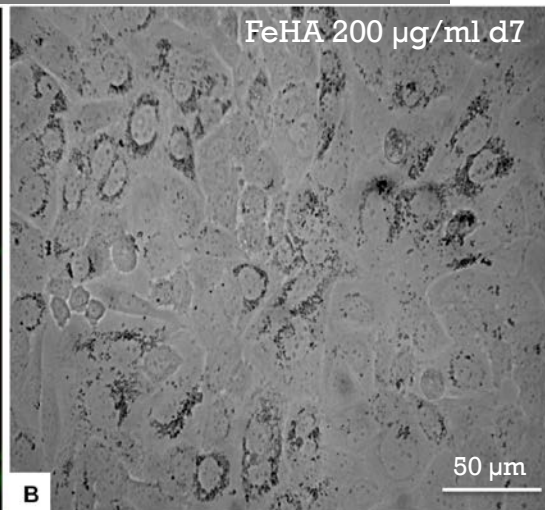
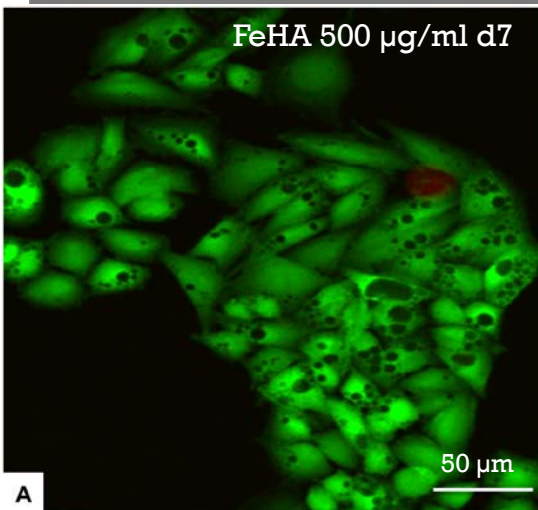


# *In vitro* evaluation of FeHA nanoparticles

FeHA NPs POSITIVELY INFLUENCE CELL PROLIFERATION COMPARED TO HA



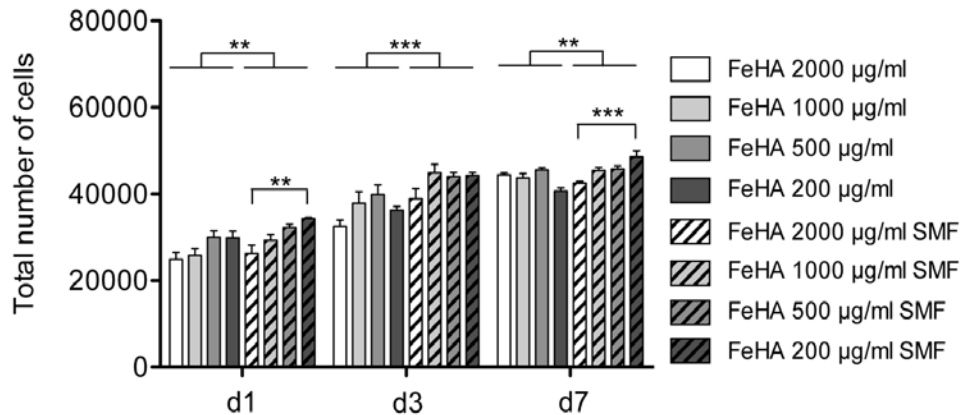
Nanoparticles were seen accumulated in the cytoplasm



GOOD BIOCOMPATIBILITY of FeHA NPs

Panseri et al.  
2012  
J Nanobiotech

# ***In vitro* evaluation of FeHA nanoparticles under APPLICATION of a MAGNETIC FIELD**



Cell proliferation



**POSITIVE EFFECT OF FeHA NANOPARTICLES IS AMPLIFIED BY MAGNETIC FIELD APPLICATION (320 mT)**

## **NOVEL SUPERPARAMAGNETIC FeHA NANOPARTICLES**

- ✧ Enhance cell proliferation compared to HA NPs
- ✧ The positive effect is significantly increased when a MAGNETIC FIELD is applied

Panseri et al.  
2012  
J Nanobiotech



# Regenerative Medicine

The magnetic scaffold as an in vivo operating station with external controll able to give a prolonged assistance to tissue regeneration

TO INCREASE REGENERATIVE POTENTIAL IN AGING AND  
IN CASE OF DEGENERATIVE DISEASE

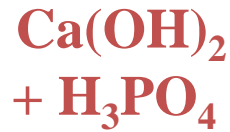
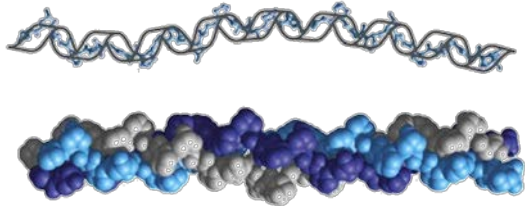
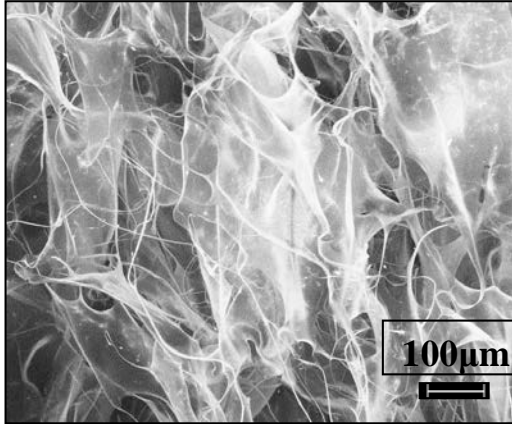




# BIOMINERALIZATION

## Bio-hybrid Magnetic composite

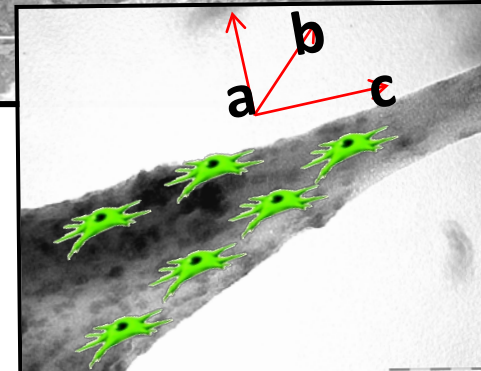
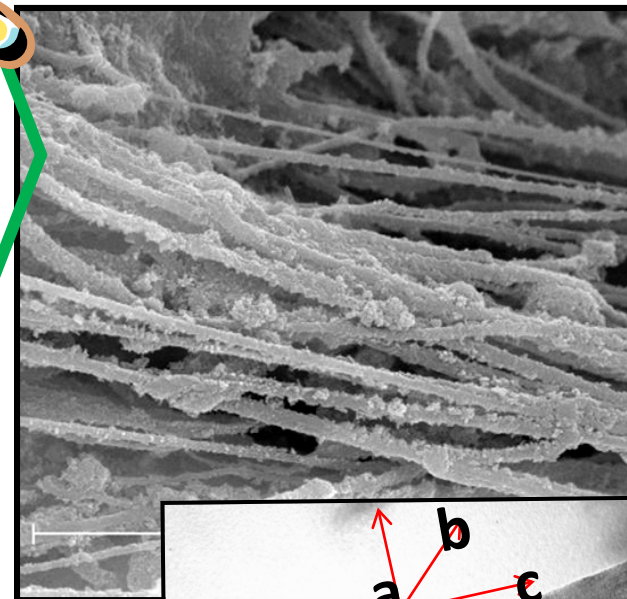
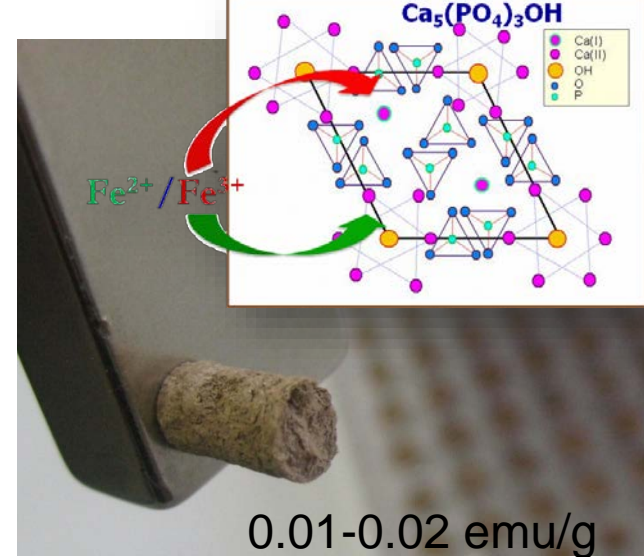
*Collagen*



