On the Use of Calcium Phosphate Nanoparticles as Agent for Magnetic and Nuclear in Vivo Imaging

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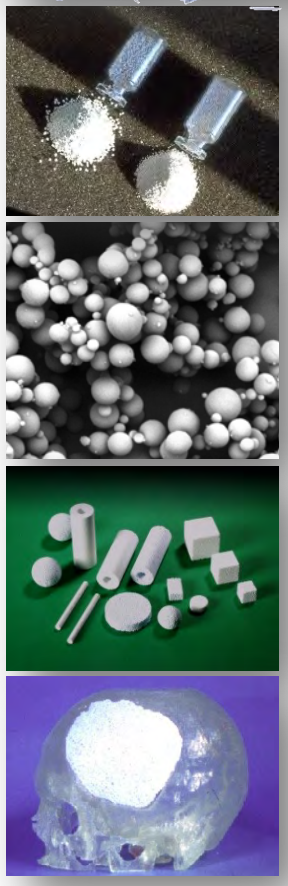
- BIOMATERIALS
- ENERGY & ENVIRONMENT
- HIGH-TECH & NANOTECHNOLOGY
- CULTURAL ERITAGE

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

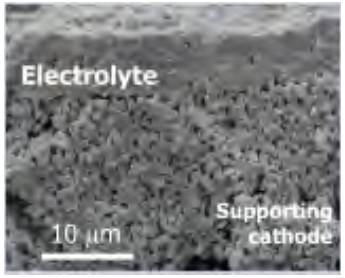
BIOMATERIALS

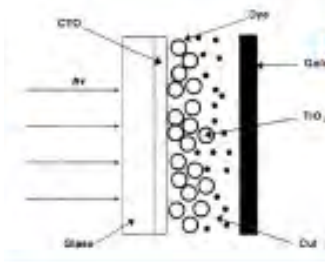


CULTURAL ERITAGE

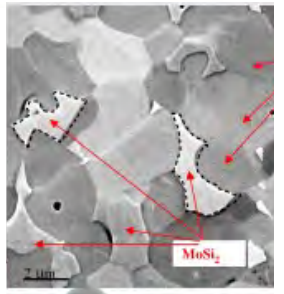
PIEZOELECTRIC CERAMICS

CERAMIC FOR ENERGY

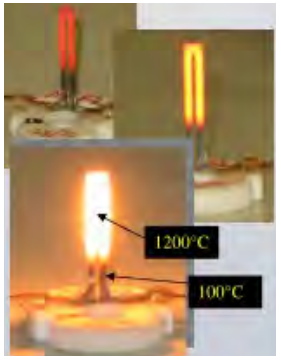




UHTC- ULTRA-REFRACTORY STRUCTURAL CERAMICS



Nose tip for space vehicle



Electroconductive ceramics

Faenza (RA)


Svizzera
(Switzerland)
Davos Platz
Bolzano
Bozen
Cortina
d'Ampezzo
Klagenfurt am
Wörthersee
Villach
Jesenice
Bled
Kranj
Crans-Montana
Trento
Trient
Udine
Škofja Loka
Verbier
Lugano
Como
Varese
Bergamo
Schio
Treviso
Trieste
Biella
Legnano
Monza
Brescia
Vicenza
Padova
Venezia
Koper
Novara
Milano
Verona
Zevio
Rijeka
Vigevano
Legnago
Este
Torino
Pavia
Piacenza
Rovinj
Labin
Moncalieri
Alessandria
Reggio
Emilia
Ferrara
Parma
Pula
Modena
Genova
Bologna
Ravenna
Cuneo
Savona
La Spezia
Forlì
Rimini
Alassio
San Marino
Pesaro
Viareggio
Lucca
Firenze
Nice
Sanremo
Pisa
Senigallia
Ancona


ALPHATAURI

The Research Group on Bioceramics and Bio-hybrid Composites counts 15 people among senior and young investigators (including chemists, biologists, physicists and engineers)

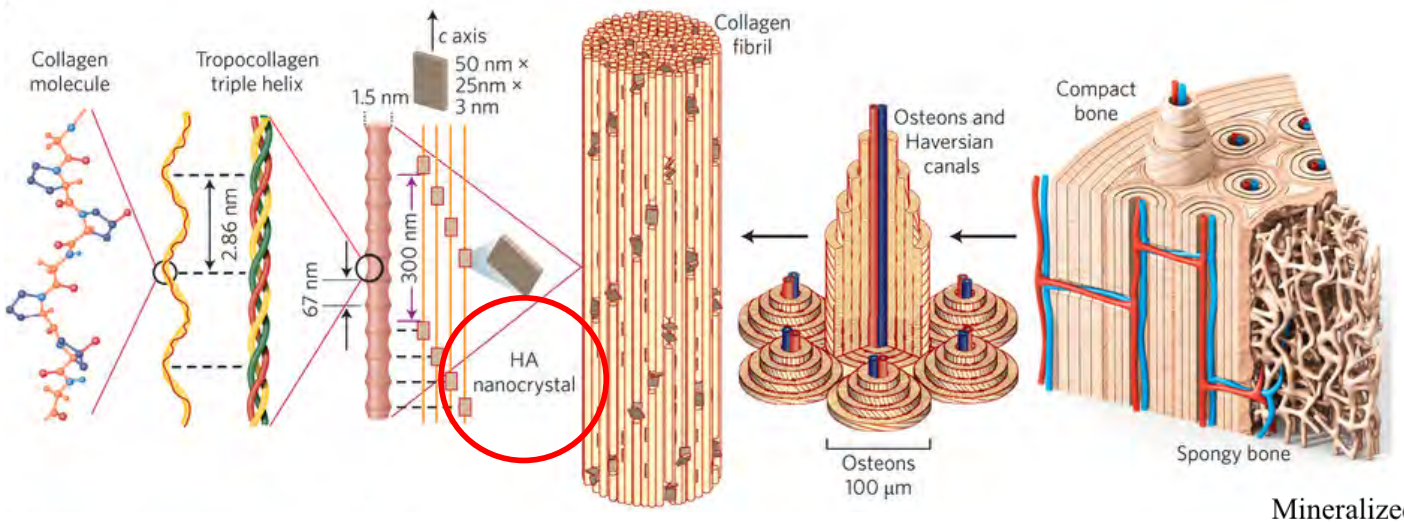
Experience in:

- **calcium phosphate-based materials for bone tissue engineering (ceramics and hybrid composites)**
- **nanoparticles**
- **biomineralization processes**
- **drug delivery systems**
- **superparamagnetic nanoparticles**
- **functionalization of biomaterials**
- ***in vitro* biological evaluation**

Facilities for the synthesis of hybrid materials, scaffolds and nanoparticles, as well as for extensive chemical, physical, thermal, morphological, magnetic, mechanical and in vitro biological characterization.

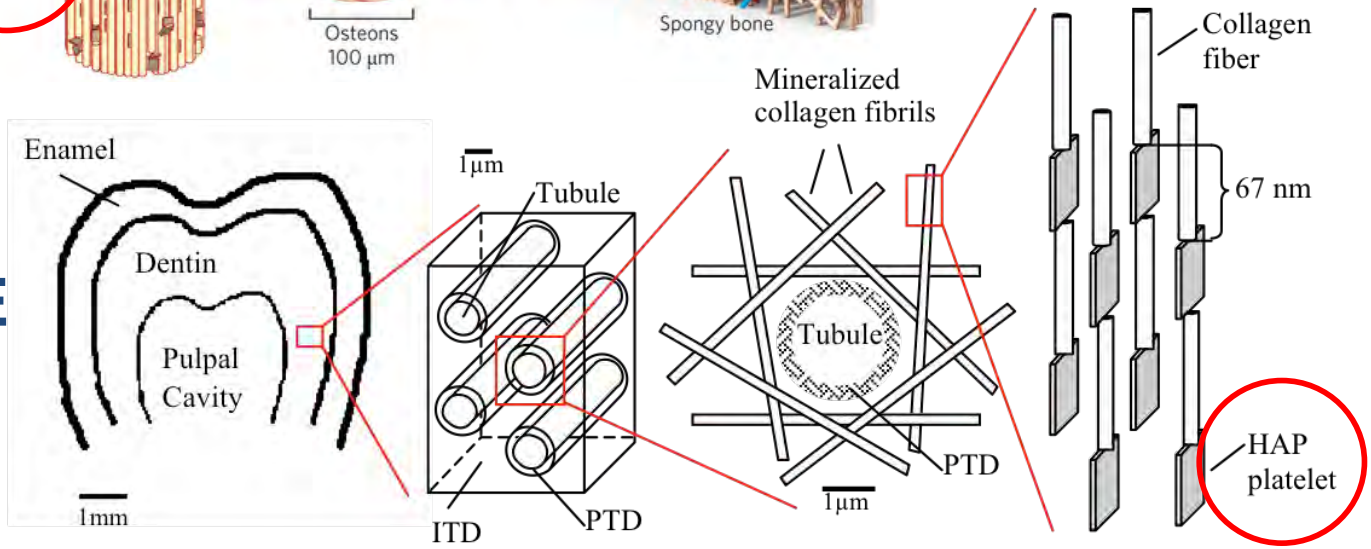
Calcium Phosphates (CaPs)

Calcium phosphates (Hydroxyapatite) in biological systems are the main inorganic components of bone, tooth and some pathological calcifications



BONE TISSUE

DENTAL TISSUE



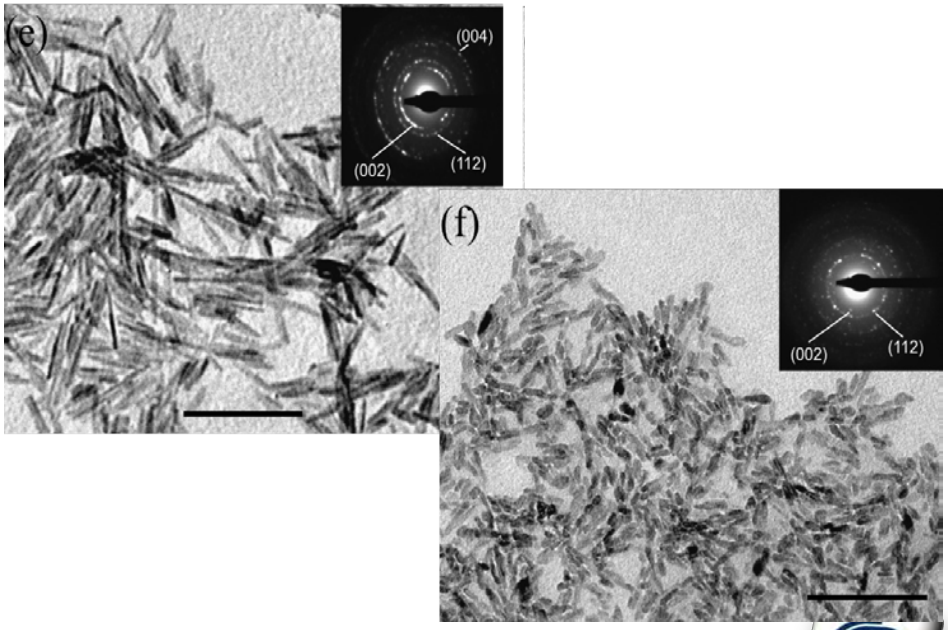
Weiner and Wagner, *Annu Rev Mater Sci,* 1998

