Nanotecnologie, magnetismo e tecniche di analisi dati in medicina

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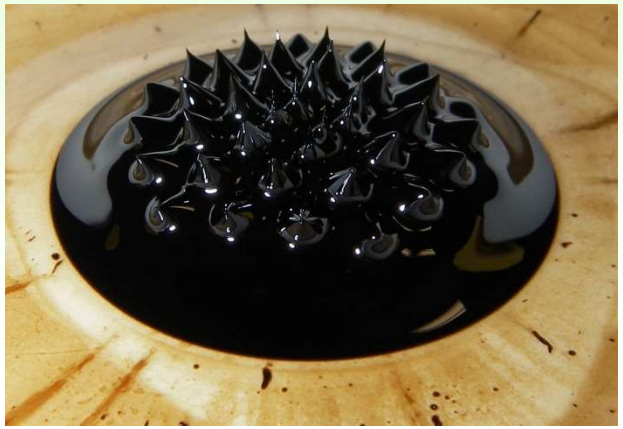
SOMMARIO

- Fisica Mesoscopica
- Nanomateriali (NM) e Nanotecnologia (NT) in biomedicina
- FB : MRI e ipertermia magnetica
- Analisi dati MRI : radiomica, diffusion-MRI, etc



Fisica Mesoscopica

«Also» intuition from R.P. Feynman (1918-1988)

WIKIPEDIA : Mesoscopic physics is a subdiscipline of **condensed matter physics** that deals with materials of **an intermediate length**. The scale of these materials can be described as being **between the nanoscale size of a quantity of atoms (such as a molecule) and of materials measuring micrometres**. ……. a mesoscopic object……. and its electronic behavior may require modeling at the level of **quantum mechanics**……

There is **no rigid definition for *mesoscopic physics*** but the systems studied are normally in the range of 100 nm (the size of a typical virus) to 1 000 nm (the size of a typical bacterium) ……. has a close connection to the fields of nanofabrication and nanotechnology.

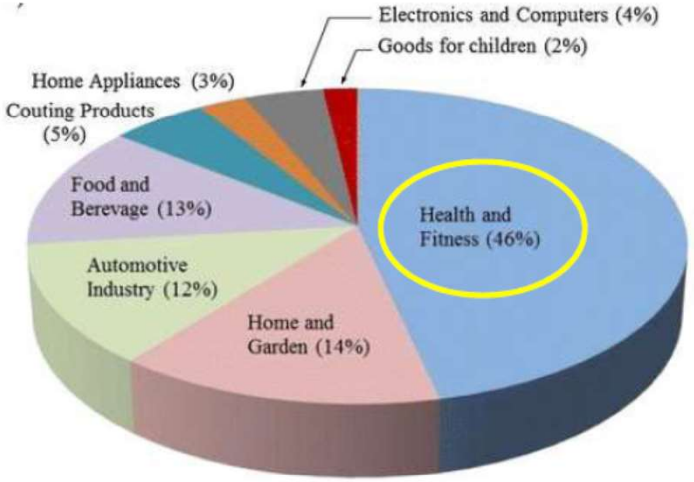
Nanotecnologie.. Come nascono?

"I don't know how to do this on a small scale in a practical way, but I do know that computing machines are very large; they fill rooms. Why can't we make them very small, make them of little wires, little elements, and by little, I mean little?"...

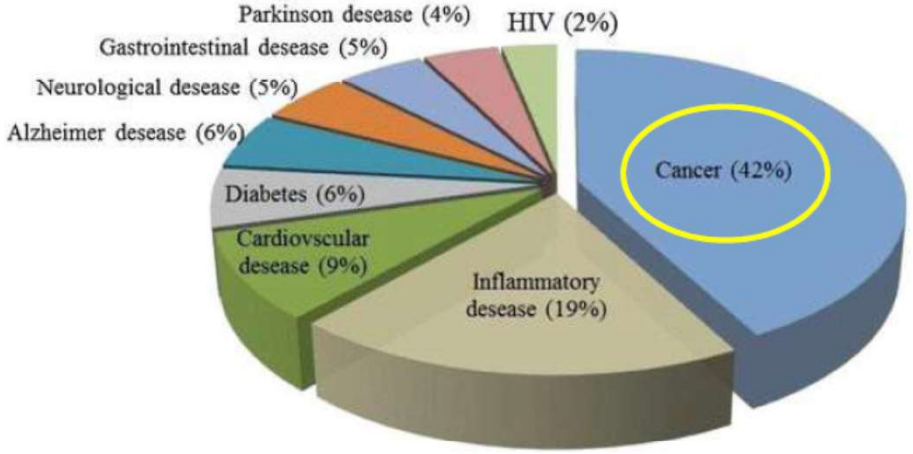
.. A friend of mine (Albert R. Hibbs) suggests a very interesting possibility for relatively small machines. He says that, although it is a very wild idea, it would be interesting in surgery if you could swallow the surgeon. You put the mechanical surgeon inside the blood vessel and it goes into the heart and ``looks'' around. It finds out which valve is the faulty one and takes a little knife and slices it out. Other small machines might be permanently incorporated in the body to assist some inadequately-functioning organ.

- Richard Feynman, "There's Plenty of Room at the Bottom" (1959)

Nanomateriali e Nanotecnologia



PERCENTUALE DI VARI
PRODOTTI DI CONSUMO
CONTENENTI NANOMATERIALI



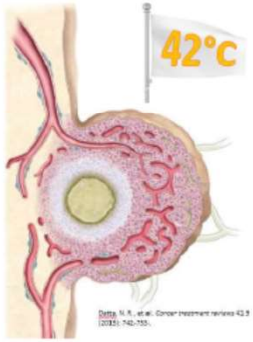
PERCENTUALE DI **ARTICOLI PUBBLICATI** SU RIVISTE SCIENTIFICHE RIGUARDANTI L'APPLICAZIONE DI NANOPARTICELLE IN VARIE MALATTIE

sulla base dei dati ottenuti dall'inventario dei prodotti di consumo [http://www.nanotechproject.org/] e Scopus (consultato il 17 giugno 2014).

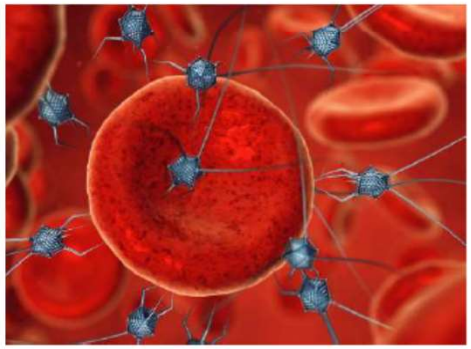
Applicazioni della nanotecnologia medica