Final pH : 7-8

Reaction Temperature: 40°C

(FeHA)/Collagene  
80/20 - 10/90 wt%

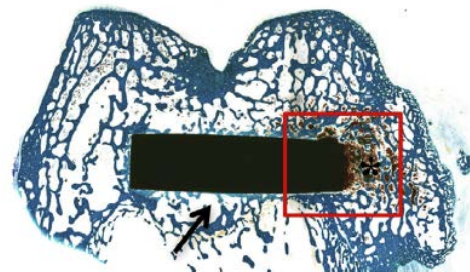
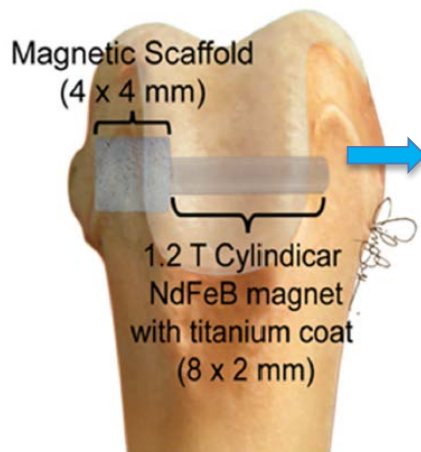
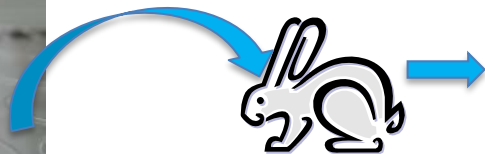
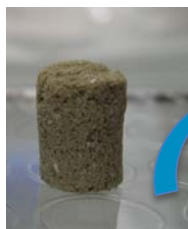


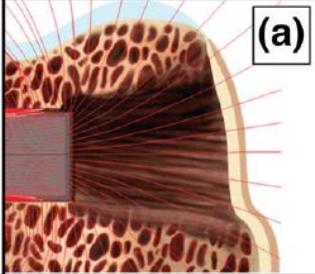
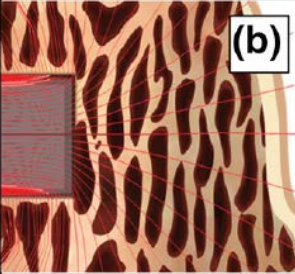
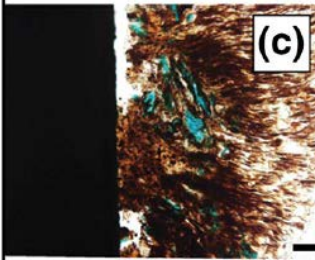
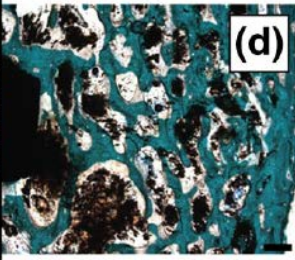
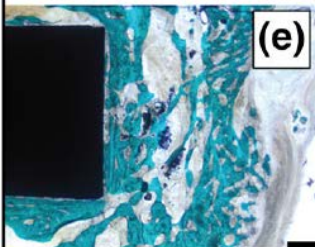
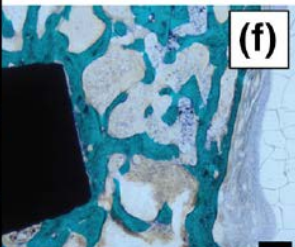
### control mechanisms

- Chemical / Compositional
- Morphological
- Structural



# Preliminary in vivo investigations



	4 weeks	12 weeks
Sketch of induced bone patterning	 (a)	 (b)
Magnetic scaffolds	 (c)	 (d)
Control groups	 (e)	 (f)

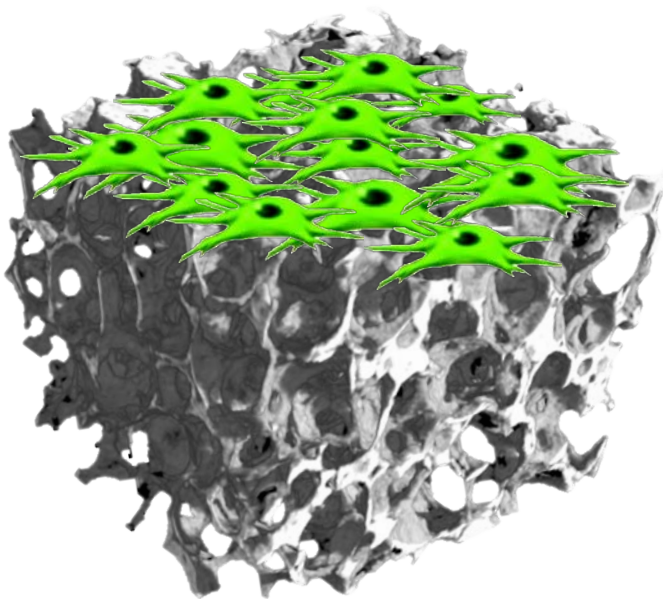
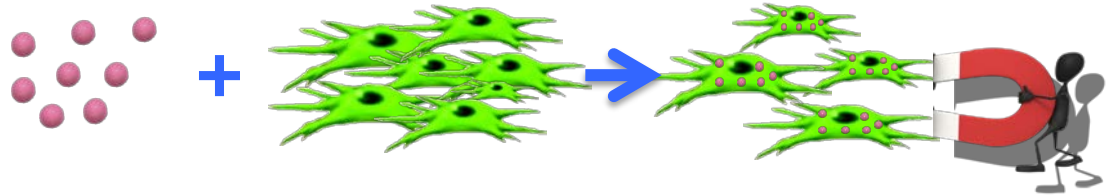
The results of this study indicate that the use of a magnetic responsive scaffolds in association with a permanent magnet may represent a **suitable route to boost bone tissue regeneration** obtaining in shorter time a well-ordered tissue architecture.



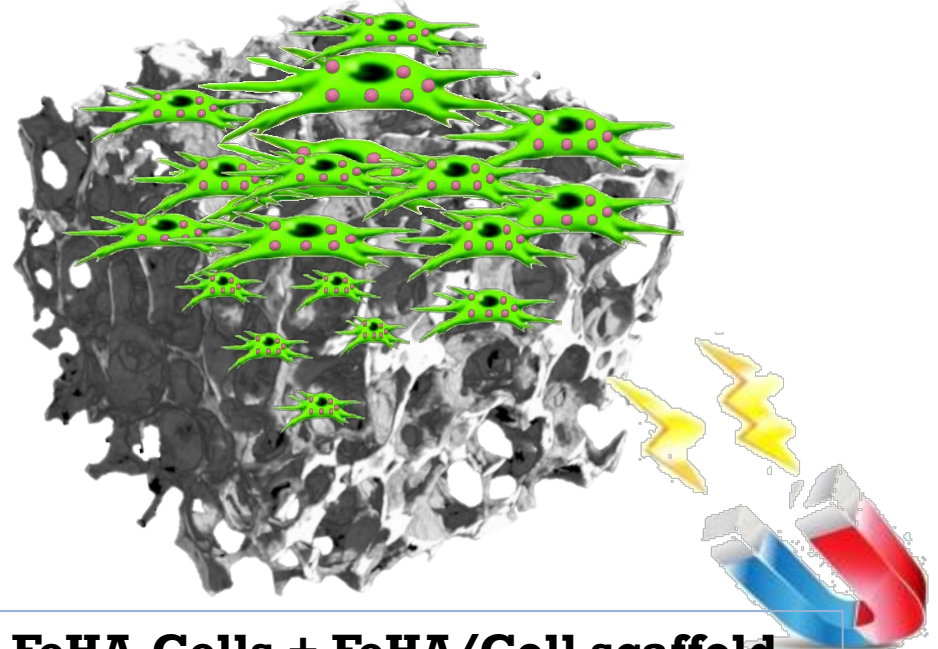
# TISSUE ENGINEERING IN ORTHOPAEDIC APPLICATIONS

**“Standard” cell seeding**

**“Magnetic” cell seeding**



**Cells + HA/Coll scaffold**



**FeHA-Cells + FeHA/Coll scaffold**





# NANOMEDICINE:

## THE FUTURE OF MEDICINE

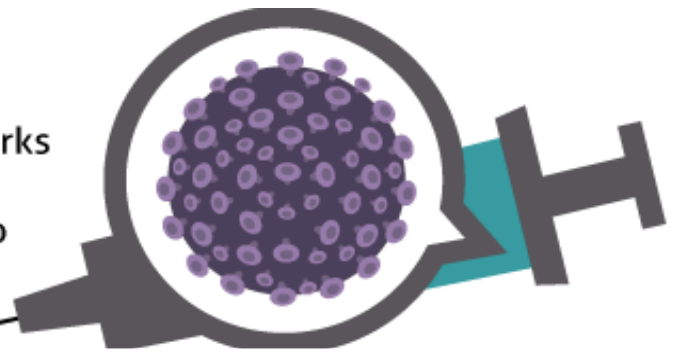
Nanomedicine, refers to highly specific medical intervention at the molecular level for curing disease or repairing damaged tissues.

Though in its infancy, could we be looking at the future of medicine?  
Early clinical trials certainly look promising.