Gomez-Morales et al., *Prog Cryst Growth Charact Mater,* 2013

Synthetic CaPs

Due to their excellent properties, such as **biocompatibility**, **bioactivity**, **osteoconductivity**, **osteoinductivity**, and **nonimmunogenicity**, synthetic CaPs are important materials to prepare devices for **bone tissue substitution and regeneration**, in the form of 3D dense or porous ceramics and as injectable cements

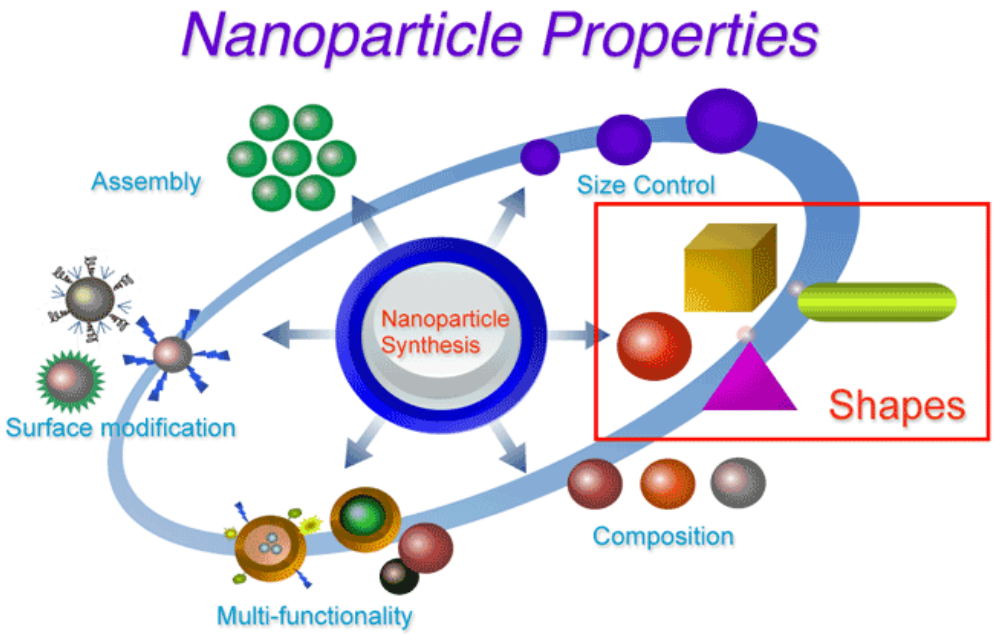
The advancements in materials science have prompted a progress in the preparation of CaPs with tailored characteristics, nano dimensions, and colloidal stability opening new interesting perspectives in different fields **not only related to bone applications**



Iafisco et al., *Exp Opin Drug Del,* 2008

CaPs (apatites) as drug nanocarriers

- Favorable biodegradability and biocompatibility
- Higher degradability and lower toxicity than silica, quantum dots, carbon nanotubes, or metallic NPs
- Higher stability than liposomes, allowing a more controlled and predictable drug delivery
- Low production cost 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

Biomimetic apatites can be recognized by the organism as a sort of endogenous material

Iafisco et al., *Langmuir,* 2008; Iafisco et al., *J Mat Chem* 2009; Iafisco et al., *Nanoscale* 2012; Iafisco et al., *J Inorg Biochem* 2012

Nanoscale

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Cite this: *Nanoscale*, 2012, **4**, 206

www.rsc.org/nanoscale

PAPER

Nanocrystalline carbonate-apatites: role of Ca/P ratio on the upload and release of anticancer platinum bisphosphonates†

Michele Iafisco,*[ab] Barbara Palazzo,[a] Gianmario Martra,[c] Nicola Margiotta,[d] Sara Piccinonna,[d] Giovanni Natile,[d] Valentina Gandin,[e] Cristina Marzano[e] and Norberto Roveri[a]

Received 22nd August 2011, Accepted 7th October 2011
DOI: 10.1039/c1nr11147g

LANGMUIR

Article

Cite This: *Langmuir* 2018, 34, 12036−12048

pubs.acs.org/Langmuir

Interaction of Folic Acid with Nanocrystalline Apatites and Extension to Methotrexate (Antifolate) in View of Anticancer Applications

Stéphanie Sarda,*[,†] Michele Iafisco,*[,‡] Patricia Pascaud-Mathieu,[†,∥] Alessio Adamiano,[‡] Monica Montesi,[‡] Silvia Panseri,[‡] Olivier Marsan,[†] Carole Thouron,[†] Agnès Dupret-Bories,[†,§] Anna Tampieri,[‡] and Christophe Drouet*[,†,‡]

Nanoscale

ROYAL SOCIETY OF CHEMISTRY

PAPER

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Cite this: *Nanoscale*, 2020, **12**, 13582

Preclinical evaluation of platinum-loaded hydroxyapatite nanoparticles in an embryonic zebrafish xenograft model†

Robin A. Nadar, ‡[a] Nandini Asokan, ‡[b,c] Lorenzo Degli Esposti, [d] Alessandra Curci, [e] Alessandra Barbanente, [e] Lukas Schlatt, [f] Uwe Karst, [f] Michele Iafisco, [d] Nicola Margiotta, [e] Michael Brand, [b] Jeroen J. J. P. van den Beucken, [a] Martin Bornhäuser [b,c,g,h] and Sander C. G. Leeuwenburgh *[a,d]

Langmuir

Article

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pH-Responsive Delivery of Doxorubicin from Citrate−Apatite Nanocrystals with Tailored Carbonate Content

Isaac Rodríguez-Ruiz,[†,‡] José Manuel Delgado-López,[†,‡] Miguel A. Durán-Olivencia,[†] Michele Iafisco,[§] Anna Tampieri,[§] Donato Colangelo,[∥] Maria Prat,[∥,*] and Jaime Gómez-Morales[†,*]

full papers

Drug Delivery

Cell Surface Receptor Targeted Biomimetic Apatite Nanocrystals for Cancer Therapy

Michele Iafisco, Josè Manuel Delgado-Lopez, Elena Maria Varoni, Anna Tampieri, Lia Rimondini, Jaime Gomez-Morales, and Maria Prat**

Research Article

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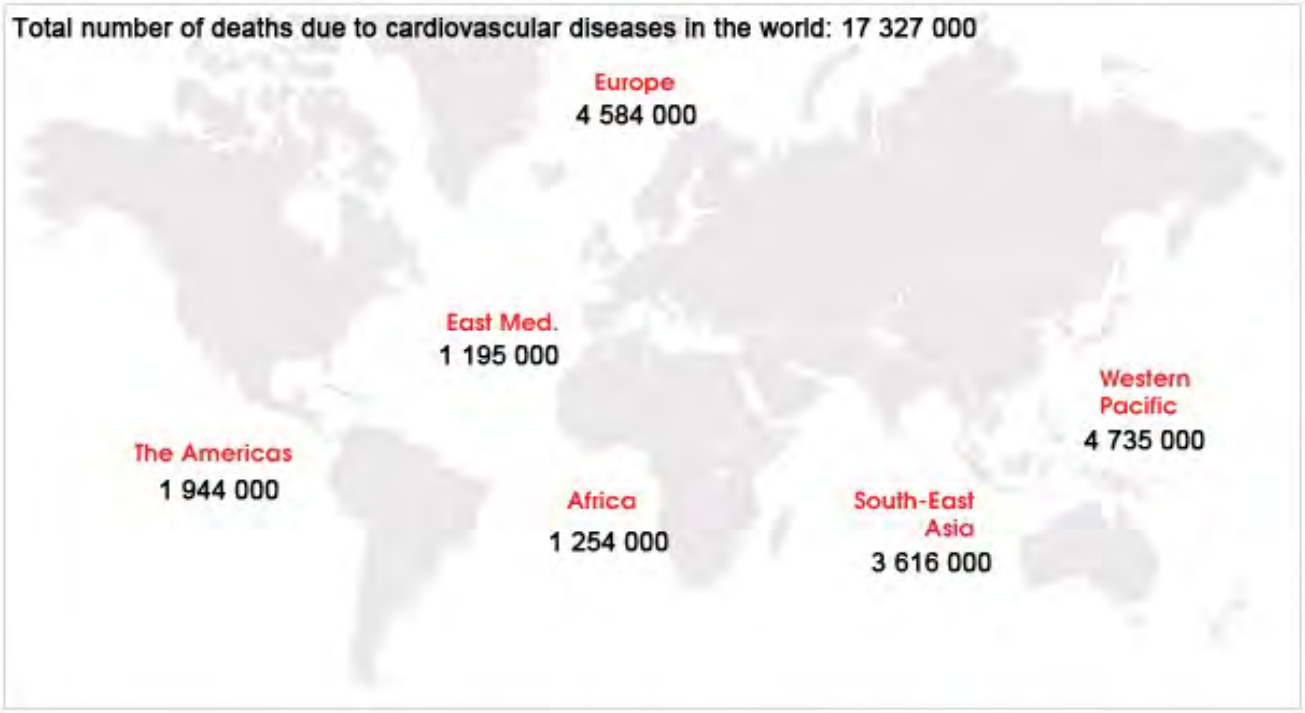
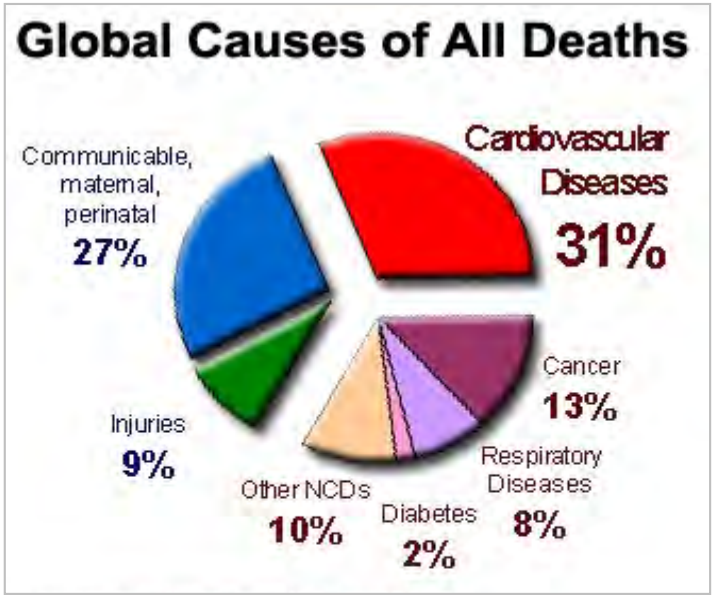
Nanomedicine