RILASCIO DI FARMACI

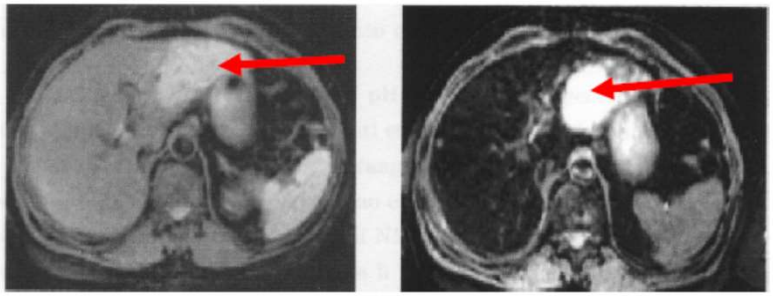
TERAPIA



CHIRURGIA



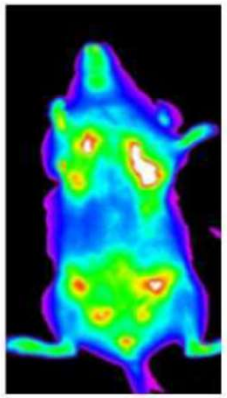
DIAGNOSTICA

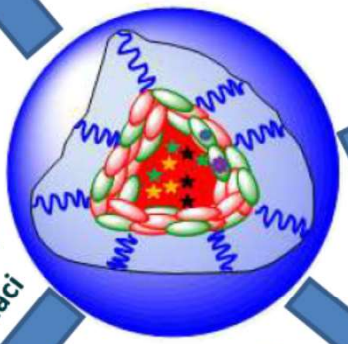


Applicazioni

Terapia fotodinamica (PDT)
Terapia fototermica

Imaging a fluorescenza nel vicino infrarosso





Farmaci

Chemio-PDT

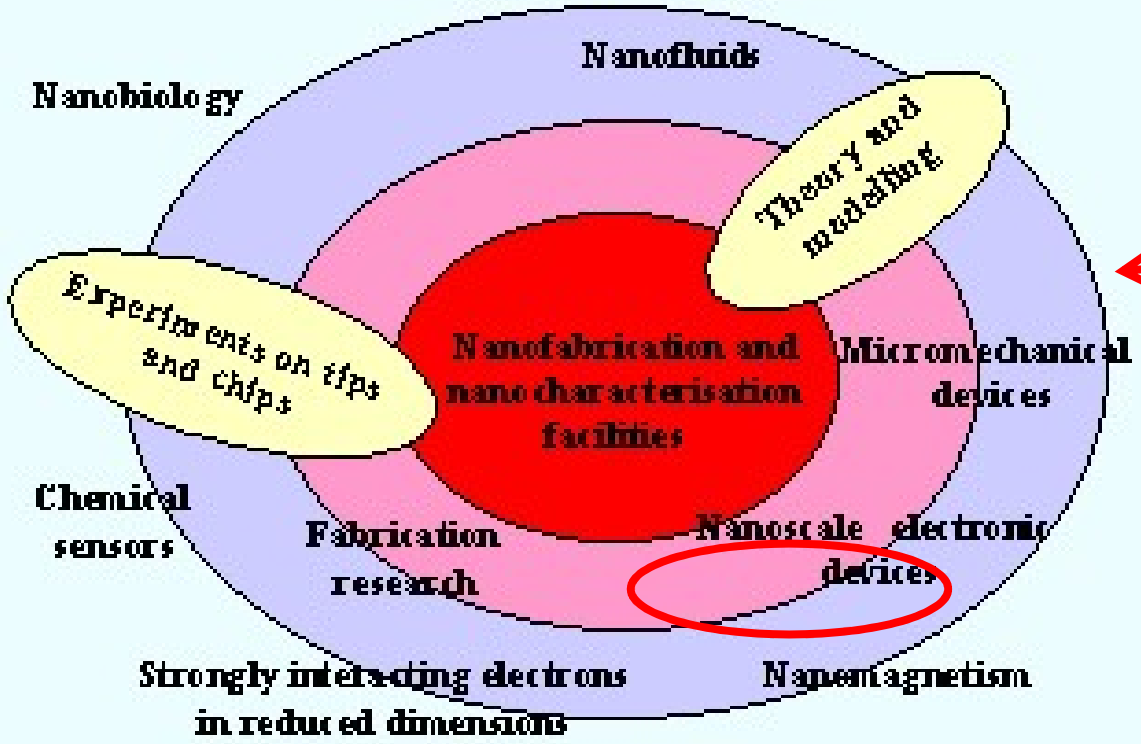
^{64}Cu

Tomografia a emissione di positroni (PET)

Gd(III)

Imaging a risonanza magnetica (MRI)

Nanoparticelle : interdisciplinarità e interesse nel mondo



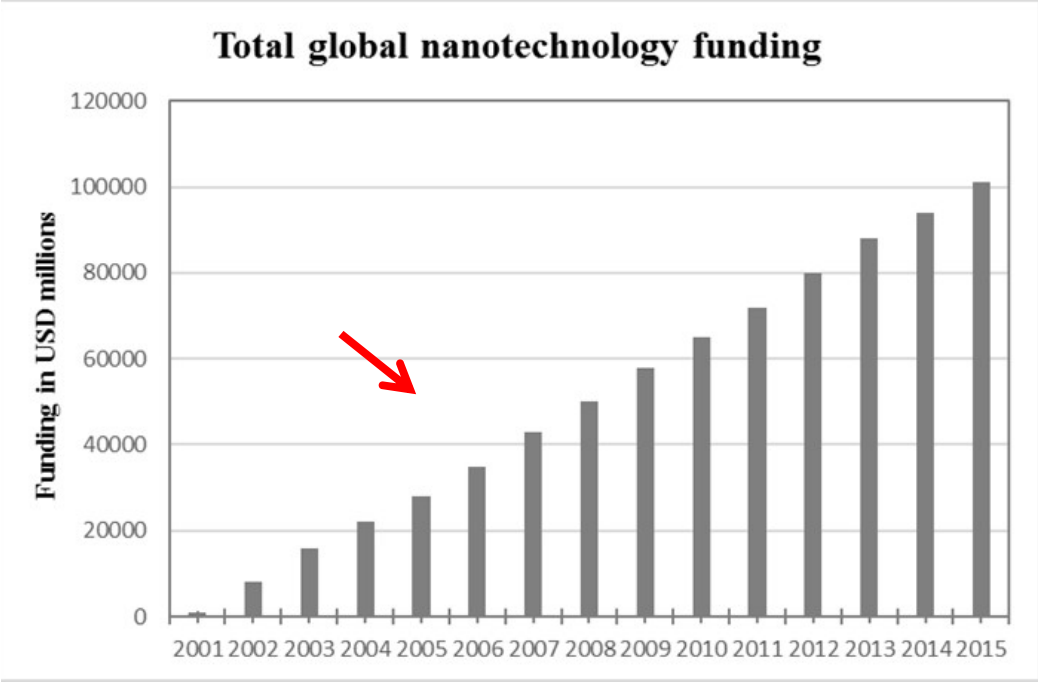
UCL Nanotechnology Center (London, UK)

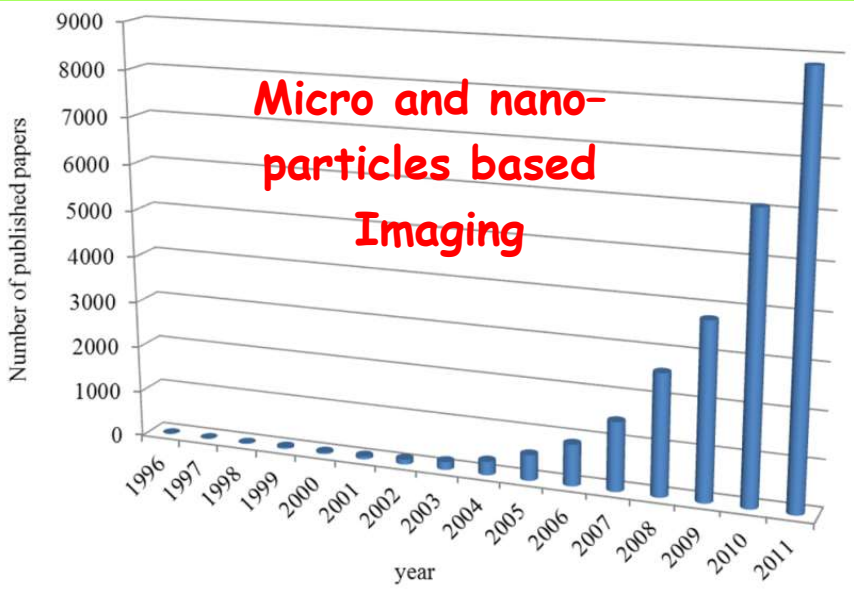
6th Global Experts Meeting & Expo on Nanomaterials and Nanotechnology, "Advances in Nanomaterials & Nanotechnology", April 21-23, 2016 Dubai, UAE

Track 4: Advances in Nanomedicine

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

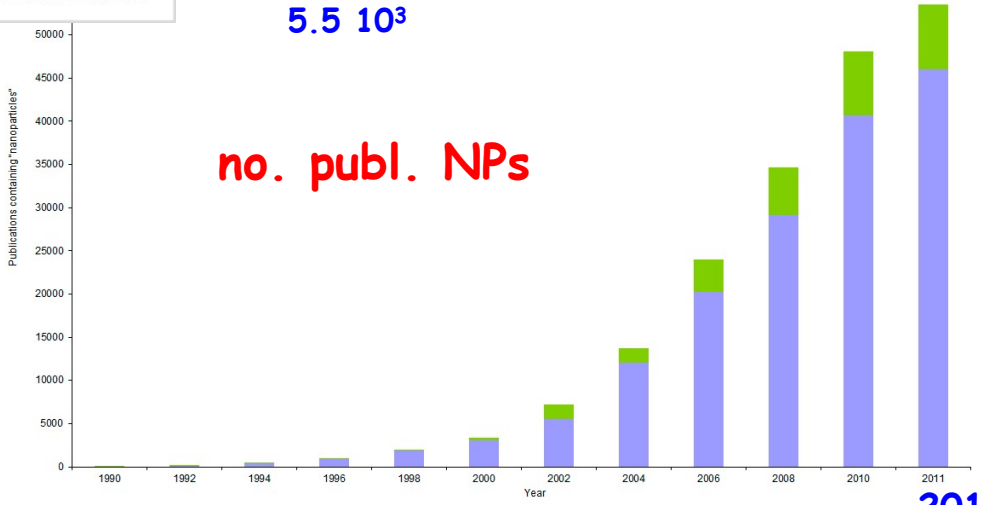
Statistiche di pubblicazioni e fondi relativi a nanomateriali e nanotecnologia