### HOW NANOMEDICINE WORKS

Nanomedicine works  
by *injecting*  
*nanoparticles* into  
the body



#### CAN BE USED TO:



Deliver  
medicine



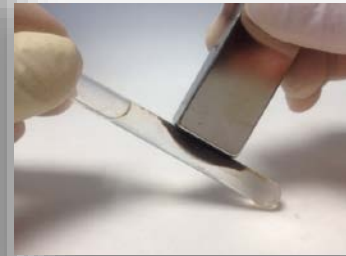
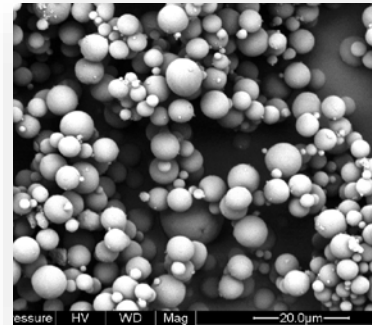
Find and treat  
disease



Repair  
damaged cells



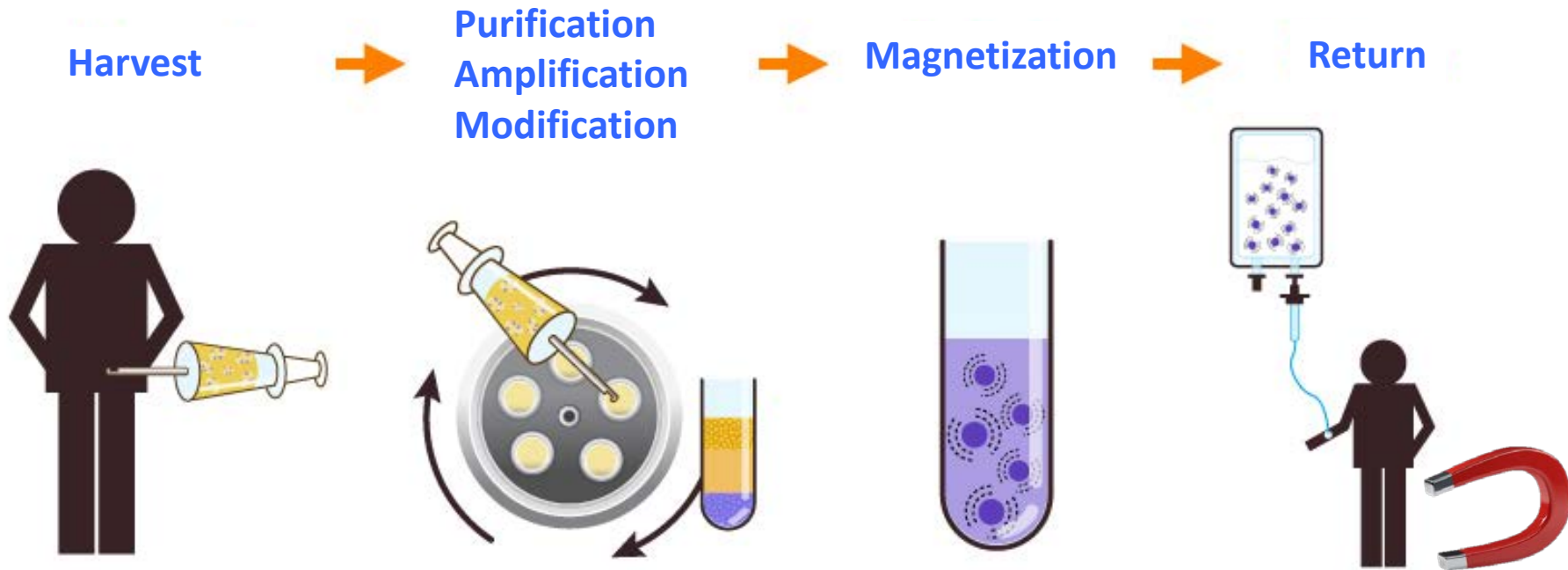
## Why use Fe-HA?



- Favorable biodegradability and biocompatibility
- Lower toxicity than silica, quantum dots, carbon nanotubes, or metallic magnetic particles
- Higher stability than liposomes, allowing a more controlled and predictable drug delivery
- Low production costs and excellent storage properties (not easily subjected to microbial degradation)
- The stability is pH-dependent: Stable at pH=7.4 but Degradable at pH=5.0 (cancerous region and lysosomes inside the cells) that allows the drug release

# ADVANCED CELL THERAPY

Magnetic Driving, Targeting, Tracking And Actuation Of Cells With FeHA NPs

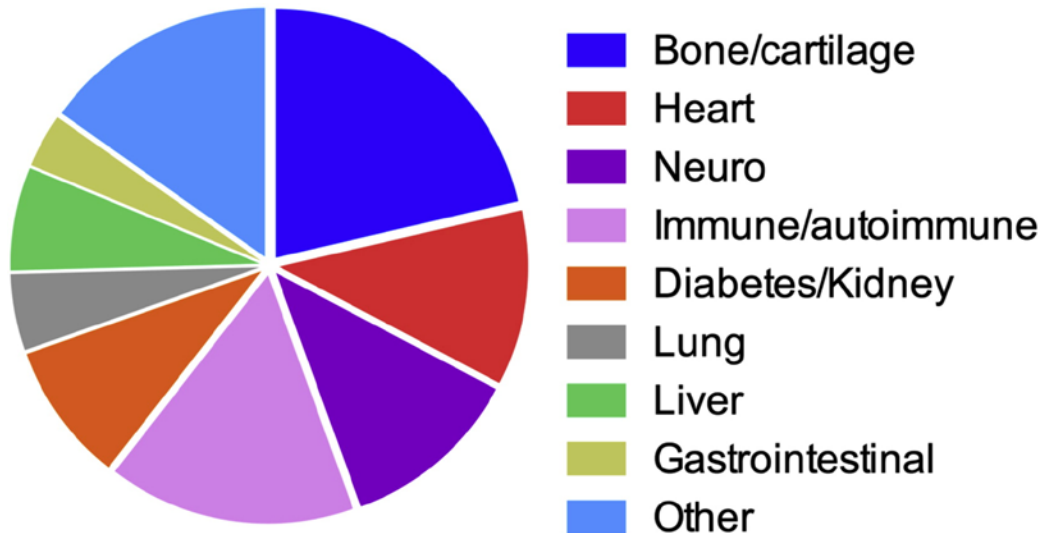


**IMPROVEMENT OF CELL DELIVERY AND RETENTION**

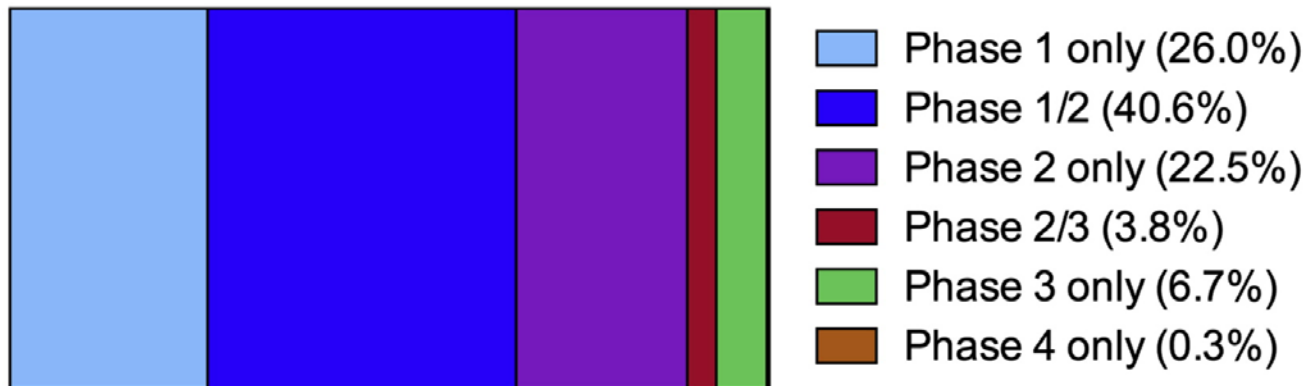
**THE NEXT PILLAR of MEDICINE**



## In 2015, n.374 registered NIH clinical trials using MSCs



3-fold expansion of trials over the number noted in 2011, but the distribution of trials by phase is much the same. **This might suggest that products are not moving out of the clinical pipeline.**



**> 90% clinical trials  
DO NOT PASS  
Phase 2**

**VERY FEW CELLS REACH THE TARGET SITE (< 1%)**

# IMPROVEMENT OF CELL DELIVERY AND RETENTION

Only PRECLINICAL studies with FDA-approved or commercially available magnetic particles using various delivery methods

**1.5-30-fold improvement in cell delivery and retention above non-magnetically targeted control experiments**



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Article

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Biomedical Nanotechnology*

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## Magnetic Labelling of Mesenchymal Stem Cells with Iron-Doped Hydroxyapatite Nanoparticles as Tool for Cell Therapy

Silvia Panseri<sup>1,\*</sup>, Monica Montesi<sup>1</sup>, Monica Sandri<sup>1</sup>, Michele Iafisco<sup>1</sup>, Alessio Adamiano<sup>1</sup>, Martina Ghetti<sup>2</sup>, Giovanna Cenacchi<sup>2</sup>, and Anna Tampieri<sup>1</sup>

<sup>1</sup> *Institute of Science and Technology for Ceramics, National Research Council, via Granarolo 64, 48018, Faenza (RA), Italy*

<sup>2</sup> *Biomedical and Neuromotor Sciences Department, University of Bologna, via Irnerio 48, 40126, Bologna, Italy*

# FeHA-cell “magnetization”

Mesenchymal  
stem cells

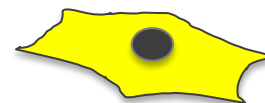
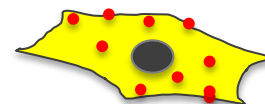
FeHA Nanoparticles