Bioinspired negatively charged calcium phosphate nanocarriers for cardiac delivery of MicroRNAs

Cardiovascular diseases (CVDs)

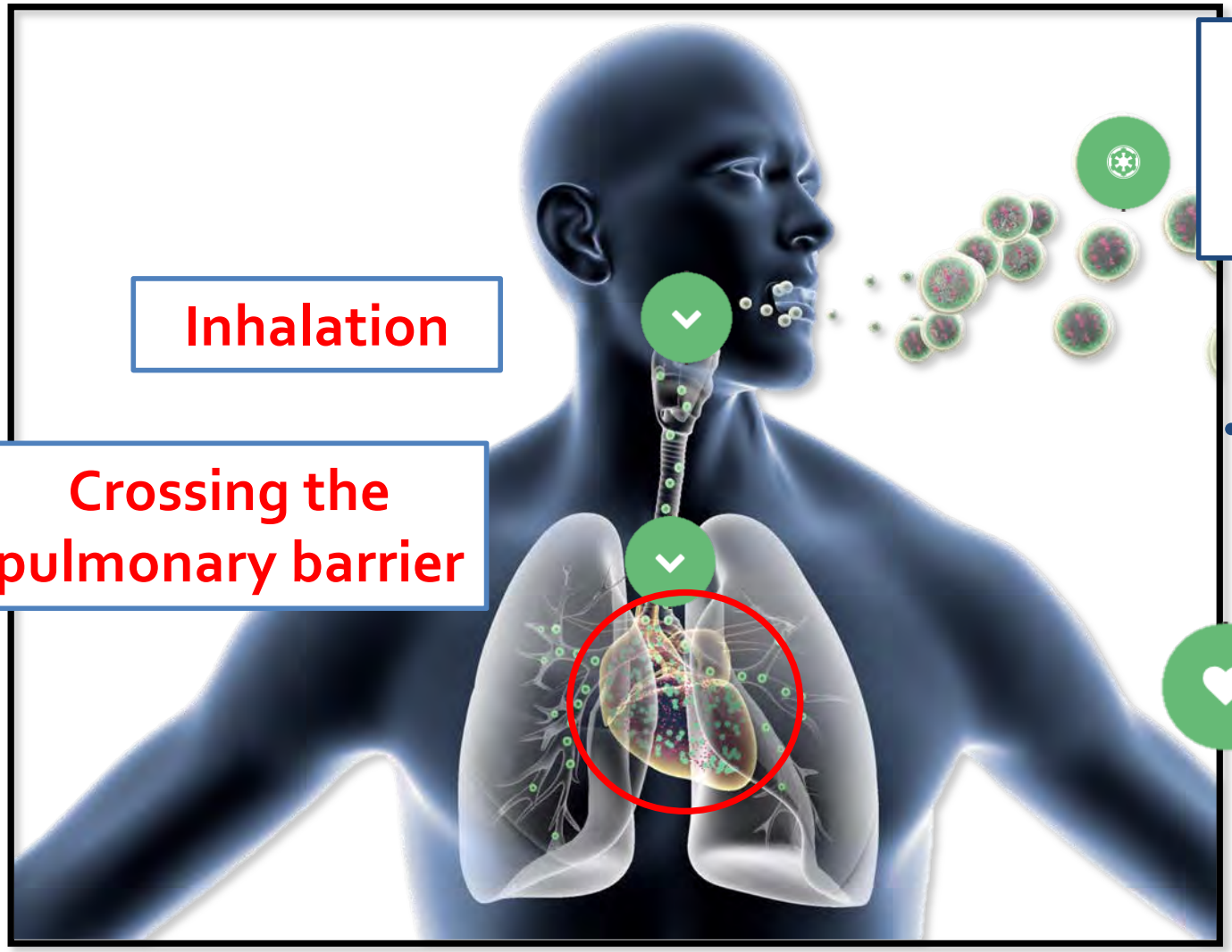




World Health Organization, 2019

- ***CVD is the number one cause of death globally***
- ***An estimated 17.9 million people died each year for CVDs (31% of all global deaths)***
- ***The number of people who die from CVDs will increase to reach about 23.3 million by 2030***

WHO. Cardiovascular diseases. www.who.int/cardiovascular_diseases/en/



Inhalation

Crossing the pulmonary barrier

CaP Nanoparticles *loading drugs*

- miRNAs
- Peptides
- Active pharmaceutical ingredients

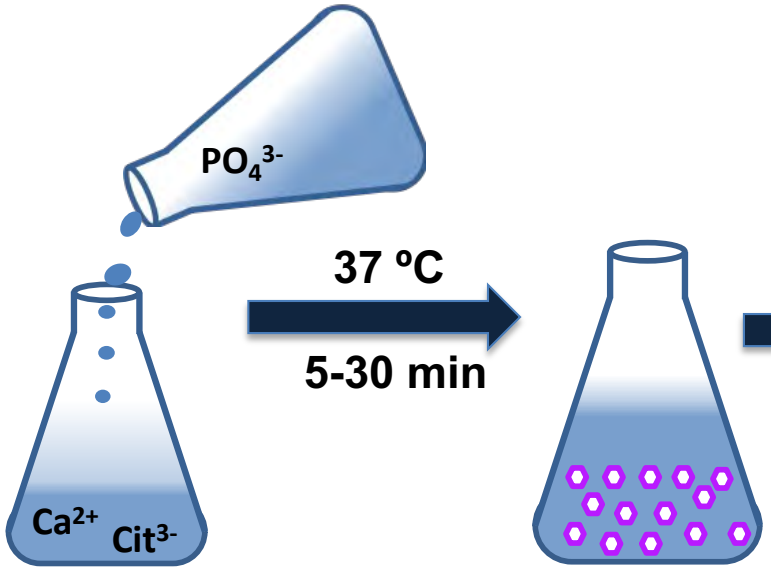
Reaching the the heart

- Fast action
- Less side effects
- Not invasive

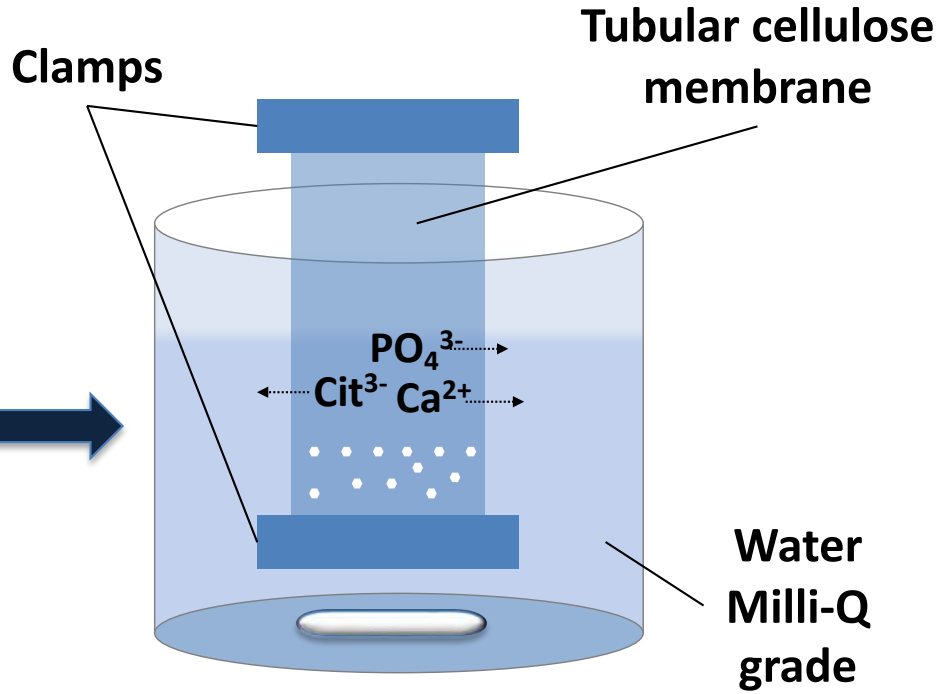
A NEW PARADIGM FOR CARDIAC DRUG ADMINISTRATION

CaP-NPs preparation

Na_2HPO_4 (120 mM)

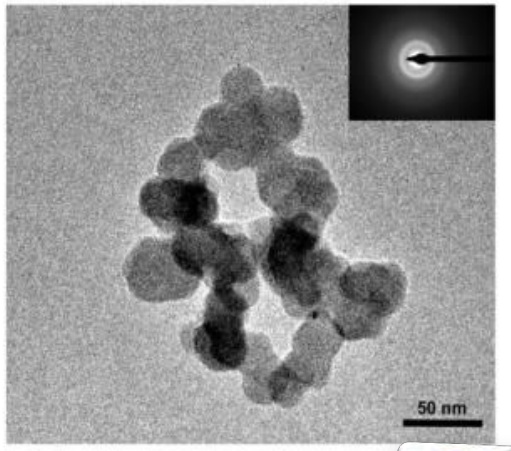


$CaCl_2$ (100 mM)
+
$Na_3Citrate$ (200–400 mM)



6 hrs.