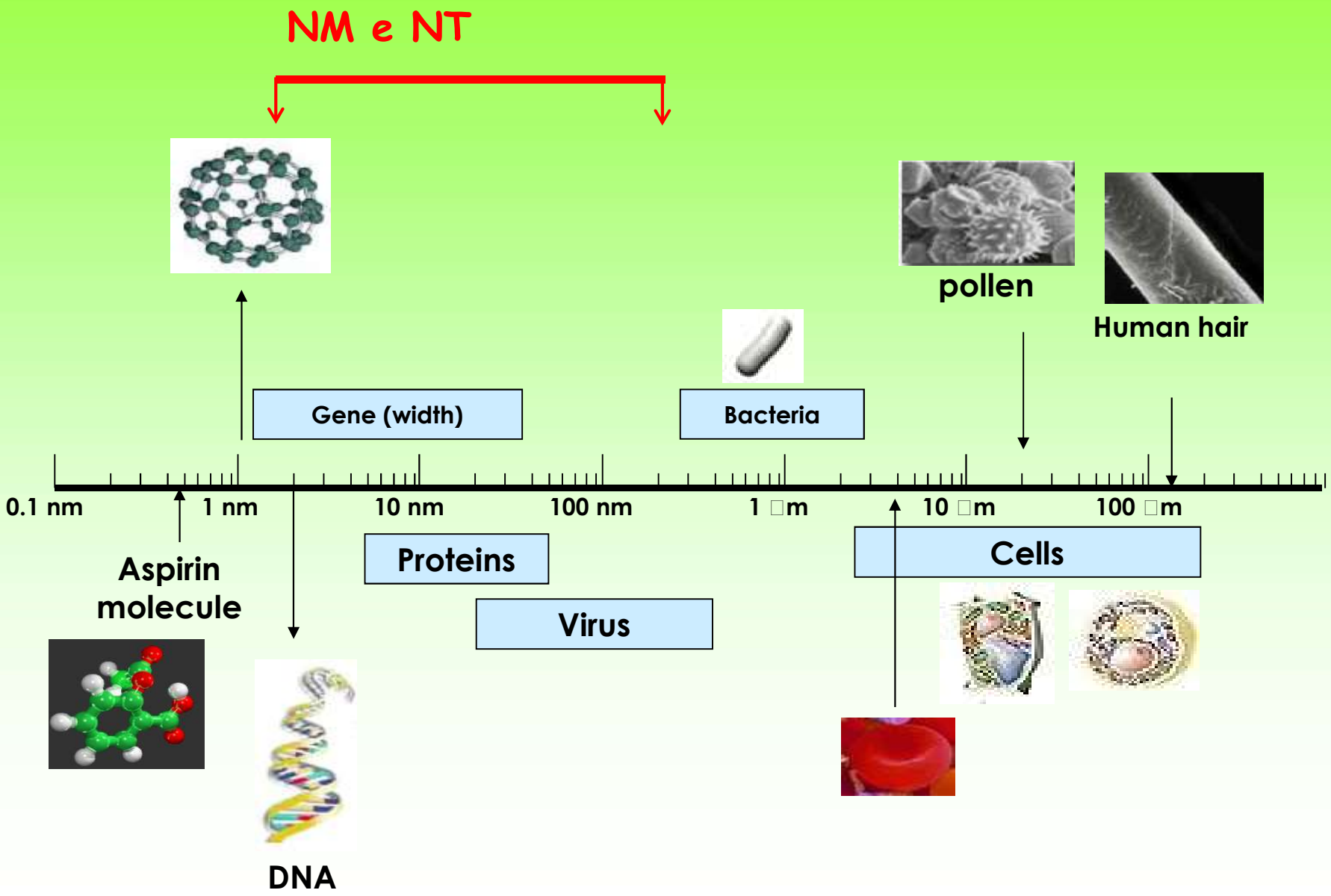
5.5 10^3

no. publ. NPs



2011

Perchè nanomateriali e nanotech in biomedicina



Alcuni esempi «non» magnetici

Prodotti commerciali (clinici) . I

International Journal of Nanomedicine

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REVIEW

Nanopharmaceuticals (part 1): products on the market

Volkmar Weissig[1]
Tracy K Pettinger[2]
Nicole Murdock[3]

Table 1 Approved drugs commonly referred to as "nanopharmaceuticals"

Name	Description	Mechanism of action	Approval/indication
1) Liposomes			
AmBisome®	Amphotericin B encapsulated in liposomes (60–70 nm) composed of hydrogenated soy phosphatidylcholine, cholesterol, and distearoyl phosphatidylglycerol (2/0.8/1 molar)[13]	MPS targeting: Liposomes preferentially accumulate in organs of the MPS. Negative charge contributes to MPS targeting. Selective transfer of the drug from lipid complex to target fungal cell with minimal uptake into human cells has been postulated[14,17]	FDA 1997 Systemic fungal infections (IV)
DaunoXome®	Daunorubicin citrate encapsulated in liposomes (45 nm) composed of distearoyl phosphatidylcholine and cholesterol (2/1 molar)[18,19]	Passive targeting via EPR effect: Concentration of available liposomal drug in tumors exceeds that of free drug. Liposomal daunorubicin persists at high levels for several days[20]	FDA 1996 HIV-related KS (IV)
DepoCyt®	Cytarabine encapsulated in multivesicular liposomes (20 µm; classified as nanopharmaceutical based on its individual drug containing "chambers") made from dioleoyl lecithin, dipalmitoyl phosphatidylglycerol, cholesterol, and triolein[21]	Sustained release: This formulation of cytarabine maintains cytotoxic concentrations of the drug in the cerebrospinal fluid for more than 14 days after a single 50 mg injection[22]	FDA 1999/2007 Lymphomatous malignant meningitis (IV)
DepoDur®	Morphine sulfate encapsulated in multivesicular liposomes (17–23 µm; per se not a nanopharmaceutical – classified as such based only on its individual drug containing "nano-sized chambers") made from dioleoyl lecithin cholesterol, dipalmitoyl phosphatidylglycerol, tricaprylin, and triolein	Sustained release: After the administration into the epidural space, morphine sulfate is released from the multivesicular liposomes over an extended period of time[23,24]	FDA 2004 For treatment of chronic pain in patients requiring a long-term daily around-the-clock opioid analgesic (administered into the epidural space)
Doxil®	Doxorubicin hydrochloride encapsulated in Stealth® liposomes (100 nm) composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero3-phosphoethanolamine sodium, fully hydrogenated soy phosphatidylcholine, and cholesterol[9]	Passive targeting via EPR effect: Extravasation of liposomes by passage of the vesicles through endothelial cell gaps present in solid tumors. Enhanced accumulation of doxorubicin in lesions of AIDS-associated KS after administration of PEG-liposomal doxorubicin[25]	FDA 1995 AIDS-related KS, multiple myeloma, ovarian cancer (IV)
Inflexal® V	Influenza virus antigens (hemagglutinin, neuraminidase) on surface of 150 nm liposomes	Mimicking native antigen presentation: Liposomes mimic the native virus structure, thus allowing for cellular entry and membrane fusion.[26] Retention of the natural presentation of antigens on liposomal surface provides for high immunogenicity[27,28]	Switzerland 1997 Influenza vaccine
Marqibo®	Vincristine sulfate encapsulated in sphingomyelin/cholesterol (60/40, molar) 100 nm liposomes	Passive targeting via EPR effect: Extravasation of liposomes through fenestra in bone marrow endothelium	FDA 2012 Acute lymphoid leukemia, Philadelphia chromosome-negative, relapsed or progressed (IV)
Mepact™	Mifamurtide (synthetic muramyl tripeptide-phosphatidylethanolamine) incorporated into large multilamellar liposomes composed of 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine and 1,2-dioleoyl-sn-glycero-3-phospho-L-serine[29]	MPS targeting: The drug, an immune stimulant, is anchored in negatively charged liposomal bilayer membrane	Europe 2009 Non-metastasizing resectable osteosarcoma (IV)
Myocet®	Doxorubicin encapsulated 180 nm oligolamellar liposomes composed of egg phosphatidylcholine/cholesterol (1/1, molar)	MPS targeting: Forms "MPS depot", slow release into blood circulation resembles prolonged infusion[30]	Europe 2000 Metastatic breast cancer (IV)
Visudyne®	Verteporfin in liposomes made of dimyristoyl-phosphatidylcholine and egg phosphatidylglycerol (negatively charged); lyophilized cake for reconstitution	Drug solubilization: Rendering drug biocompatible and enhancing ease of IV administration. No other apparent function of liposomes. Liposomal formulation instable in the presence of serum. Fast transfer of verteporfin from Visudyne® to lipoproteins[31]	FDA 2000 Photodynamic therapy of wet age-related macular degeneration, pathological myopia, ocular histoplasmosis syndrome (IV)

(Continued)

Table 1 (Continued)