In agitation,  
30 min,  
37°C

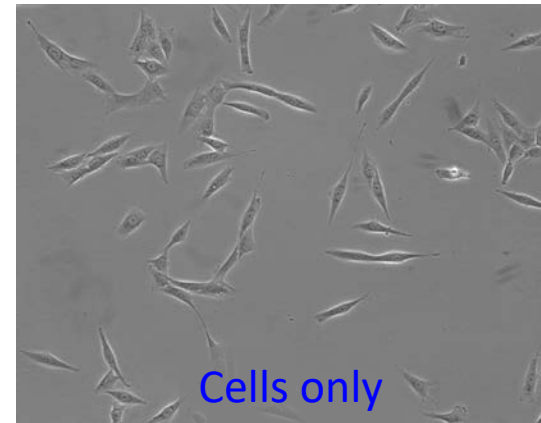
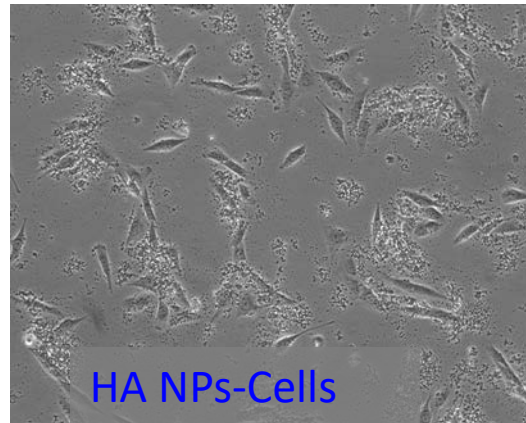
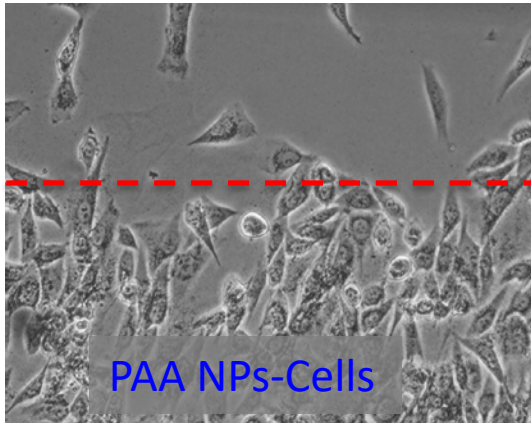
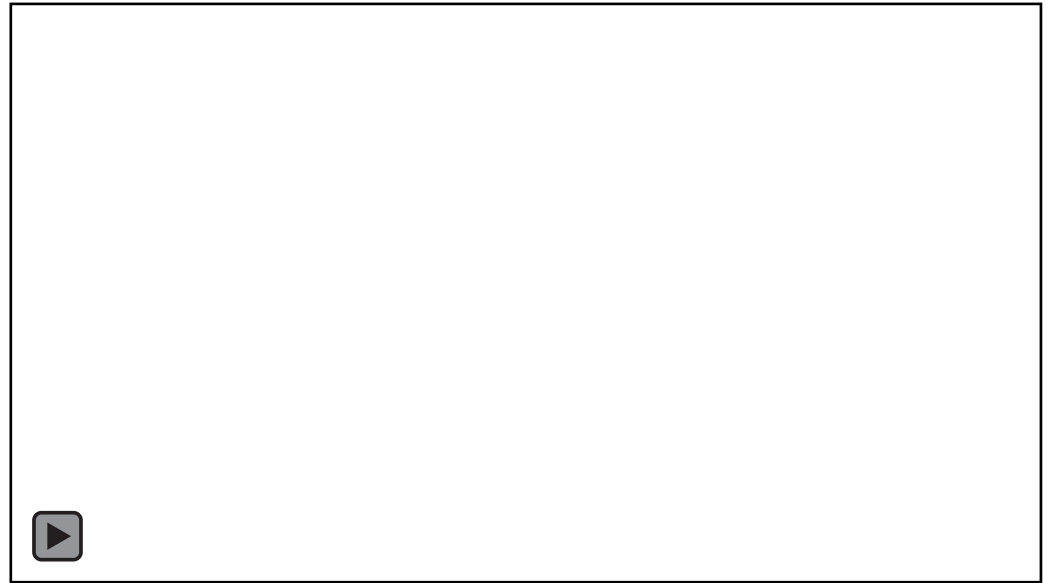
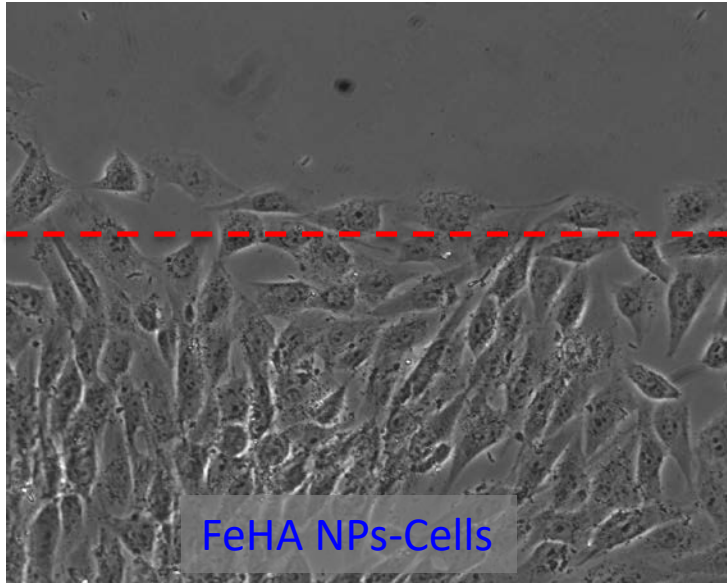


“MAGNETIC” CELLS

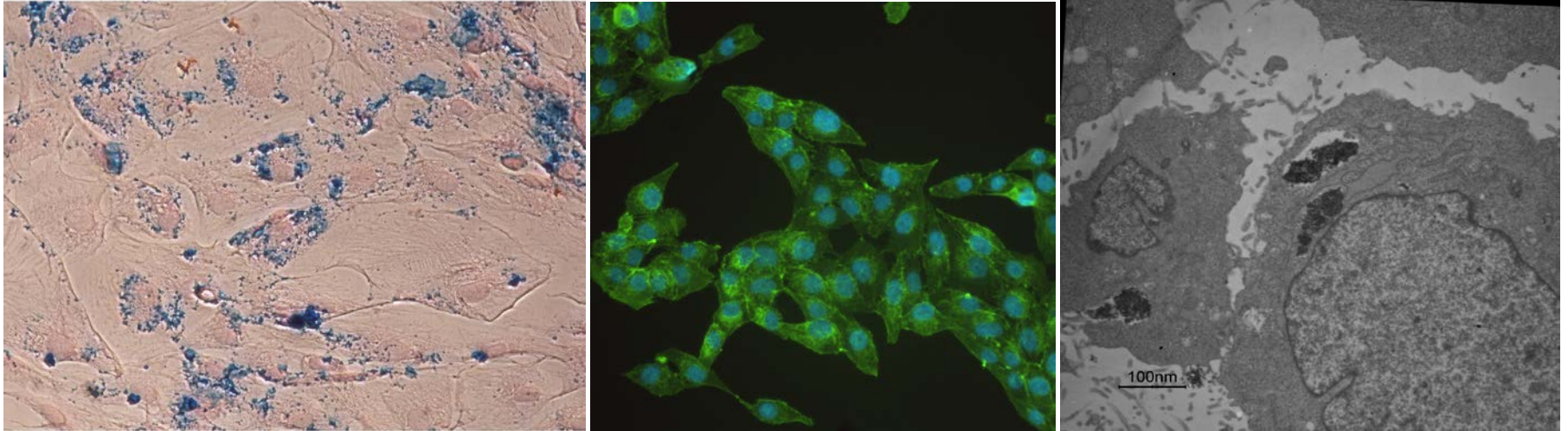




# MAGNETIC CELLS



# Magnetic Labelling of Mesenchymal Stem Cells with Iron-Doped Hydroxyapatite Nanoparticles as Tool for Cell Therapy

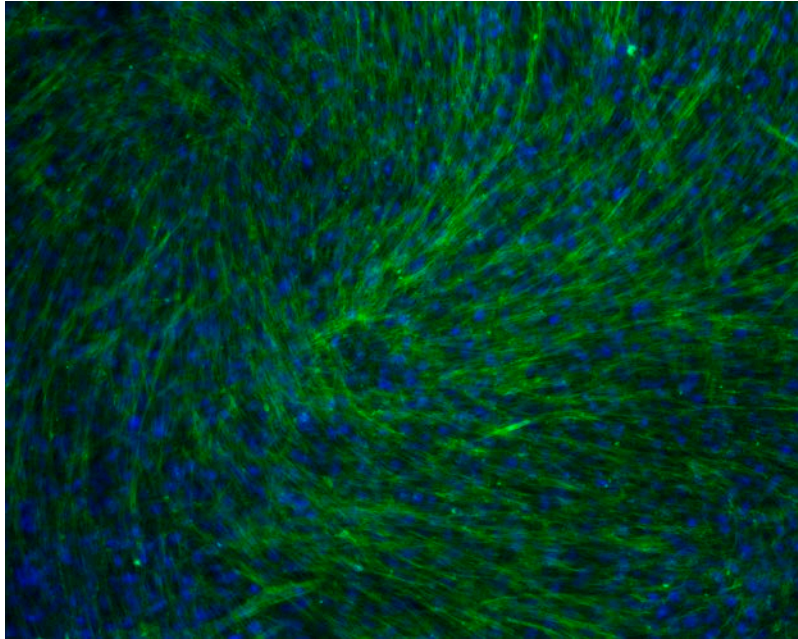


**CELL MORPHOLOGY IS NOT NEGATIVELY AFFECTED BY THE PRESENCE OF FEHA NPS**

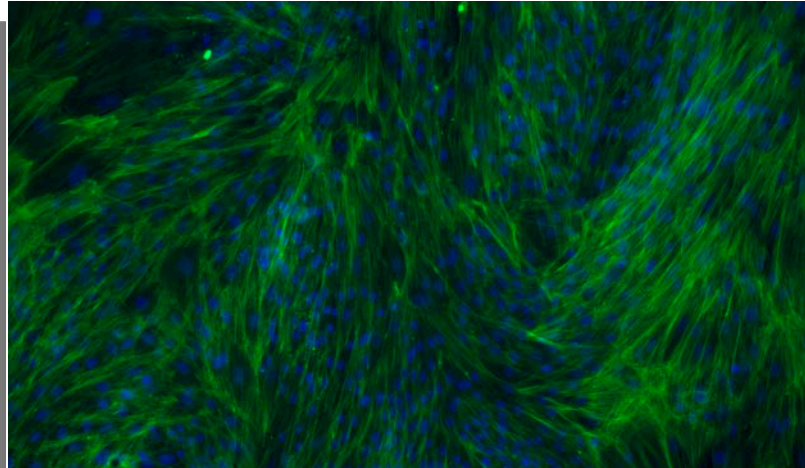
**CELL VIABILITY IS NOT NEGATIVELY AFFECTED BY THE PRESENCE OF FEHA NPS**  
(Several concentrations, up to 7 days)