Z-average = 70-90 nm
ζ-potential = -30/-35 mV

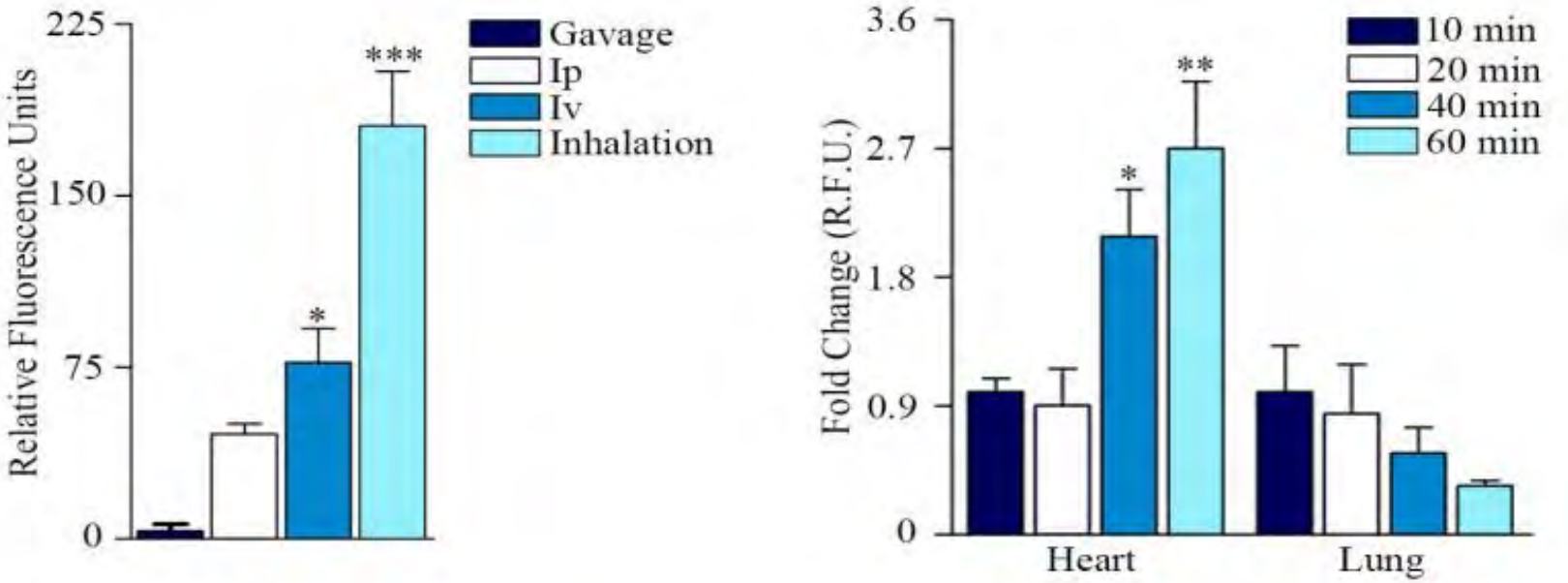


One-pot bioinspired synthesis method, in which citrate acts as a stabilizing agent and regulator of crystal growth of CaP-NPs at the early stage of crystallization

Di Mauro, Iafisco et al. *Nanomedicine UK* 2016

In vivo administration of CaP-NPs by inhalation

Quantification of fluorescence signals from heart tissue of mice treated with CaP-Cy7 via gavage, intraperitoneal (IP), intravenous (IV), and inhalation administration

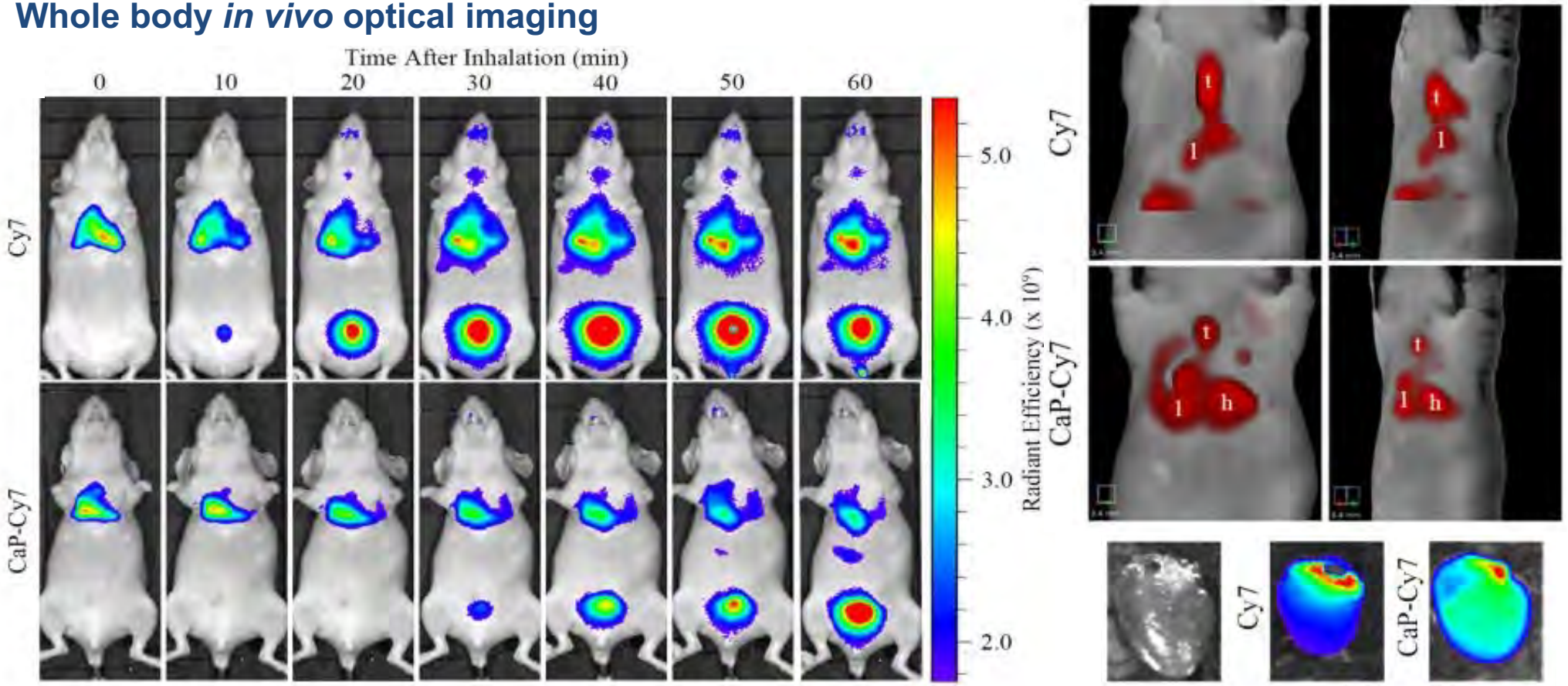


- **Enteral administration did not generate any significant cardiac targeting at 40 min, parenteral administration and in particular inhalation gave a significant and rapid delivery of CaP-Cy7 to the myocardium**
- **The time-course of CaP-Cy7 myocardial accumulation was paralleled by a reduction of pulmonary signal suggesting a continuous passage of NPs across the pulmonary-barrier**