Name	Description	Mechanism of action	Approval/indication
2) Lipid-based (non-liposomal) formulations			
Abelcet®	Amphotericin B complex 1:1 with DMPC and DMPG (7:3), >250 nm, ribbon like structures of a bilayered membrane[15]	MPS targeting: Selective transfer of drug from lipid complex to fungal cell with minimal uptake into human cells has been postulated[21,22]	FDA 1995 and 1996 Marketed outside USA as Amphocil® Systemic fungal infections (IV)
Amphotec®	Amphotericin B complex with cholesteryl sulfate (1:1). Colloidal dispersion of disc-like particles, 122 nm ×4 nm[13]	MPS targeting	
3) PEGylated proteins, polypeptides, aptamers			
Adagen®	PEGylated adenosine deaminase[24] One enzyme molecule is modified with up to 17 strands of PEG, MW 5,000, 114 oxymethylene groups per strand	Increased circulation time and reduced immunogenicity PEGylation generally increases hydrodynamic radius, prolongs circulation and retention time, decreases proteolysis, decreases renal excretion, and shields antigenic determinants from immune detection without obstructing the substrate-interaction site[23,24]	FDA 1990 Adenosine deaminase deficiency – severe combined immunodeficiency disease
Cimzia®	PEGylated antibody (Fab' fragment of a humanized anti-TNF-alpha antibody)		FDA 2008 Crohn's disease, rheumatoid arthritis
Neulasta®	PEGylated filgrastim (granulocyte colony-stimulating factor)		FDA 2002 Febrile neutropenia, In patients with nonmyeloid malignancies; prophylaxis (SC)
Oncaspar®	PEGylated L-asparaginase		FDA 1994 Acute lymphoblastic leukemia
Pegasys®	PEGylated interferon alfa-2b		FDA 2002 Hepatitis B and C
PegIntron®	PEGylated interferon alfa-2b		FDA 2001 Hepatitis C
Somavert®	PEGylated human growth hormone receptor antagonist		FDA 2003 Acromegaly, second-line therapy
Macugen®	PEGylated anti-VEGF aptamer		FDA 2004 Intravitreal Neovascular age-related macular degeneration
Mircera®	PEGylated epoetin beta (erythropoietin receptor activator)		FDA 2007 Anemia associated with chronic renal failure in adults
4) Nanocrystals			
Emend®	Aprepitant as nanocrystal	Increased bioavailability due to increased dissolution rate: Below 1,000 nm, the saturation solubility becomes a function of the particle size leading to an increased saturation solubility of nanocrystals, which in turn increases the concentration gradient between gut lumen and blood, and consequently the absorption by passive diffusion[27]	FDA 2003 Emesis, antiemetic (oral)
Megace ES®	Megestrol acetate as nanocrystal		FDA 2005 Anorexia, cachexia (oral)
Rapamune®	Rapamycin (sirolimus) as nanocrystals formulated in tablets		FDA 2002 Immunosuppressant (oral)
Tricor®	Fenofibrate as nanocrystals		FDA 2004 Hypercholesterolemia, hypertriglyceridemia (oral)
Triglide®	Fenofibrate as insoluble drug-delivery microparticles		
5) Polymer-based nanoformulations			
Copaxone®	Polypeptide (average MW 6.4 kDa) composed of four amino acids (glatiramer)	No mechanism attributable to nanosize. Based on its resemblance to myelin basic protein, glatiramer is thought to divert as a "decoy" an autoimmune response against myelin	FDA 1996/2014 Multiple sclerosis (SC)
Eligard®	Leuprolide acetate (synthetic GnRH or LH-RH analog) incorporated in nanoparticles composed of PLGH copolymer (DL-lactide/glycolide; 1/1, molar)	Sustained release[28]	FDA 2002 Advanced prostate cancer (SC)
Genexol®	Paclitaxel in 20–50 nm micelles[29] composed of block copolymer poly(ethylene glycol)-poly(D,L-lactide)	Passive targeting via EPR effect	South Korea 2001 Metastatic breast cancer, pancreatic cancer (IV)

(Continued)

Prodotti commerciali (clinici) . II

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REVIEW

Nanopharmaceuticals (part 1): products on the market

Volkmar Weissig[1]
Tracy K Pettinger[2]
Nicole Murdock[3]

Table 1 *(Continued)*

Name	Description	Mechanism of action	Approval/indication
Opaxio®	Paclitaxel covalently linked to solid nanoparticles composed of polyglutamate	Passive targeting via EPR effect: Drug release inside solid tumor via enzymatic hydrolysis of polyglutamate	FDA 2012 Glioblastoma
Renagel®	Cross-linked poly allylamine hydrochloride,[45] MW variable	No mechanism attributable to nano size. Phosphate binder	FDA 2000 Hyperphosphatemia (oral)
Zinostatin stimalamer®	Conjugate protein or copolymer of styrene-maleic acid and an antitumor protein NCS.[41] Synthesized by conjugation of one molecule of NCS and two molecules of poly(styrene-co-maleic acid)[42]	Passive targeting via EPR effect[43]	Japan 1994 Primary unresectable hepatocellular carcinoma
6) Protein–drug conjugates			
Abraxane®	Nanoparticles (130 nm) formed by albumin with conjugated paclitaxel[44,45]	Passive targeting via EPR effect: Dissociation into individual drug-bound albumin molecules, which may mediate endothelial transcytosis of paclitaxel via albumin-receptor mediated pathway[46,47]	FDA 2005 Metastatic breast cancer, non-small-cell lung cancer (IV)
Kadcyla®	Immunoconjugate. Monoclonal antibody (against human epidermal growth factor receptor-2)–drug (DM1, a cytotoxin acting on microtubule) conjugate, linked via thioether	No mechanism attributable to nano size	FDA 2013 Metastatic breast cancer
Ontak®	Recombinant fusion protein of fragment A of diphtheria toxin and subunit binding to interleukin-2 receptor	Fusion protein binds to interleukin-2 receptor, followed by receptor-mediated endocytosis; fragment A of diphtheria toxin then released into cytosol where it inhibits protein synthesis[48]	FDA 1994/2006 Primary cutaneous T-cell lymphoma, CD25-positive, persistent or recurrent disease
7) Surfactant-based nanoformulations			
Fungizone® (also referred to as "conventional AMB")	Lyophilized powder of amphotericin B with added sodium deoxycholate. Forms upon reconstitution colloidal (micellar) dispersion	Drug solubilization: Rendering drug biocompatible and enhancing ease of administration after IV injection No other apparent function of micelles, which dissociate into monomers following dilution in circulation	FDA 1966 Systemic fungal infections (IV)
Diprivan®	Oil-in-water emulsion of propofol in soybean oil/glycerol/egg lecithin	Drug solubilization: Rendering drug biocompatible and enhancing ease of administration after IV injection	FDA 1989 Sedative–hypnotic agent for induction and maintenance of anesthesia (IV)
Estrasorb™	Emulsion of estradiol in soybean oil, polysorbate 80, ethanol, and water	Drug solubilization	FDA 2003 Hormone replacement therapy during menopause (transdermal)
8) Metal-based nanoformulations			
Feridex®	Superparamagnetic iron oxide nanoparticles coated with dextran. Iron oxide core 4.8–5.6 nm, hydrodynamic diameter 80–150 nm	MPS targeting: 80% taken up by liver and up to 10% by spleen within minutes of administration. Tumor tissues do not take up these particles and thus retain their native signal intensity[24]	FDA 1996 Liver/spleen lesion MRI (IV) Manufacturing discontinued in 2008
Feraheme™ (Ferumoxytol)	Superparamagnetic iron oxide nanoparticles coated with dextran. Hydrodynamic diameter >50 nm	MPS targeting: Iron released inside macrophages, subsequently enters into intracellular storage iron pool, or is transferred to plasma transferrin	FDA 2009 Treatment of iron deficiency anemia in adults with chronic kidney disease
NanoTherm®	Aminosilane-coated superparamagnetic iron oxide 15 nm nanoparticles	Thermal ablation: Injecting iron oxide nanoparticles exposed to alternating magnetic field causing the nanoparticles to oscillate, generating heat directly within the tumor tissue	Europe 2013 Local ablation in glioblastoma, prostate, and pancreatic cancer (intratumoral)

(Continued)

Table 1 *(Continued)*

Name	Description	Mechanism of action	Approval/indication
9) Virosomes			
Gendicine®	Recombinant adenovirus expressing wildtype-p53 (rAd-p53)	"[…] the adenoviral particle infects tumor target cells and delivers the adenovirus genome carrying the therapeutic p53 gene to the […] nucleus […] The expressed p53 gene appears to exert its antitumor activities"[49]	People's Republic of China 2003 Head and neck squamous cell carcinoma
Rexin-G®	Gene for dominant-negative mutant form of human cycline G1, which blocks endogenous cyclin-G1 protein and thus stops cell cycle, inserted into retroviral core (replication-incompetent retrovirus) devoid of viral genes. About 100 nm particle	Targeted gene therapy: This retrovirus-derived particle targets specifically exposed collagen, which is a common histopathological property of metastatic tumor formation[50,51]	Philippines 2007 For all solid tumors

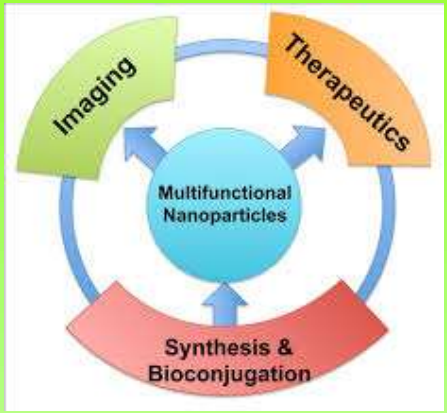
Abbreviations: DMPC, dimyristoylphosphatidylcholine; DMPG, dimyristoyl phosphatidylglycerol; EPR, enhanced permeability and retention; FDA, US Food and Drug Administration; GnRH, Gonadotropin-releasing hormone; IV, intravenous; KS, Kaposi's sarcoma; LH-RH, Luteinizing hormone-releasing hormone; MPS, Mononuclear phagocyte system; MRI, magnetic resonance imaging; MW, molecular weight; NCS, neocarzinostatin; PEG, polyethylene glycol; PLGH, poly-(D,L-lactide-co-glycolide); SC, subcutaneous.