# FeHA-cell “magnetization”

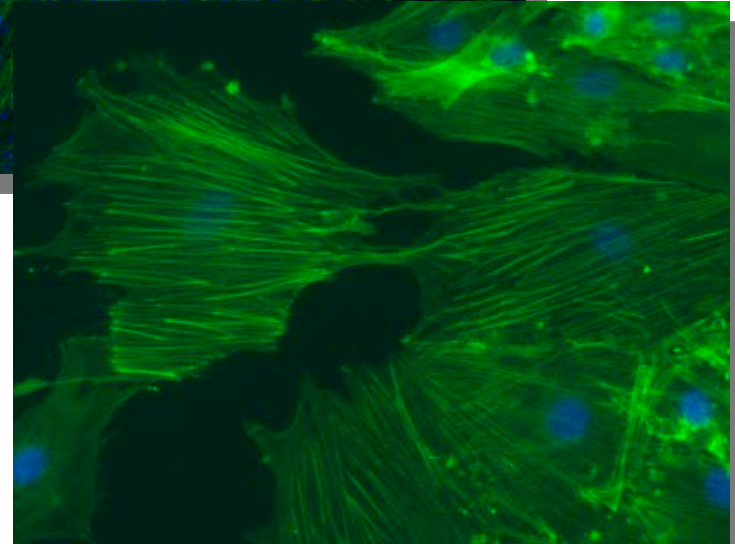
Control cells



“Magnetic” cells



“Magnetic” Cell morphology and proliferation is comparable to control cells with or without external magnetic field application

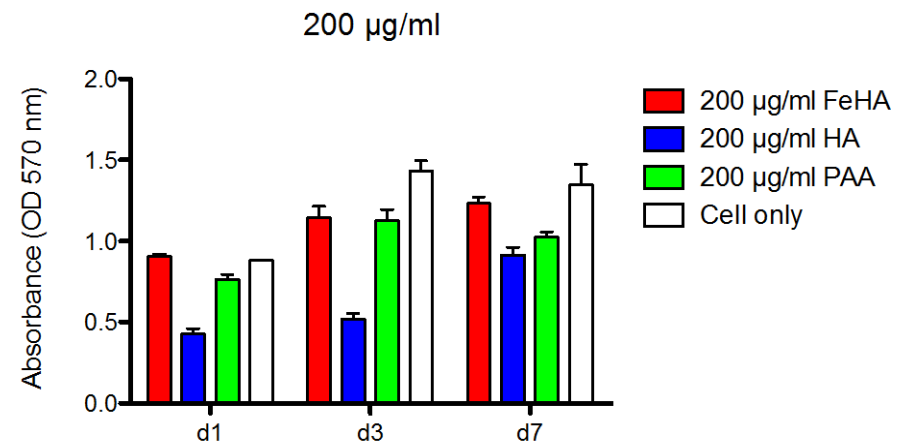
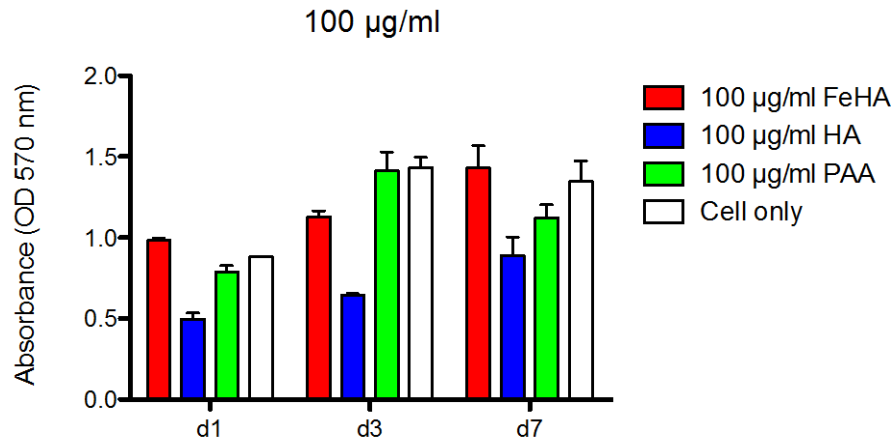
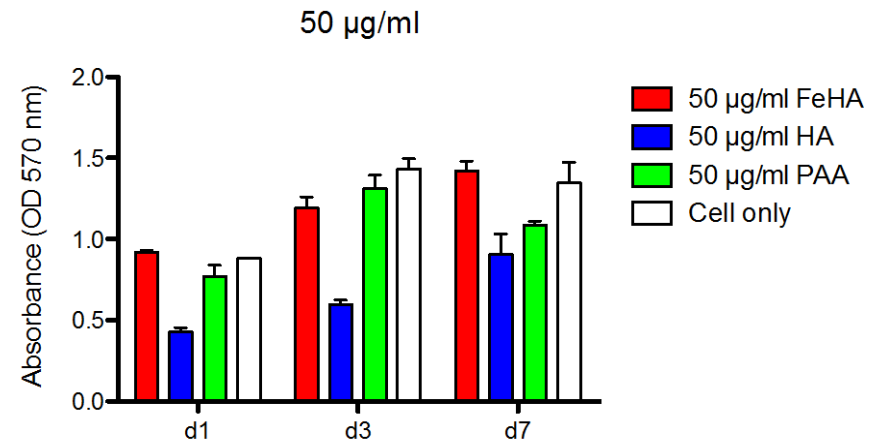
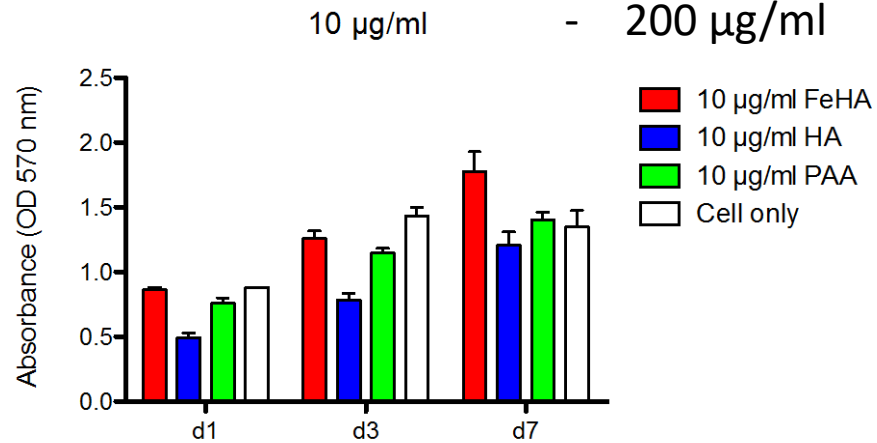




# Mesenchymal Stem CELLS PROLIFERATION

FeHA NPs versus PAA-NPs:

- 10  $\mu\text{g/ml}$
- 50  $\mu\text{g/ml}$
- 100  $\mu\text{g/ml}$
- 200  $\mu\text{g/ml}$