Miragoli, Iafisco et al. *Sci. Transl. Med.* 2018

In vivo administration of CaP-NPs by inhalation

Whole body *in vivo* optical imaging

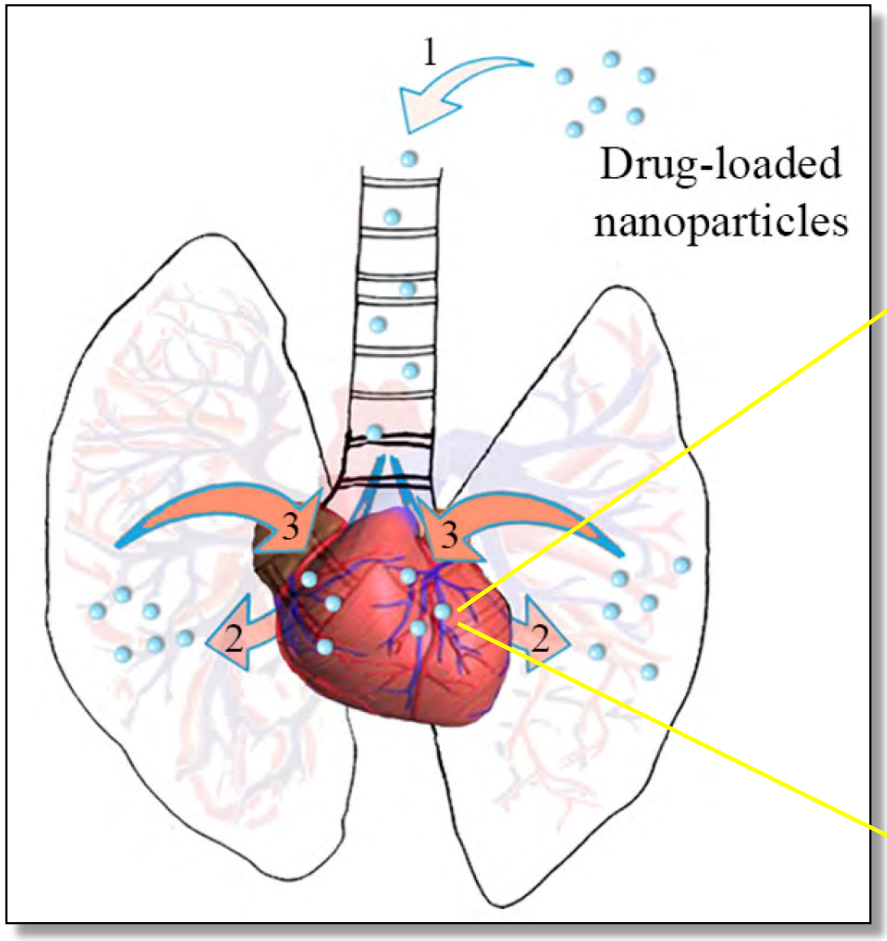


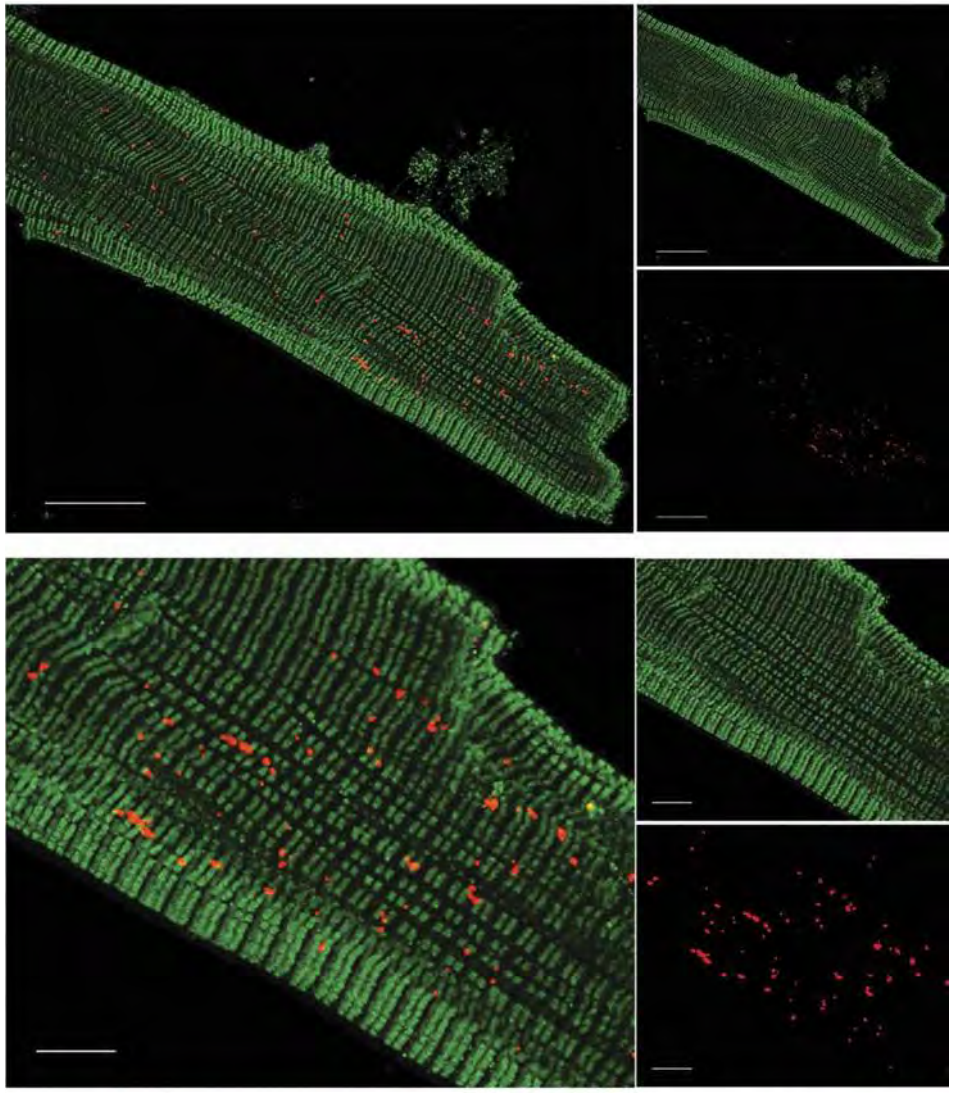
Gradual accumulation in the mediastinum, esophagus, and trachea. A delayed clearance of inhaled CaP-Cy7 compared to Cy7 alone

Effective delivery of CaP-Cy7 from the pulmonary tree to the bloodstream and to the myocardium was confirmed with 3D-FMT analyses

Miragoli, Iafisco et al. *Sci. Transl. Med.* 2018

In vivo administration of functionalized CaP-NPs by inhalation

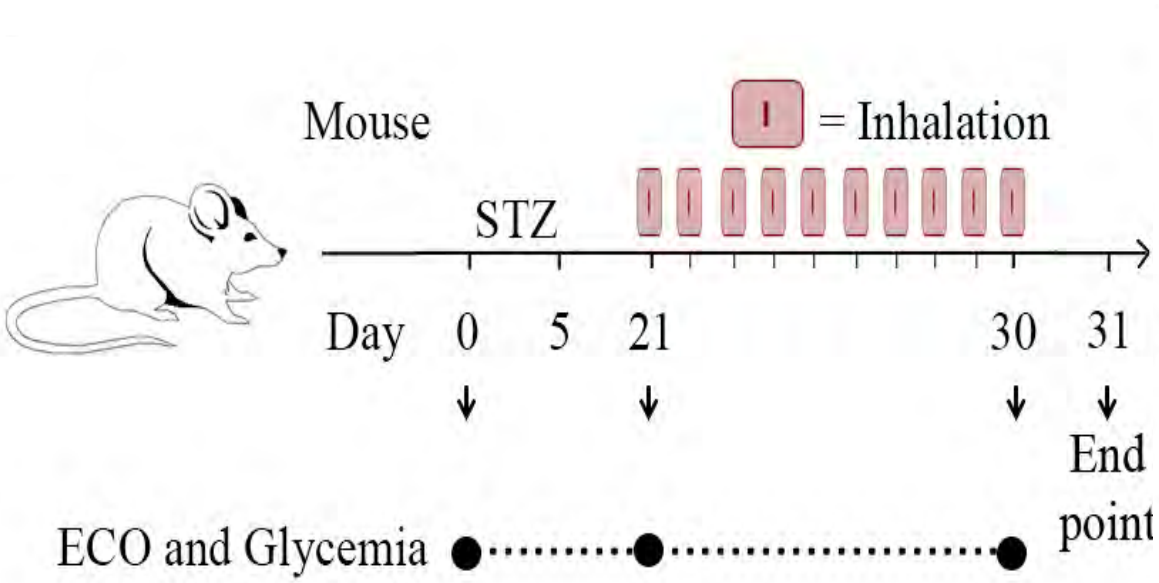




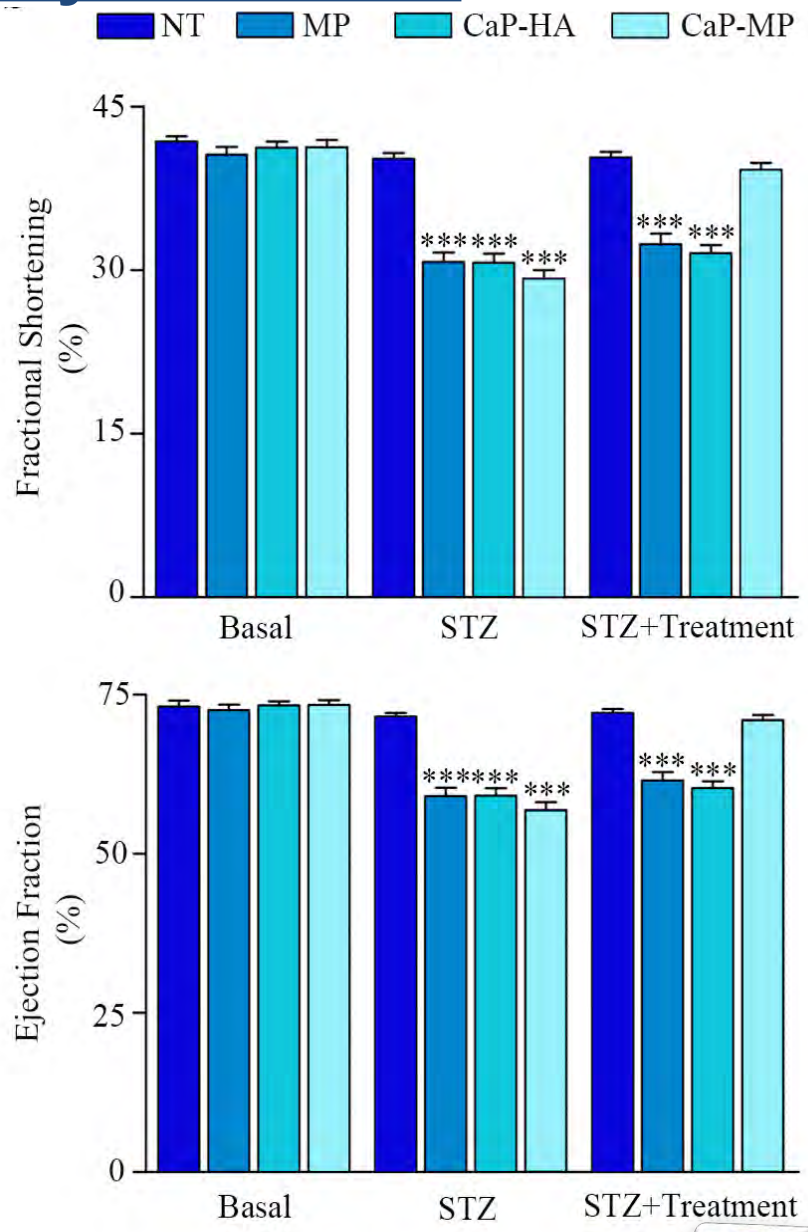
Stimulated emission depletion (STED) microscopy of isolated cardiomyocytes from mice treated with MP-Rhodamine-loaded CaPs.

Miragoli, Iafisco et al. *Sci. Transl. Med.* 2018

In vivo administration of CaP-MP by inhalation



mouse model of diabetic cardiomyopathy



STZ: streptozotocin
HA: scrambled peptide
MP: mimetic peptide improving cardiac contractility

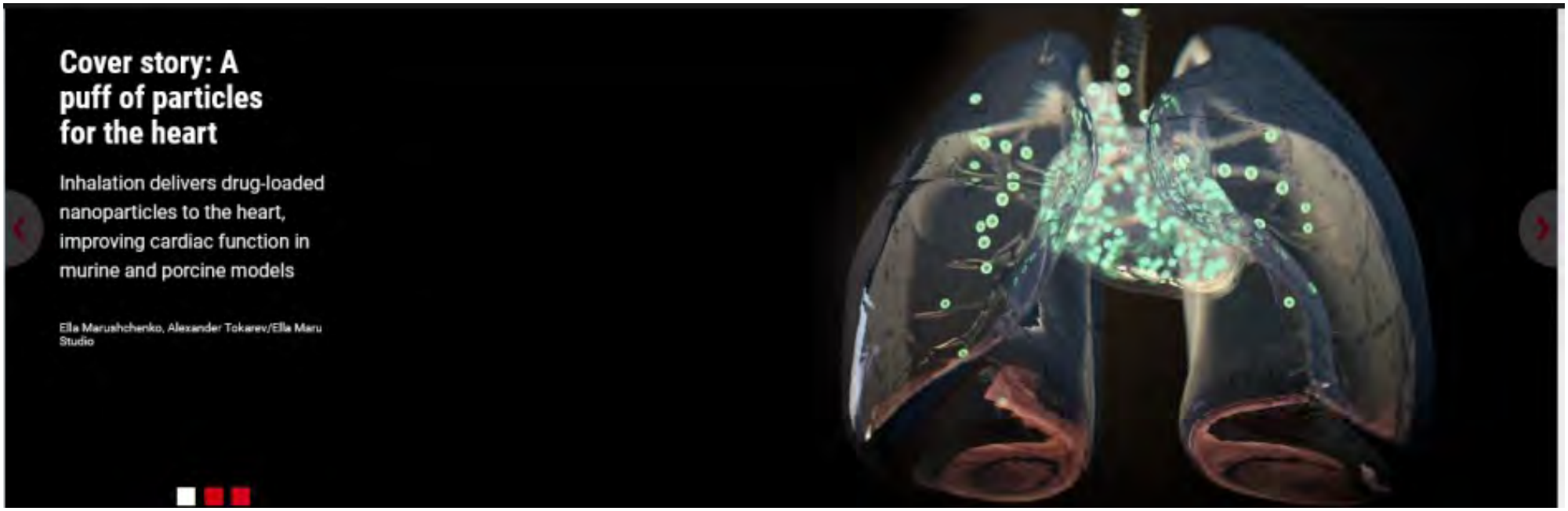
Treatments with CaP-MP led to a complete recovery of cardiac function as shown by echocardiographic assessment of left ventricular function