Un primo (?) esempio di farmaco nano- antitumorale : ABRAXANE

ABRAXANE (protein-bound Paclitaxel) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.
It uses the albumin (responsible of mcarrying nutrients to tumour cells) -activated gp60-receptors pathway (it activates caveolin).
Paclitaxel is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug. Paclitaxel is classified as a "plant alkaloid," a "taxane" and an "antimicrotubule agent."

Video youtube sul funzionamento di ABRAXANE :
https://www.youtube.com/watch?v=BsLLZxXLSfA

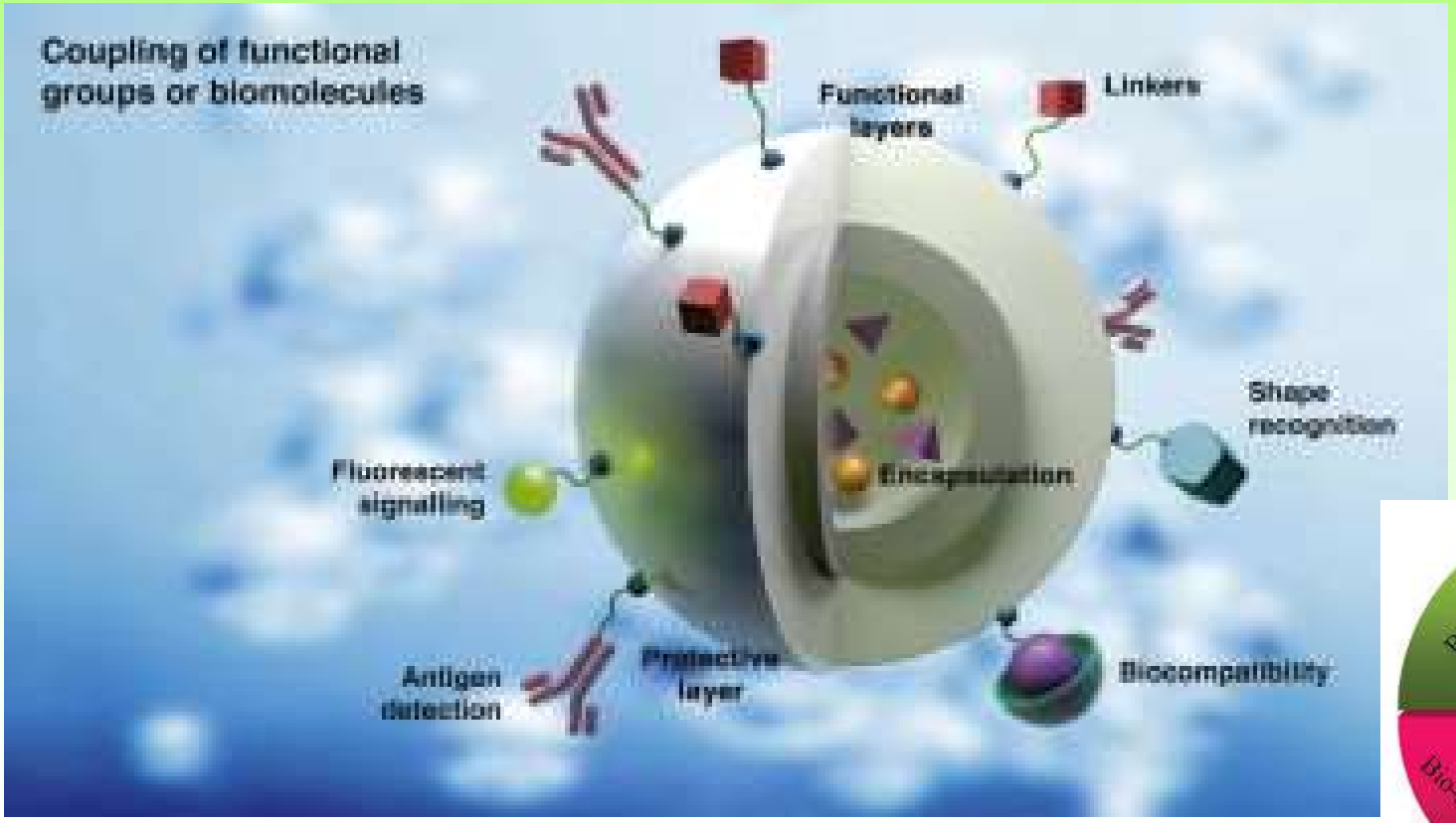
M. Ferrari (Houston) and co-workers



Scopo finale delle ricerche attuali: NM multifunzionali

e.g. Imaging multimodale, «Teranostica», etc

(teranostica = terapia + diagnostica)



Esempi di

nanotecnologie/nanomateriali

Nanoparticelle di Au come «Radiation therapy enhancers» in-vitro e in-vivo

(radiosensibilizzazione con NP ad alto-Z)

Interazione radiazione-NP

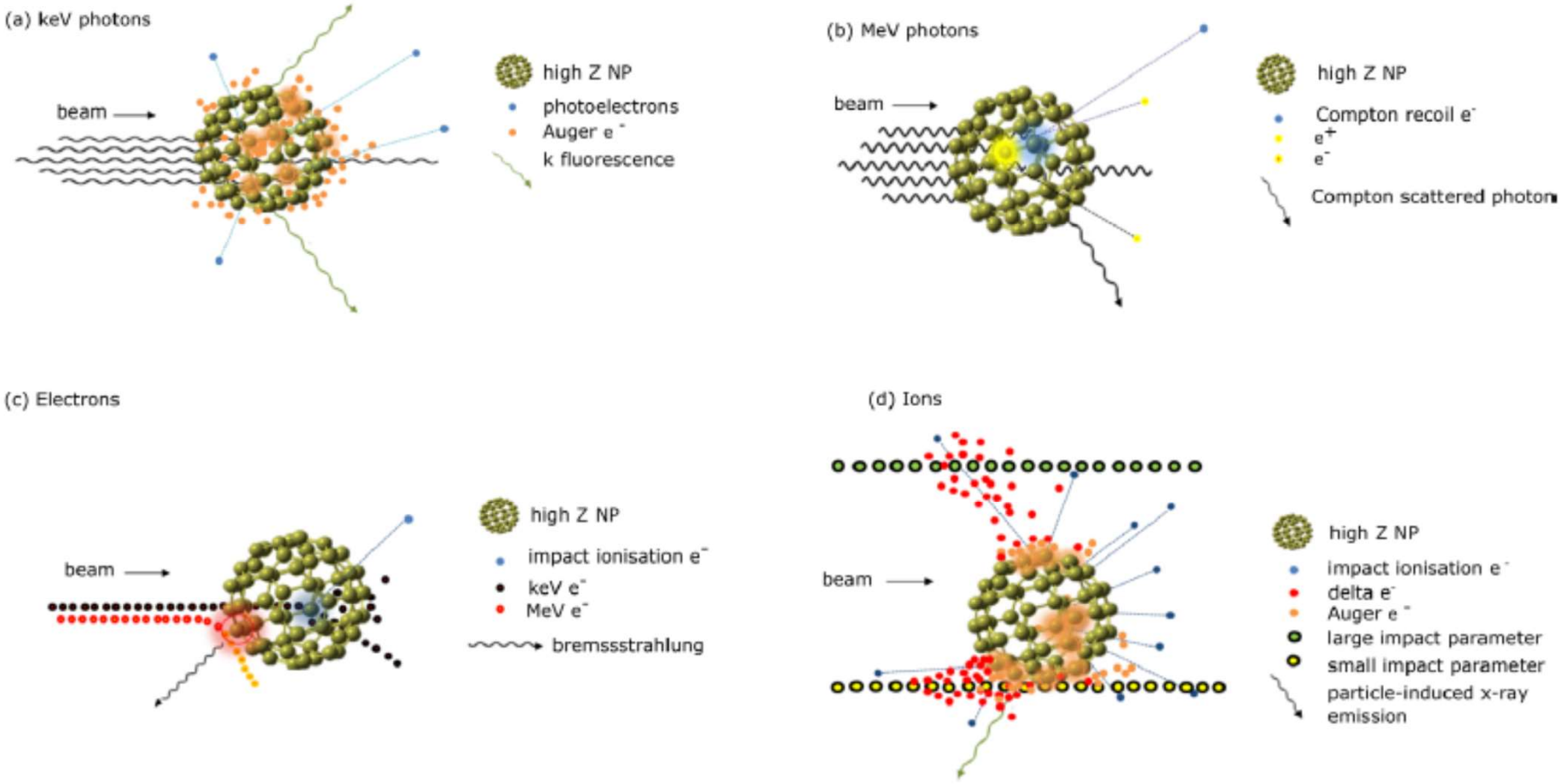


Figure 1. Schematic illustration of inelastic interactions with a high-*Z* nanoparticle for: (a) incident keV photons (orange clouds represent photoelectric events); (b) incident MeV photons (blue and yellow clouds represent Compton scatter and pair production events, respectively); (c) incident electrons (blue and red clouds represent large and small impact parameters leading to ionisation and bremsstrahlung, respectively); and (d) inicident ions (orange clouds indicate impact ionisation events). Image provided by Gholami, University of Sydney. Reproduced with permission from Y Gholami.