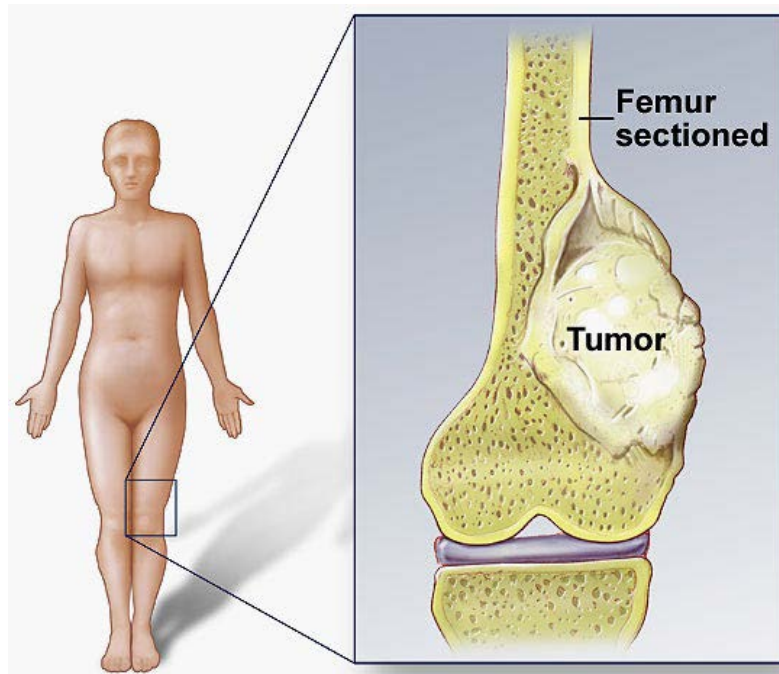


**FeHA NPs DO NOT AFFECT CELL PROLIFERATION**

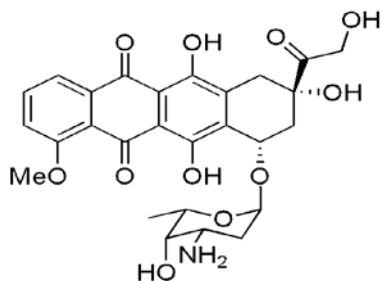
# DRUGS

## OSTEOSARCOMA

Teens are the most commonly affected age group



### Superparamagnetic iron-doped nanocrystalline apatite as a delivery system for doxorubicin

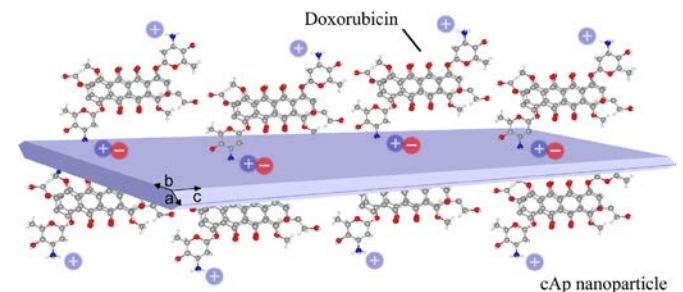
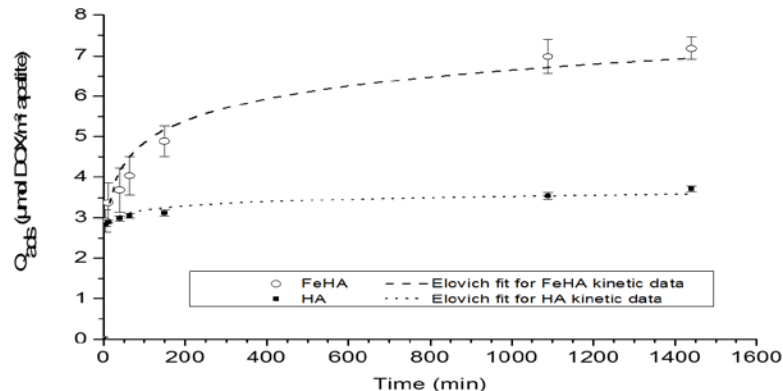


Doxorubicin (DOX)

- Promising potential against solid tumors
- Strong visible adsorption and fluorescence emission
- Uptake and release from NPs easily monitored
- Dose-dependent toxic side effects
- Cardiotoxicity

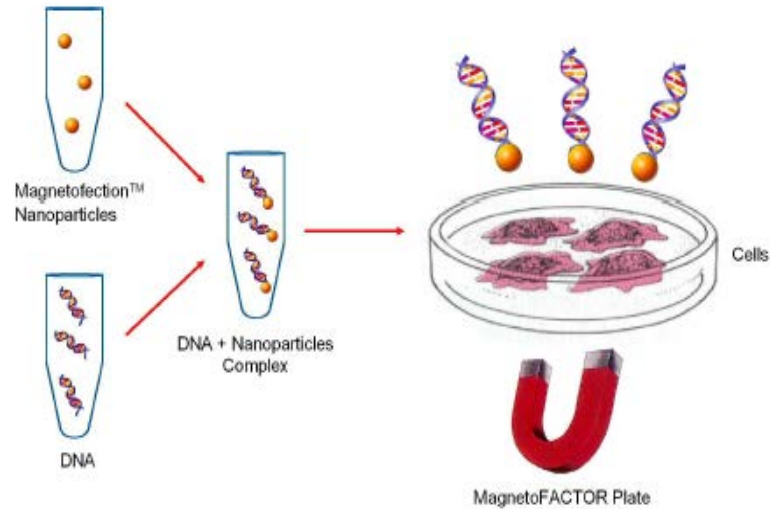
# Superparamagnetic iron-doped nanocrystalline apatite as a delivery system for doxorubicin

- (i) FeHA displayed higher affinity for DOX due to good affinity of the drug for the iron
- (ii) Good stability of the bonding between DOX and FeHA
- (iii) The release of DOX from FeHA was also assessed in the presence of a PEMF
- (iv) *in vitro* assays demonstrated that DOX loaded on FeHA was able to exert its cytotoxic activity on SAOS-2 cells at the same level as free DOX





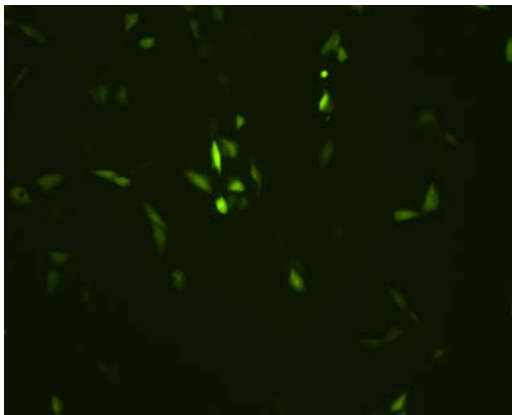
# FeHA NPs for Gene Transfection Technology: *“Magnetofection”*



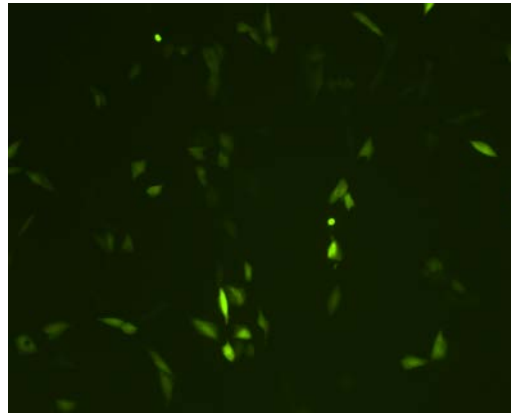
FeHA could be use to transfect cells with GFP

It exploits magnetic force exerted upon gene vectors associated with FeHA to draw the vectors into the target cells.

- **Greatly Improved transfection rates**
- **Short process time**
- **Low vector doses**



SPIONs



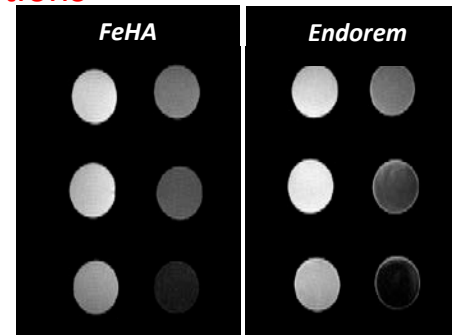
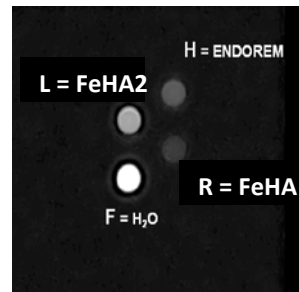
FeHA NPs

**GENES**

**GENE/CELL THERAPY**

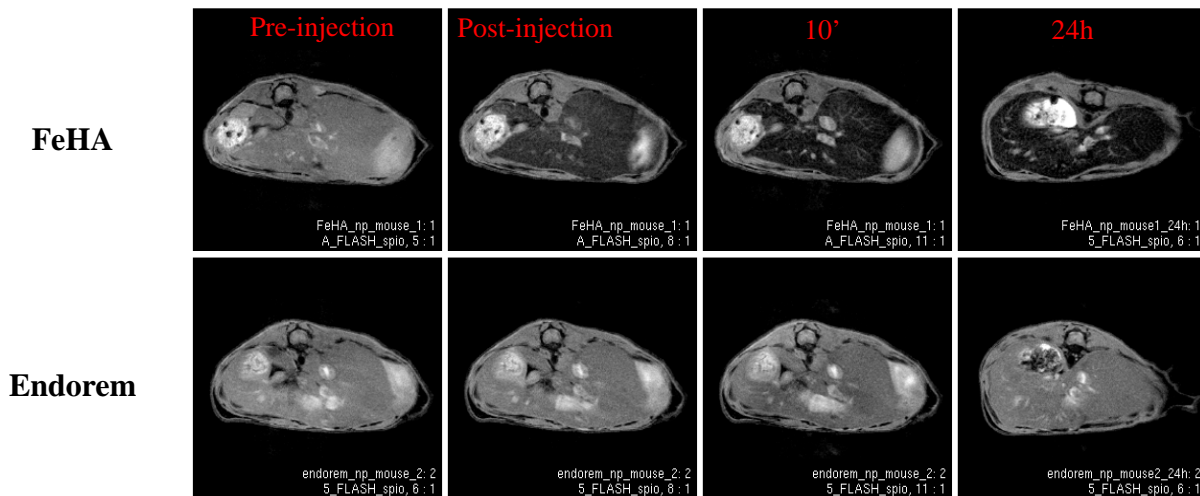
# T2-weighted image of Fe-HA compared to the commercial negative contrast agent ENDOREM and to water without contrast agent in it.