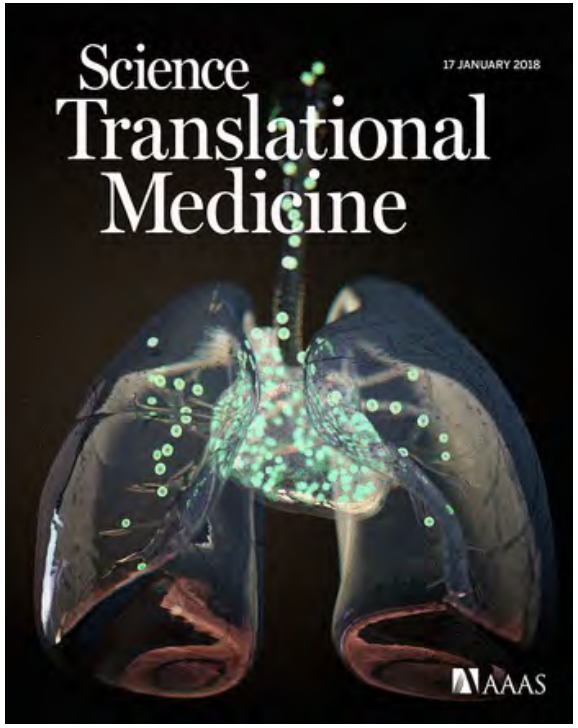
Miragoli, Iafisco et al. *Sci. Transl. Med.* 2018

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

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

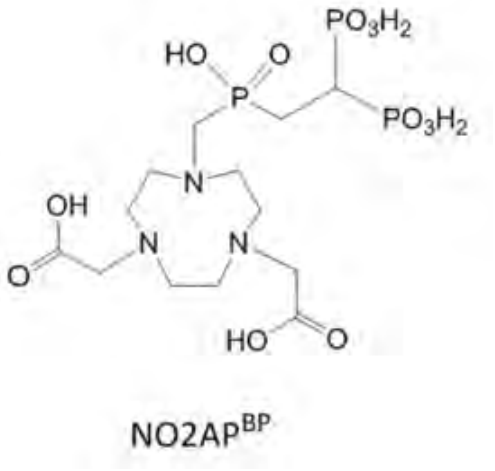
Inhaled Nanoparticles – Good Ones, That Is

By Derek Lowe | January 26, 2018

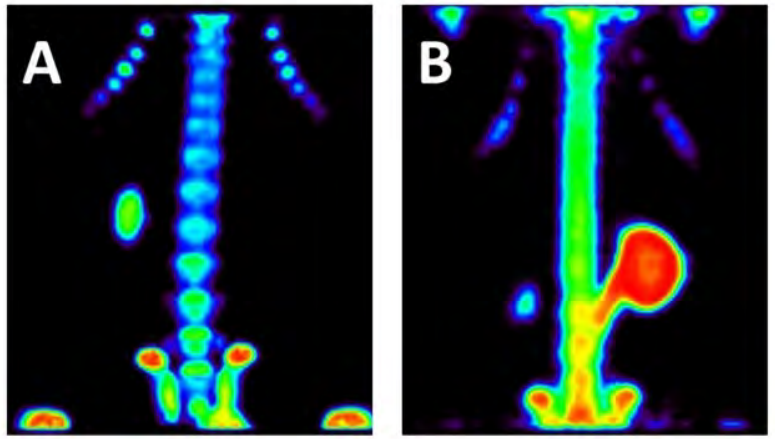
Imaging

The non-invasive in vivo monitoring of NPs behavior is of paramount importance to assess their biosafety, to determine their mechanisms of action and the organs they interact with, and also to find their optimal architecture for desired usage

Positron Emission Tomography (PET) represents an ideal tool for such



$NO2AP^{BP}$



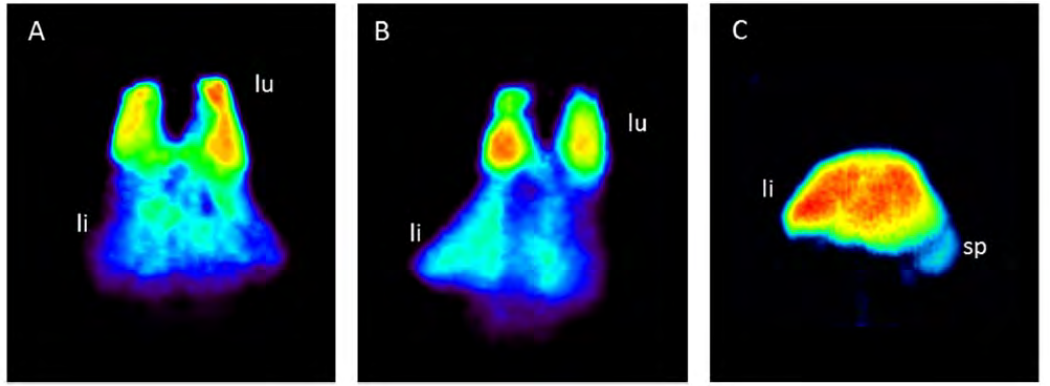
$[^{68}Ga]NO2AP^{BP}$

Labeling by surface functionalization

$[^{18}F]NaF$

Direct incorporation of the radioisotope

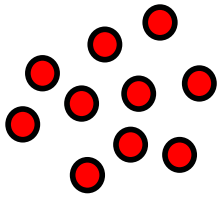
AP-$[^{18}F]NaF$ **AP-$[^{68}Ga]NO2AP^{BP}$** **Cit-AP-$[^{68}Ga]NO2AP^{BP}$**



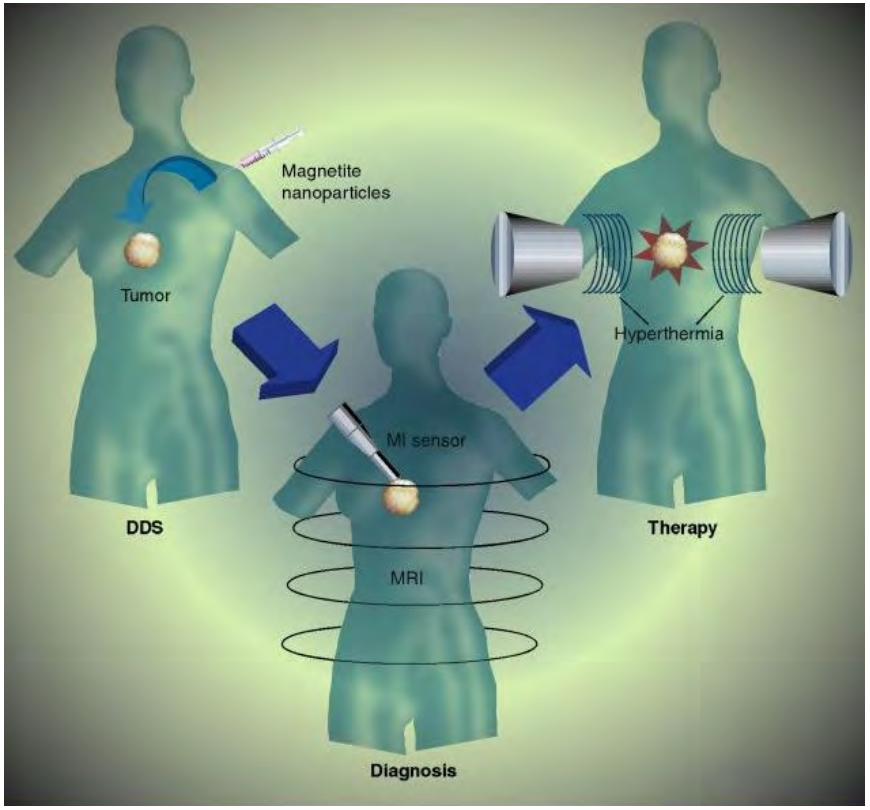
Sandhofer et al., *ACS Appl Mater Interfaces*, 2015.

Magnetic nanoparticles as drug carriers

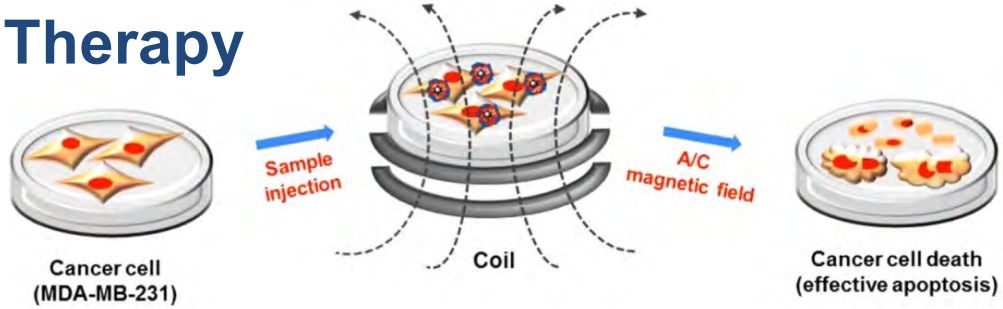
Manipulated upon application of magnetic fields



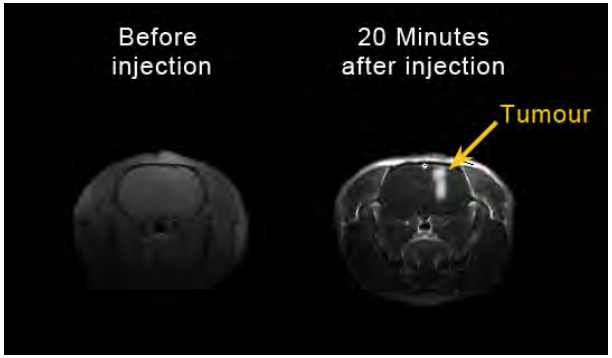
Remote control of the drug by application of an external magnetic field