Sopravvivenza cellulare (radiobiologia)

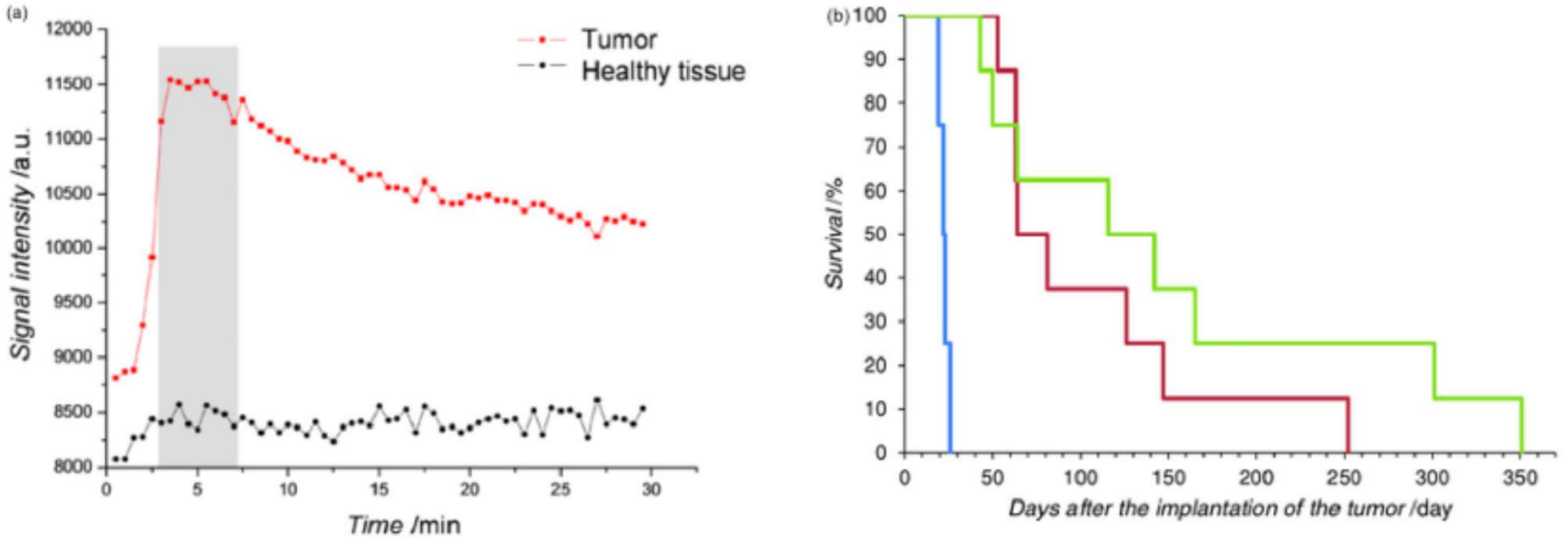


Figure 4. (a) Temporal profile of the the MRI signal intensity in tumour and in healthy tissue in the brain of a 9LGS-bearing rat after IV injection of Gd-chelated AuNPs, with the grey area showing maximal signal contrast; (b) survival curves of 9LGS-bearing rats following treatment with microbeam radiation therapy (MRT) 5 min after IV injection of Gd-chelated AuNPs (green curve, $n = 8$) and treatment with MRT only (red curve, $n = 8$), compared to no treatment (blue curve, $n = 4$). Reprinted with permission from Miladi *et al* (2014). Copyright 2014 John Wiley and Sons, Inc. all rights reserved.

NP di *Ag* per effetti antimicrobici

Tossicità in-vivo di NP di *Ag* utili Per effetti antimicrobici

Recordati et al. Particle and Fibre Toxicology (2016) 13:12
DOI 10.1186/s12989-016-0124-x

Particle and Fibre Toxicology

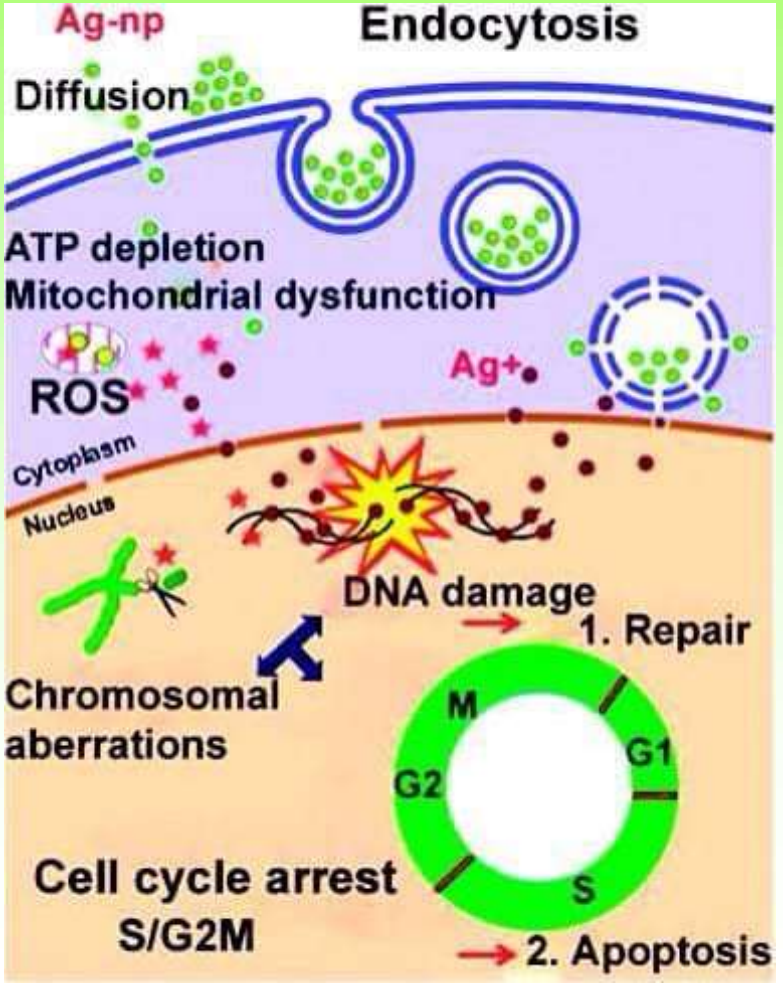
RESEARCH Open Access

Tissue distribution and acute toxicity of silver after single intravenous administration in mice: nano-specific and size-dependent effects

Camilla Recordati[1*†], Marcella De Maglie[1,2†], Silvia Bianchessi[1], Simona Argentiere[1], Claudia Cella[1,3], Silvana Mattiello[2], Francesco Cubadda[4], Federica Aureli[4], Marilena D'Amato[4], Andrea Raggi[4], Cristina Lenardi[1,3,5], Paolo Milani[1,3,5] and Eugenio Scanziani[1,2]

- Background: **Silver nanoparticles (AgNPs)** are an important class of nanomaterials used as **antimicrobial agents** for a wide range of medical and industrial applications.

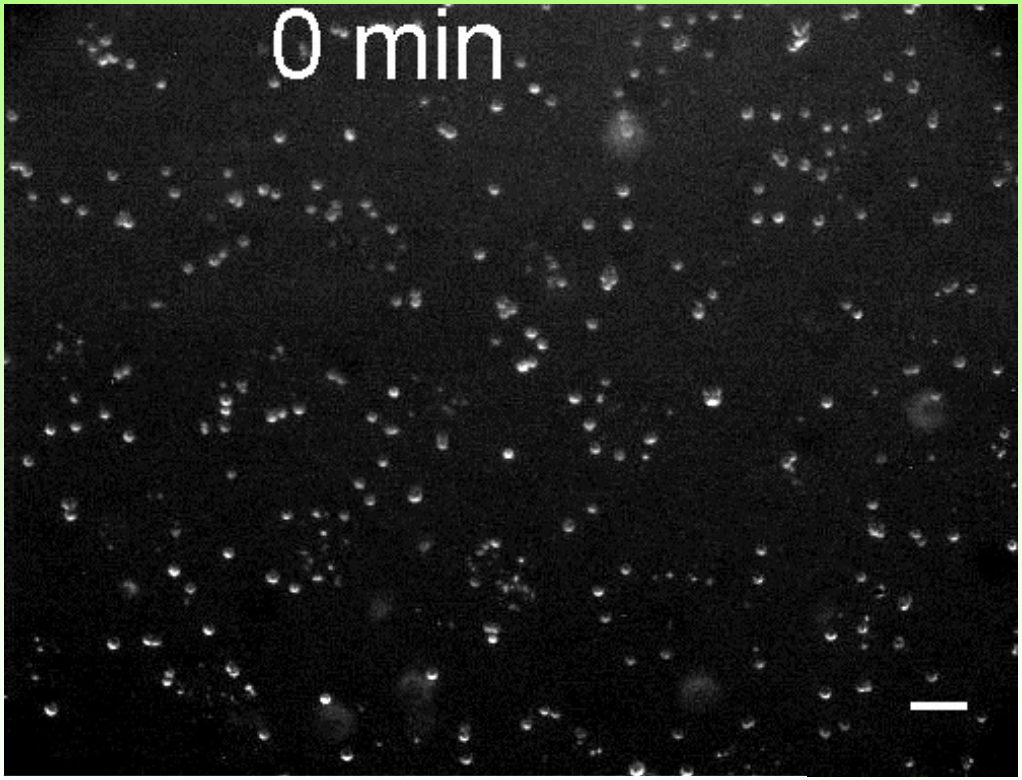
- Toxicity of AgNPs and impact of their physicochemical characteristics in vivo need to be comprehensively characterized.