*MRI images at a field intensity of 0.2 T (~8.5 MHz)  
commonly used for clinical investigation of diseases in  
articulations*



*The higher the  
concentration  
The higher the contrast*

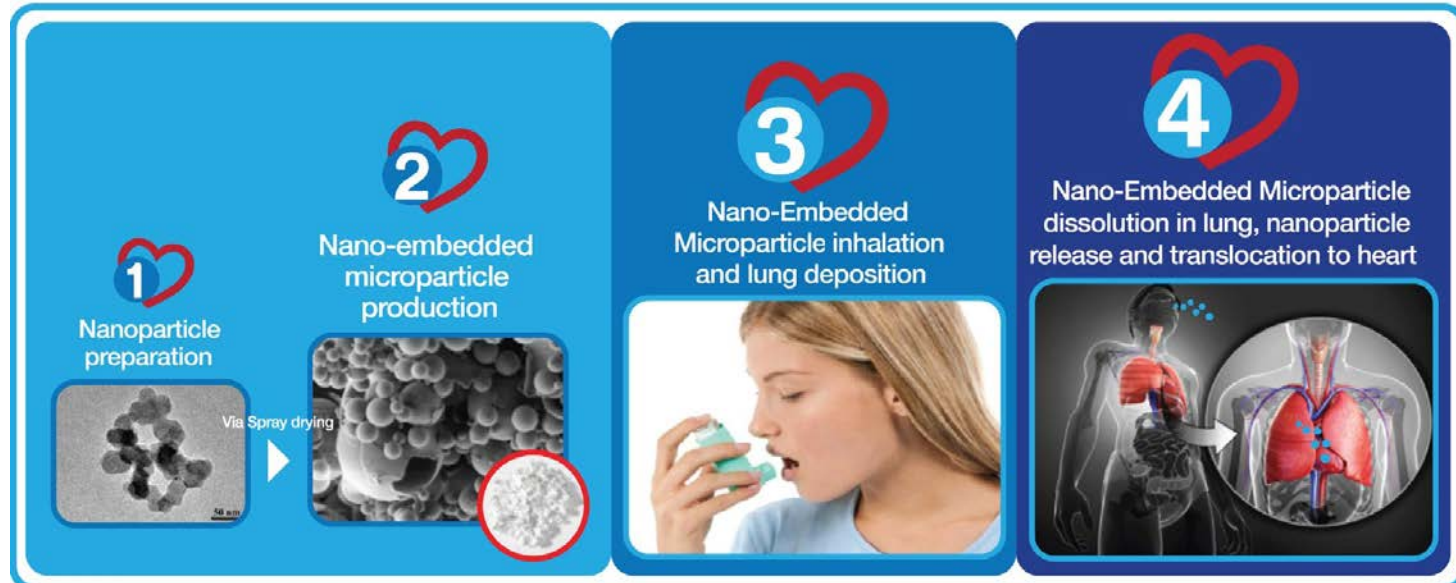
T2 mapping – Sequences collected on the livers of two mouse treated by intravenous injection with a citrate solution respectively of FeHA and Endorem to have a dose of 2 mg/kg of iron.



Cardio Ultraefficient nanoParticles for Inhalation of Drug products



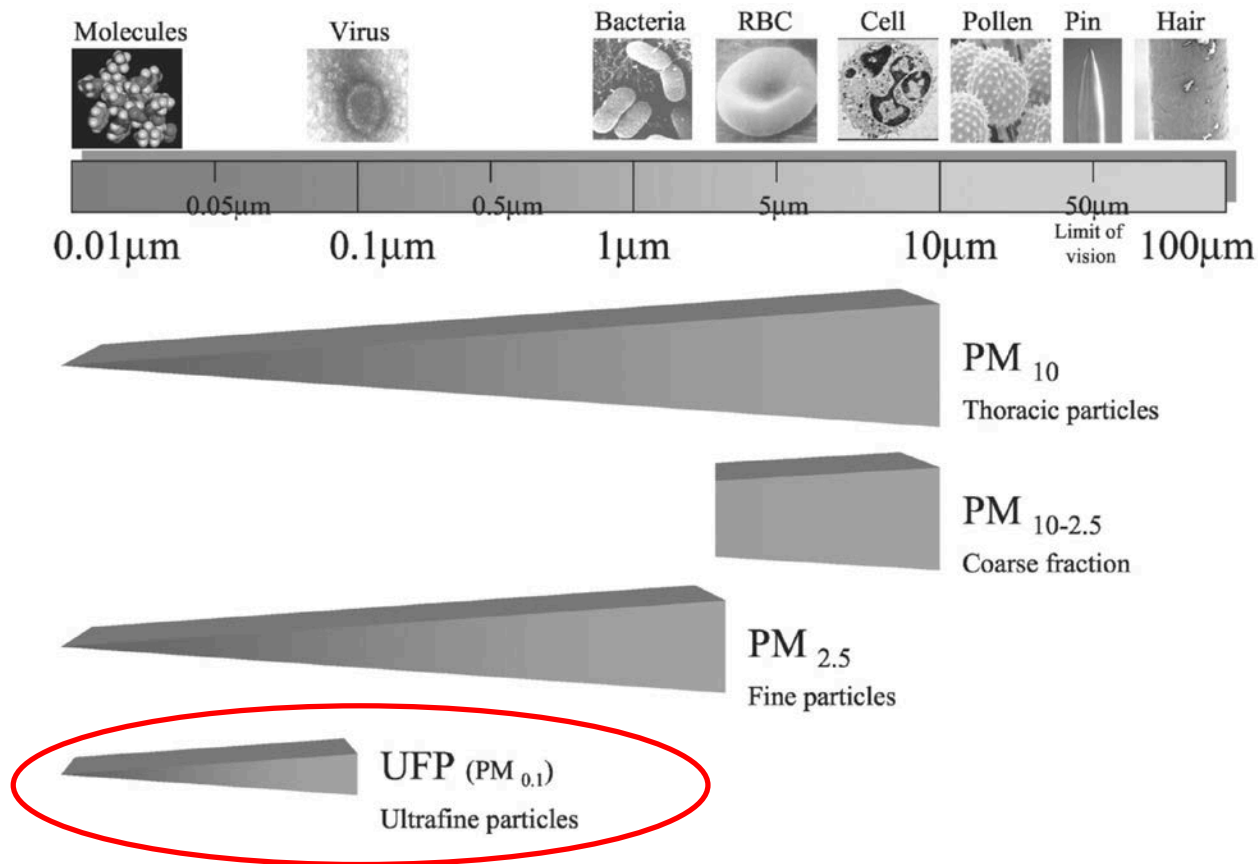
## THE BREATHING HEART CONCEPT





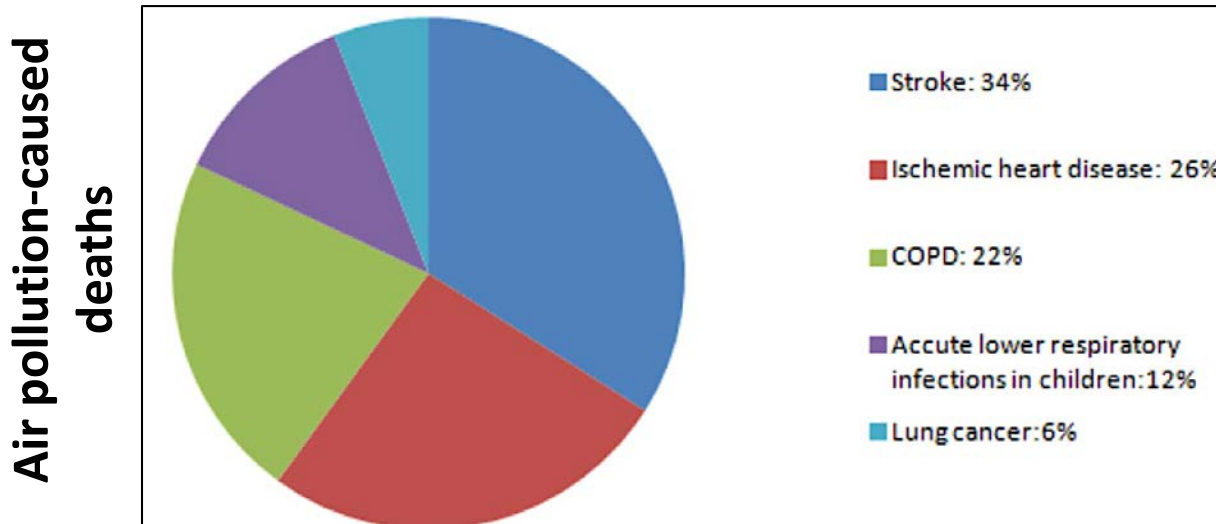
# The dark side of the coin

## Linking Air Pollution and Heart Disease



# The dark side of the coin

## Linking Air Pollution to Heart Disease



- Ambient particulate air pollution is a risk factor not only for respiratory diseases but also for acute cardiovascular events
- Particulate (ultrafine < 100 nm PM) air pollution triggers myocardial infarction, increases hospital admissions for cardiovascular diseases

# The bright side of the coin

Towards a novel clinical approach

## **Prediction:**

*Heart disease may be treated with  
**ad hoc non-toxic and biodegradable  
nanoparticles** that deliver specific  
pharmacological drugs to the heart via  
inhalation*