Therapy

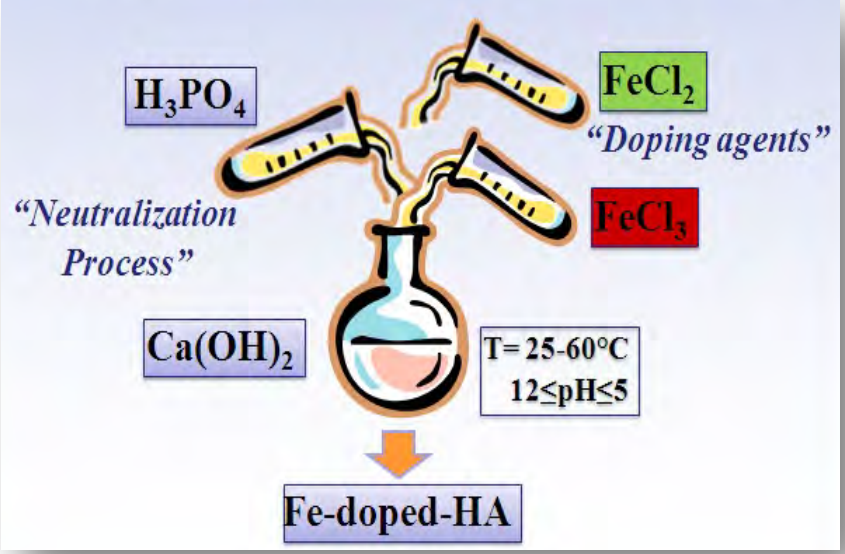


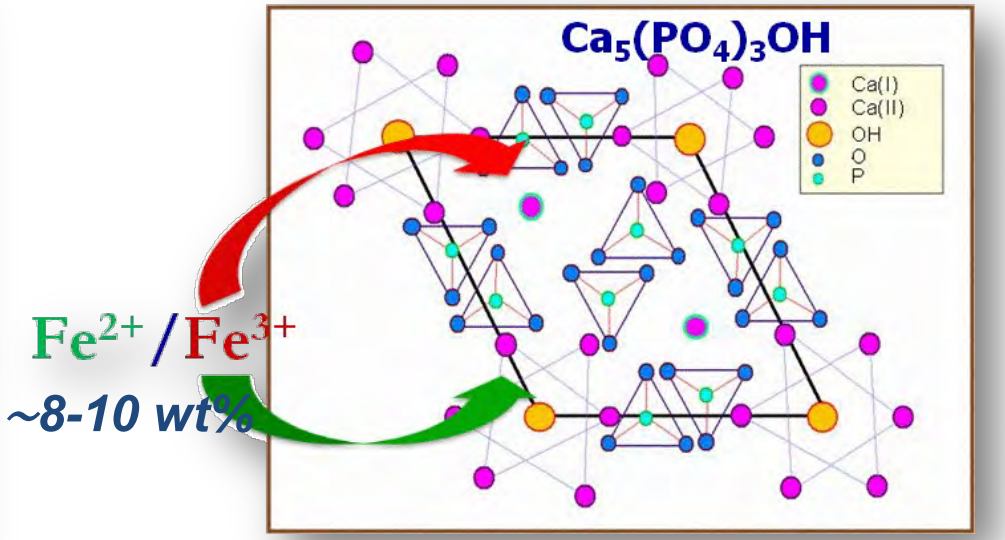
Diagnosis

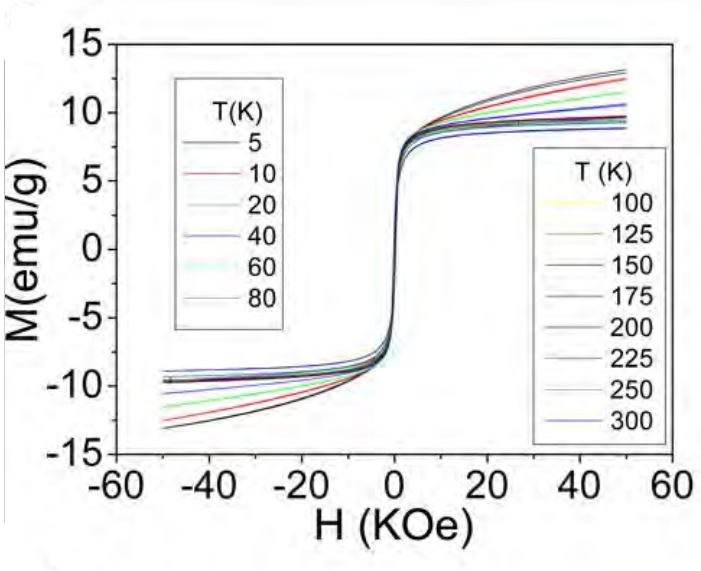


Reddy et al. *Chem. Rev.* 2012; Arruebo et al. *Nano Today* 2007; Iafisco et al. *Chem. Mater.* 2013

Superparamagnetic iron-doped hydroxyapatite (FeHA)







- Partial Ca^{2+} substitution with both iron ions, simultaneous formation of iron oxide-based secondary phase (maghemite ≈3 wt%) nucleated on the surface, obtaining a composite with unusual magnetic behavior
- Saturation magnetization 8.9 emu g^{-1} at 250 K and 10.5 emu g^{-1} at 5 K. 130 emu g^{-1} of Fe at T_{room} and 163 emu g^{-1} of Fe at 5 K

Tampieri et al. *Acta Biomater.* 2012; Panseri et al. *J. Biomed. Nanotech.* 2016; Adamiano et al. *Inorg. Chem.* 2016

Journal of
Materials Chemistry B

PAPER

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Cite this: *J. Mater. Chem. B*, 2016, 4, 57

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

Michele Iafisco,*[a] Christophe Drouet,*[b] Alessio Adamiano,[a] Patricia Pascaud,‡[b] Monica Montesi,[a] Silvia Panseri,[a] Stephanie Sarda[b] and Anna Tampieri[a]

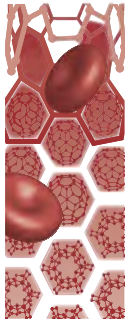
Journal of
Biomedical Nanotechnology
Vol. 12, 909–921, 2016
www.aspbs.com/jbn

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

Silvia Panseri[1,*], Monica Montesi[1], Monica Sandri[1], Michele Iafisco[1], Alessio Adamiano[1], Martina Ghetti[2], Giovanna Cenacchi[2], and Anna Tampieri[1]

Research Article

Nanomedicine

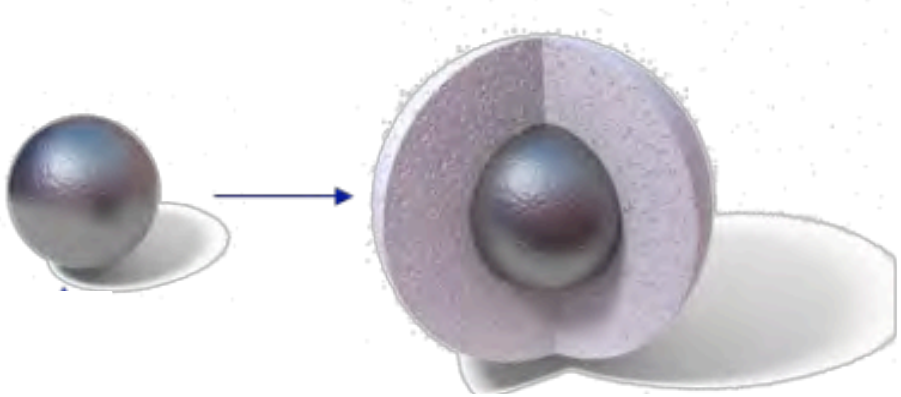


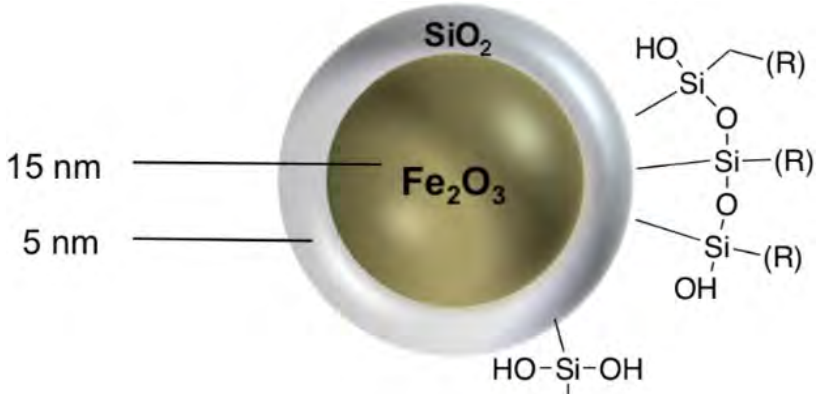
Magnetic calcium phosphates nanocomposites for the intracellular hyperthermia of cancers of bone and brain

Alessio Adamiano‡,[1], Victoria M Wu‡,[2], Francesca Carella[1], Gianrico Lamura[3], Fabio Canepa[3,4], Anna Tampieri[1], Michele Iafisco**,[1] & Vuk Uskoković*,[2,5]

MRI Contrast agents

Superparamagnetic Iron Oxide Nanoparticles (SPIONs)





…bioaccumulation of high quantity of Fe in soft tissues proved in cyrrotic liver

SCIENTIFIC REPORTS

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Iron overload by Superparamagnetic Iron Oxide Nanoparticles is a High Risk Factor in Cirrhosis by a Systems Toxicology Assessment