Ingegneria tissutale

Sistema nervoso centrale (CNS) : nano-ingegneria tissutale

Crescita confinata di cellule neurali su isole di zirconia nano-strutturate, per facilitare la formazione di un network neurale



NEURONAL CELLS CONFINEMENT BY MICROPATTERNED CLUSTER-ASSEMBLED DOTS WITH MECHANOTRANSDUCTIVE NANOTOPOGRAPHY

Carsten Schulte[1,*,#], Jacopo Lamanna[2,*,#], Andrea Stefano Moro[2], Claudio Piazzoni[1], Francesca Borghi[1], Matteo Chighizola[1], Serena Ortoleva[1], Gabriella Racchetti[2], Cristina Lenardi[1], Alessandro Podestà[1], Antonio Malgaroli[2*], Paolo Milani[1*]

Courtesy by C. Lenardi et al

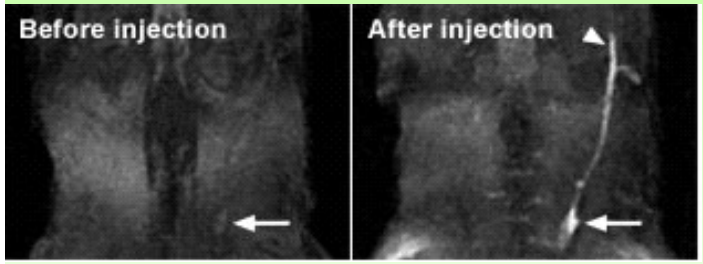
Tecnologie magnetiche

Nanoparticelle magnetiche

Utilizzo di nanoparticelle magnetiche in biomedicina

Sensori (MRI, Sentimag, MEG-SQUID, Biosensori)

SENSING

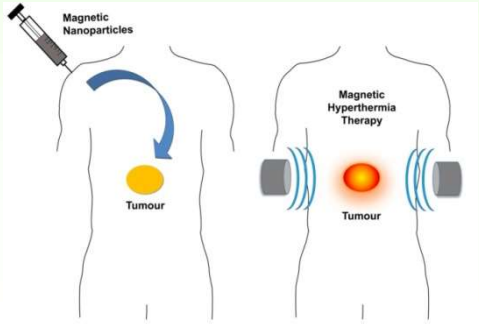


MOVING

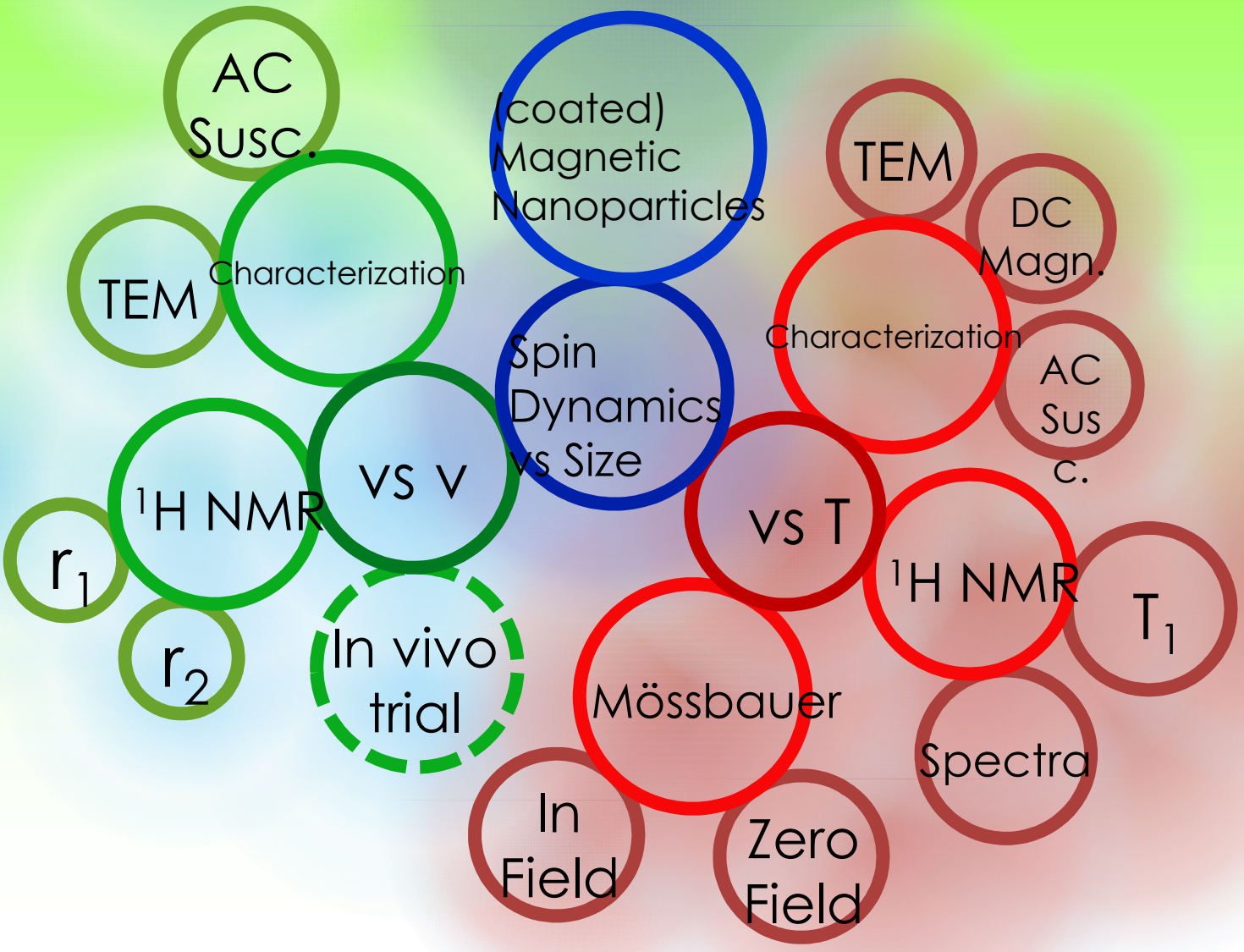
Trasporto magnetico

HEATING

Ipertermia magnetica

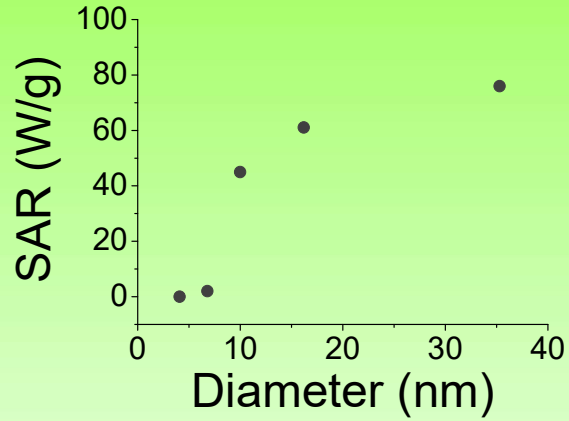


Proprietà fisiche fondamentali delle nanoparticelle

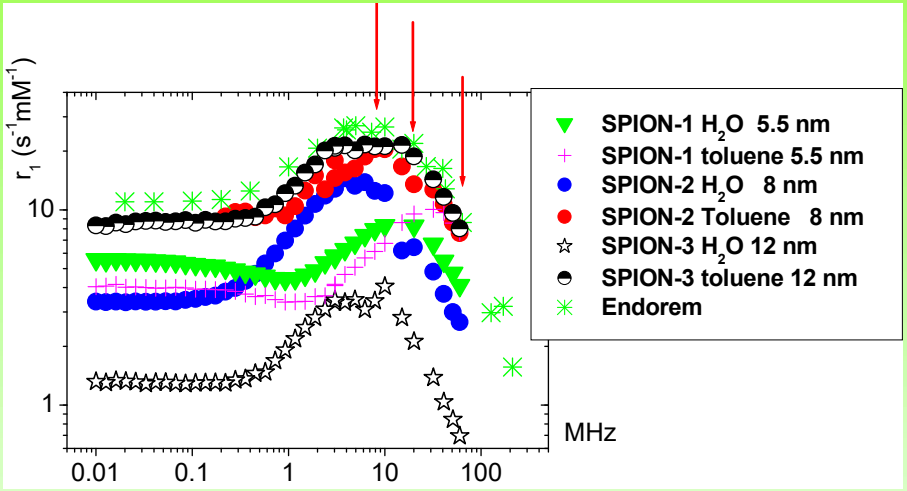


Rilassometria NMR : dale proprietà di fondamento alle applicazioni

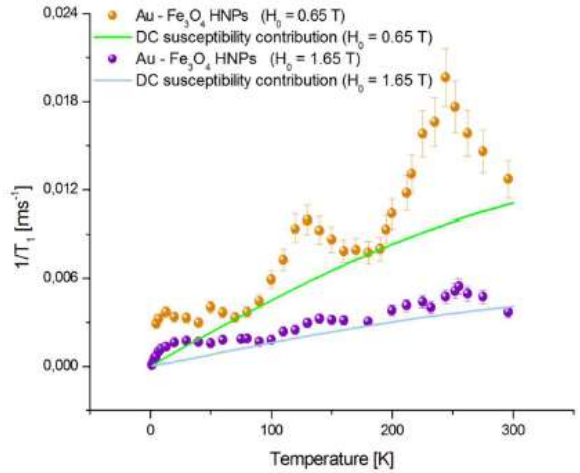
SAR in Magnetic Fluid Hyperthermia : Study of influence of microscopic features