# A NEW PARADIGM FOR CARDIAC DRUG ADMINISTRATION

**Inhalation**

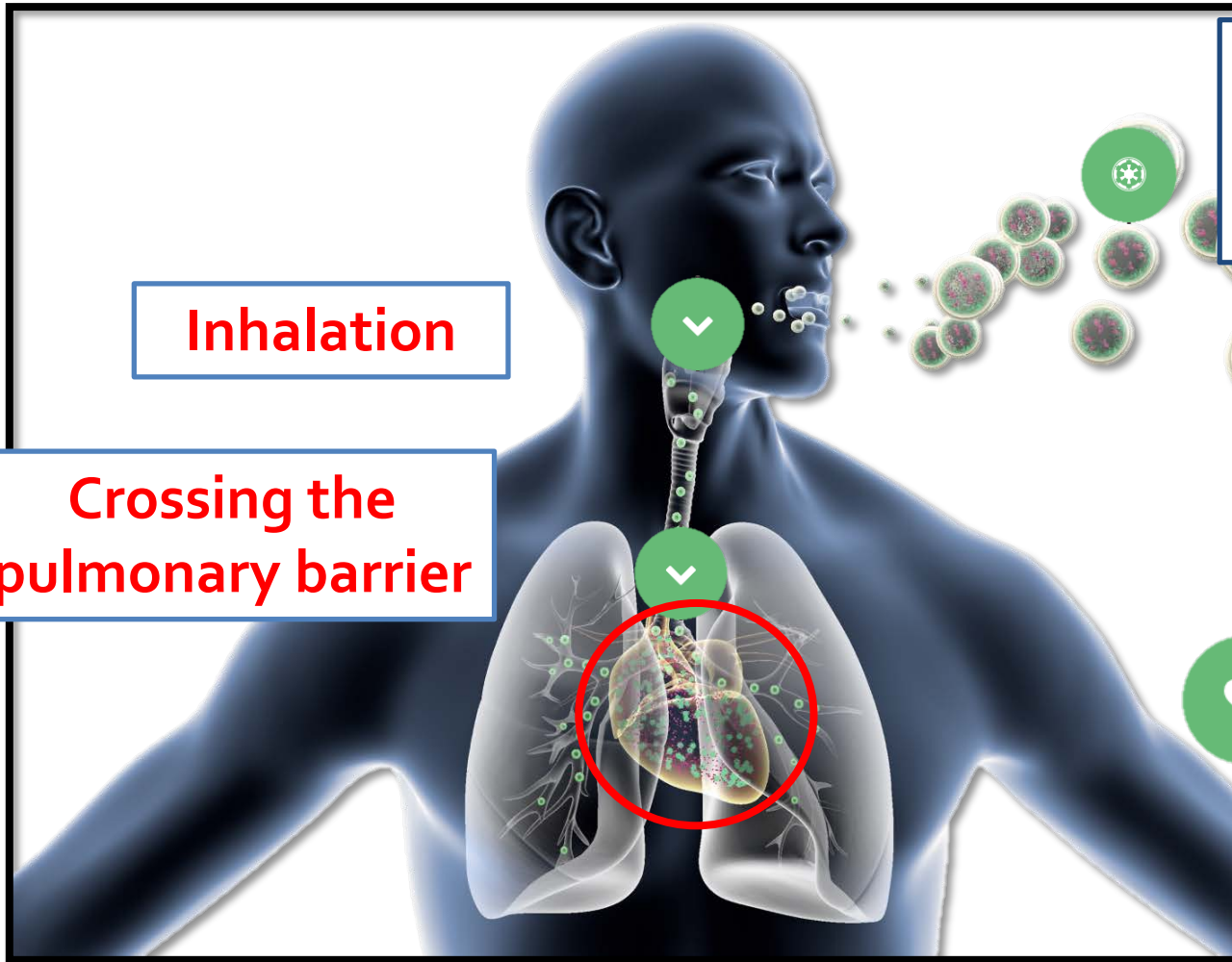
**Crossing the  
pulmonary barrier**

**Fe-CaP  
Nanoparticles**  
*loading drugs*

- miRNAs
- Peptides
- Active pharmaceutical ingredients

**One target:**  
**the heart**

- Fast action
- Less side effects
- Not invasive

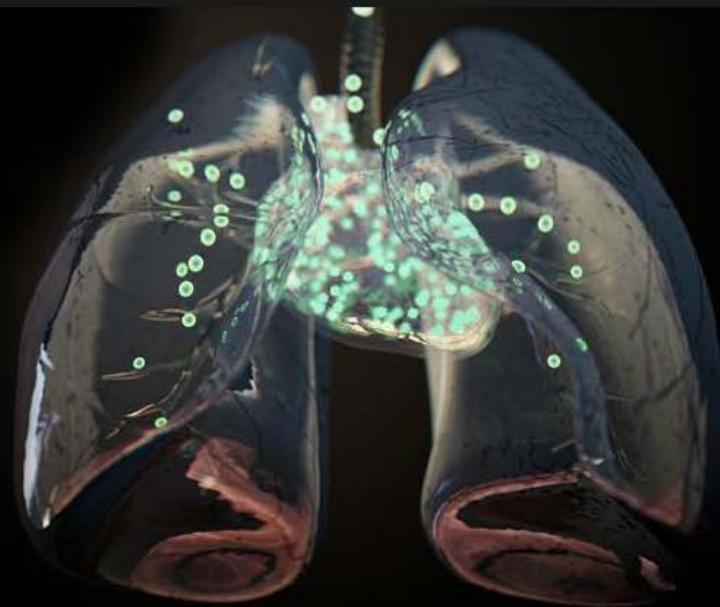




## Cover story: A puff of particles for the heart

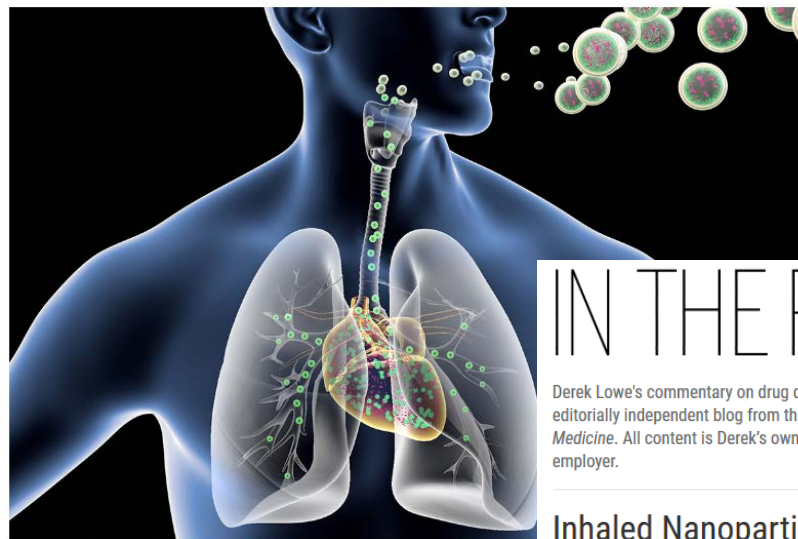
Inhalation delivers drug-loaded nanoparticles to the heart, improving cardiac function in murine and porcine models

Ella Marushchenko, Alexander Tokarev/Ella Maru Studio



DAILY NEWS 17 January 2018

## Breathing in a nanoparticle spray could prevent heart damage



An inhalable drug should get to the heart fast  
Ella Maru studio

## IN THE PIPELINE

Derek Lowe's commentary on drug discovery and the pharma industry. An editorially independent blog from the publishers of *Science Translational Medicine*. All content is Derek's own, and he does not in any way speak for his employer.



By Derek Lowe



## Inhaled Nanoparticles – Good Ones, That Is

By Derek Lowe | January 26, 2018

## Science Translational Medicine

17 JANUARY 2018

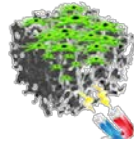


AAAS

# FeHA PLATFORM - CONCLUSION

## ➤ REGENERATIVE MEDICINE

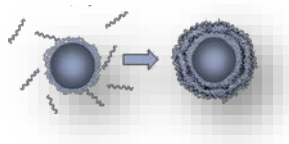
Biomimetic magnetic scaffold



## ➤ CELL THERAPY



## ➤ DIAGNOSTICS & IMAGING



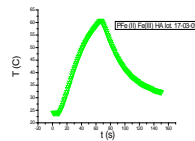
## ➤ PHARMA

Drug delivery system

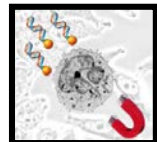


## ➤ HYPERTHERMIA

Solid tumor treatment



## ➤ GENE TRANSFECTION TECHNOLOGY: “magnetofection”

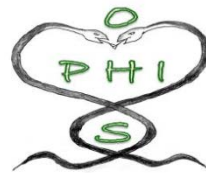


- ✓ Fully resorbable and bioactive
- ✓ Fast tissue regeneration and colonization
- ✓ Magnetic homing of grow factors/ biologics
- ✓ Improvement of cell delivery and retention
- ✓ Enhancement of cell differentiation
- ✓ MicroRNA recruitments
- ✓ Analysis on Lab-on-chip
- ✓ Recall of the FeHA+RNA via magnetic probe
- ✓ Higher contrast ability respect to SPION
- ✓ Lower iron content
- ✓ High flexibility in linking and carrying drugs
- ✓ Biomolecules stability
- ✓ Remote control release
- ✓ Multiple realese
- ✓ More efficient than magnetite in hyperthermia-based therapies
- ✓ Greatly Improved transfection rates
- ✓ Short process time
- ✓ Low vector doses

# Acknowledgments



National Research Council of Italy  
Institute of Science and Technology for Ceramics



Erasmus+