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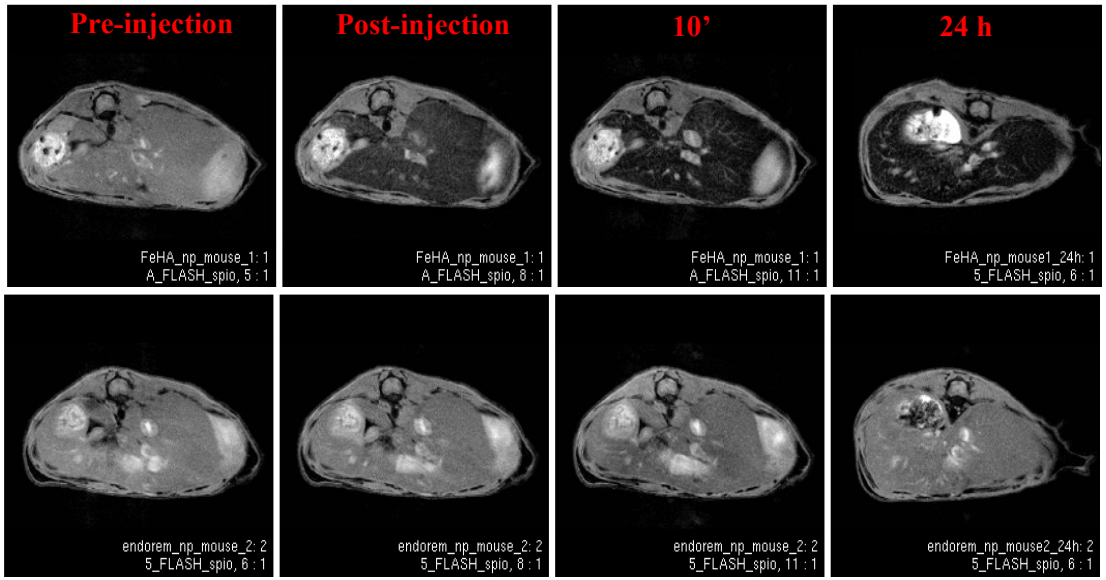
Yushuang Wei[1], Mengzhu Zhao[1], Fang Yang[1], Yang Mao[1], Hang Xie[2] & Qibing Zhou[1]

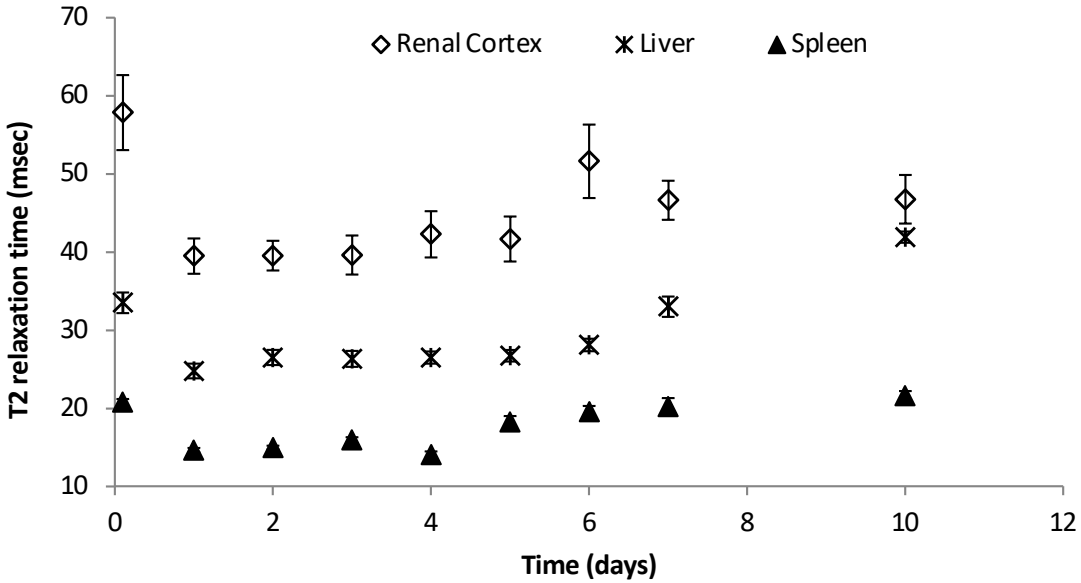
FeHA NPs as contrast agent for the liver

FeHA

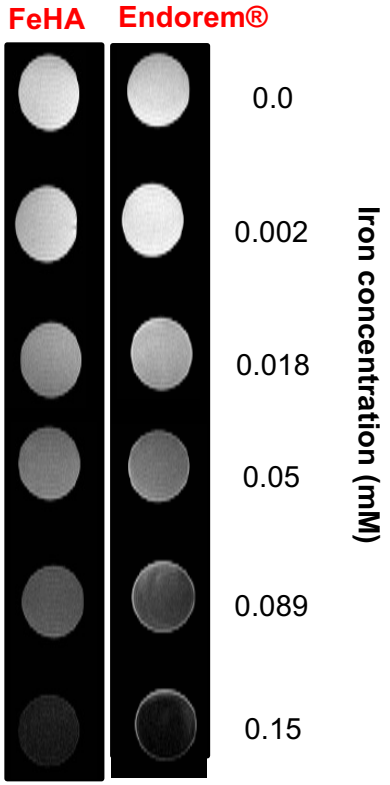
Endorem®

SPION coated dextran





T_2-weighted MRI on a 7 Tesla preclinical MR scanner

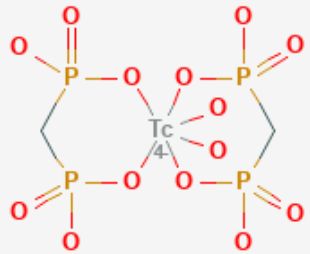


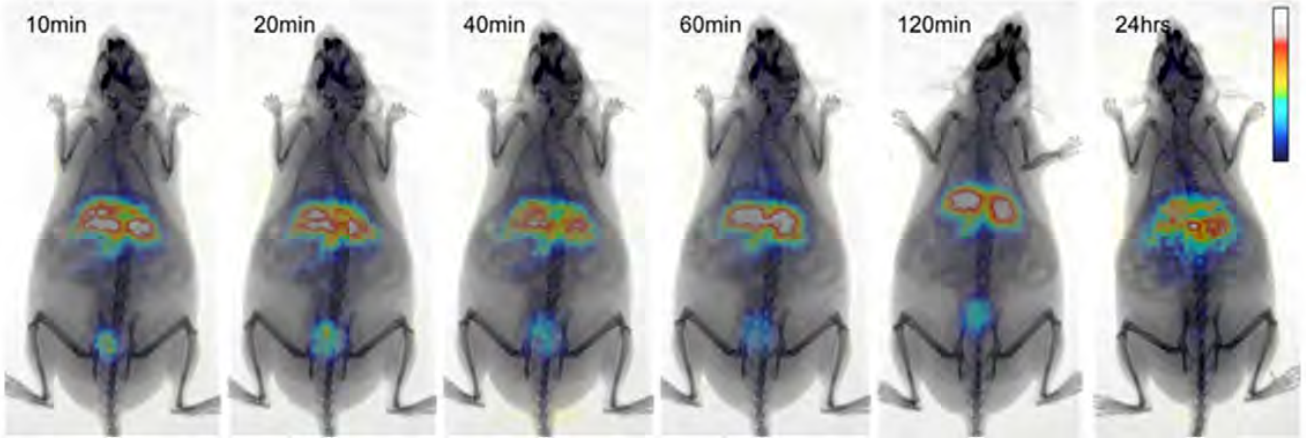
FeHA NPs are removed from filtering organs after 7 days

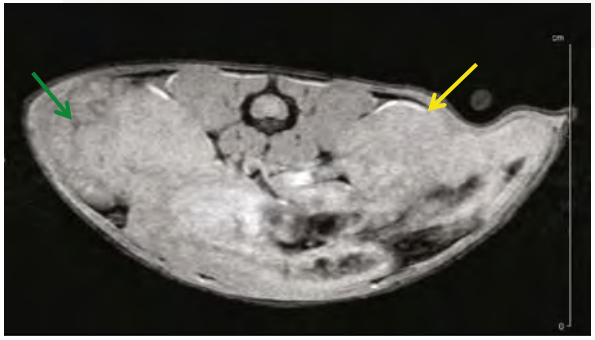
Adamiano et al. *Acta Biomater.* 2018

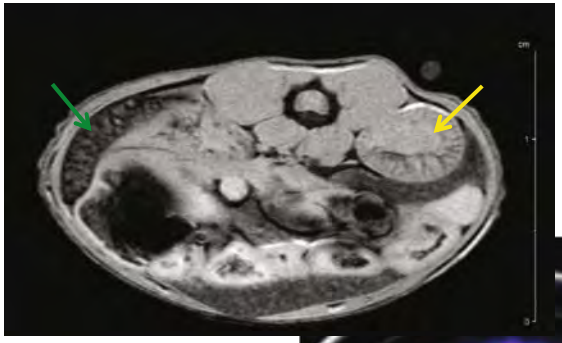
FeHA NPs as multi-modal MRI-PET/SPECT imaging agent

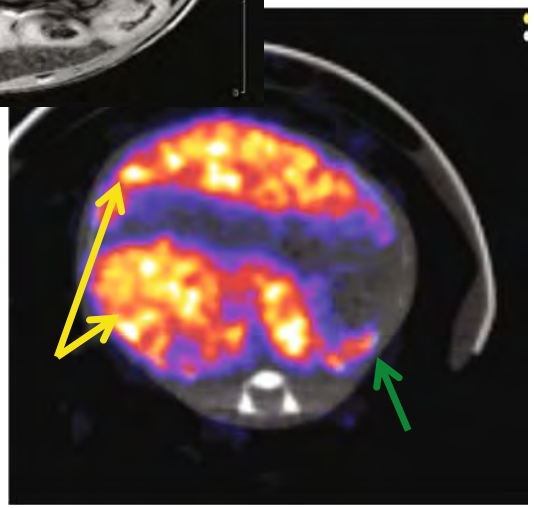
^{99M}Tc-MDP

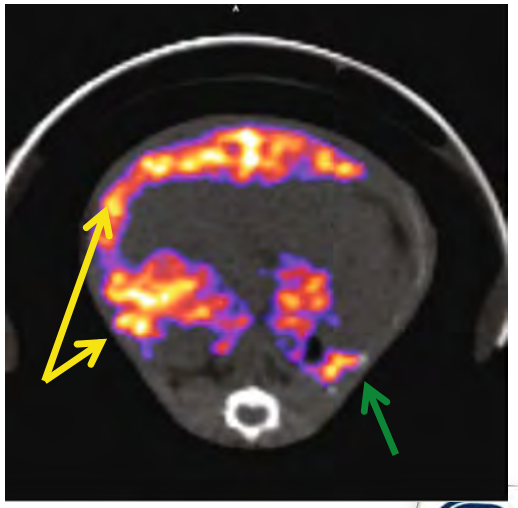












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Rouchota et al. *Molecular Imaging,* 2021

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