NMR relaxometry at room temperature



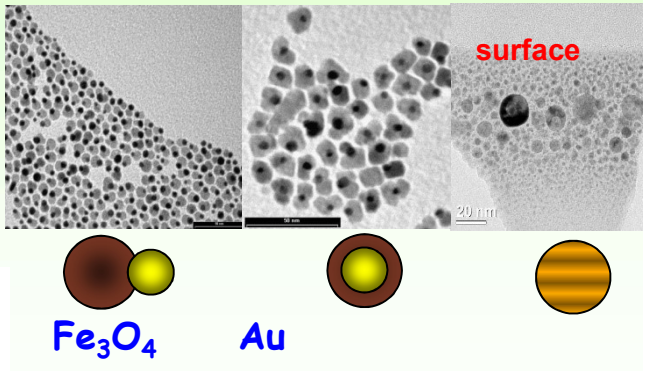
Magneto-optical nano-devices : ferrites+gold plasmon resonance and spin dynamics



Physical model for spin dynamics :

$$\frac{1}{T_1} = A\chi T\left(\frac{\tau_R}{1+\omega_L^2\tau_R} + \frac{\tau_N}{1+\omega_L^2\tau_N} + \frac{\tau_?}{1+\omega_L^2\tau_?}\right)$$

Magneto-plasmonics



Dynamic Nuclear Polarization – DNP : una nuova tecnica diagnostica

- Transfer of polarization from the electron to the nuclear spin system under irradiation of the electronic resonance

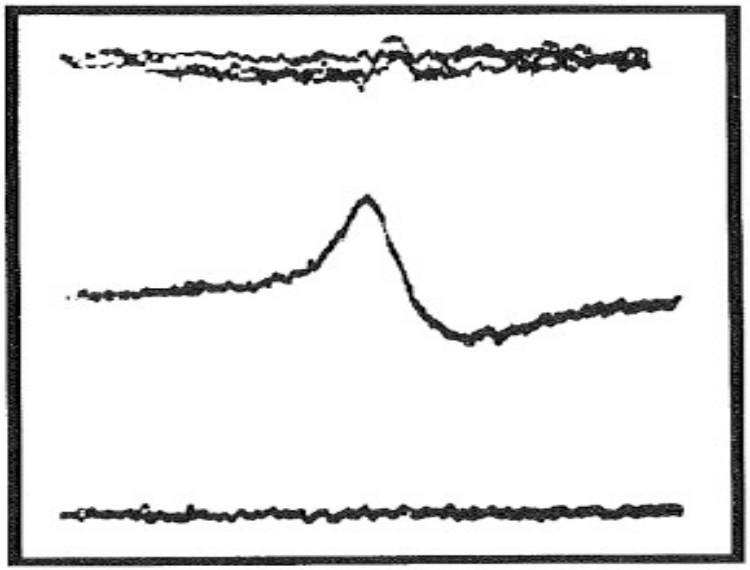
$$P_n(\%) = \varepsilon P_n^{thermal} = \varepsilon \tanh\left(\frac{\gamma \hbar H_0}{2K_B T}\right) \propto \frac{\varepsilon}{T}$$

NON EQUILIBRIUM HYPERPOLARIZED STATE

- In Metals and solutions
  Overhauser Effect

- In solids doped with radicals
  Solid State Effect (SE)

SE: non interacting electrons



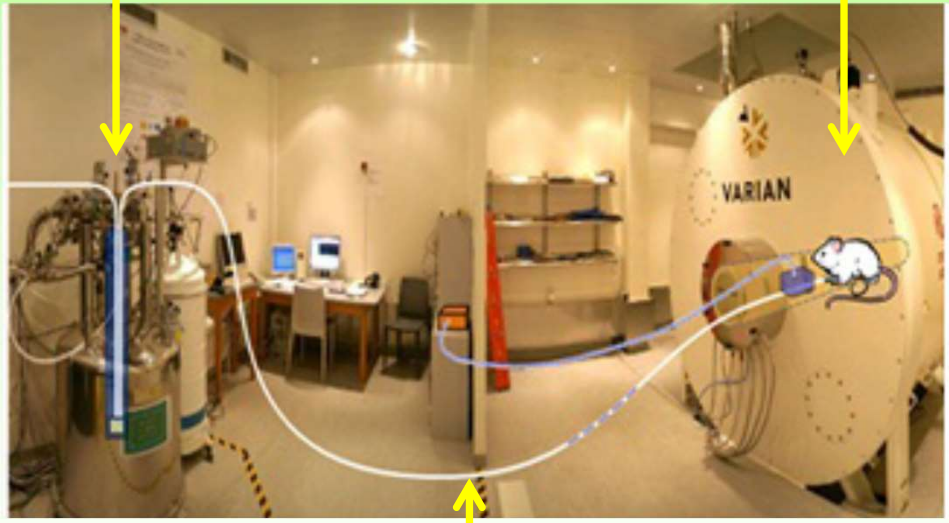
Carver, T. R.; Slichter, C. P. (1953). "Polarization of Nuclear Spins in Metals". *Physical Review* **92** (1): 212–213.

DNP per Imaging metabolico

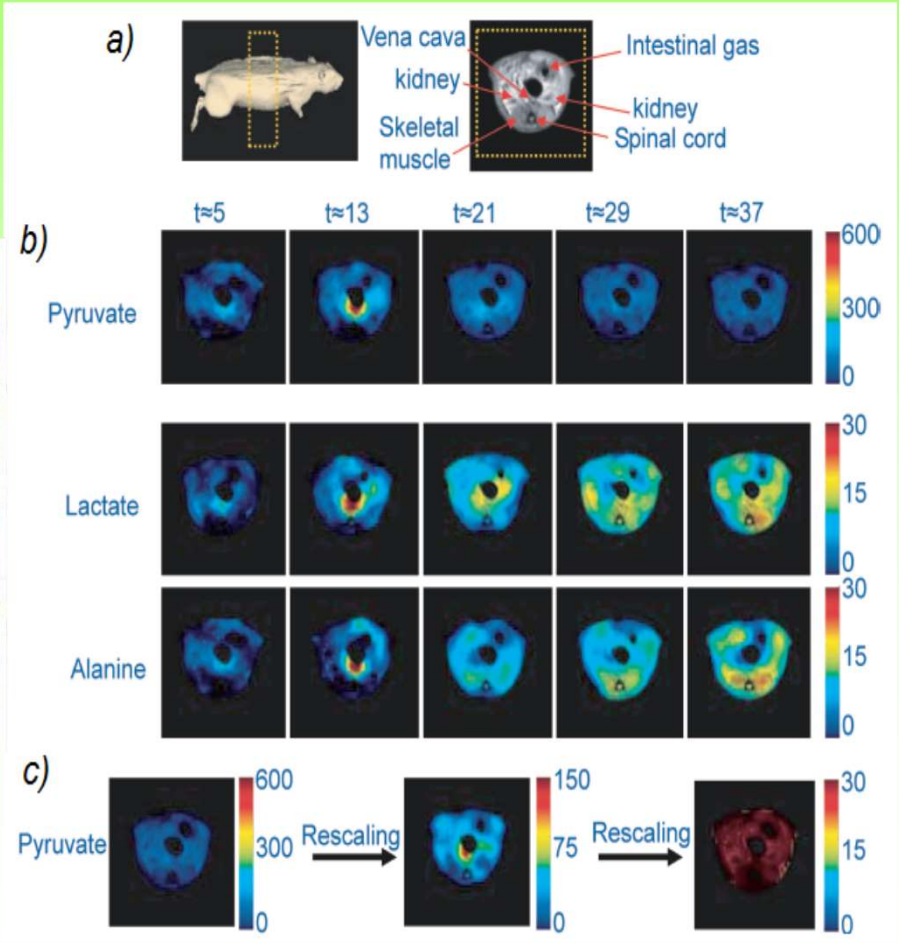
- Solutions of ^{13}C labelled metabolites and paramagnetic radicals (about 10 mM)
- Thermal mixing (TM) at low temperature (1.2 K) and high magnetic fields (3.35T)

Polarization and dissolution

Injection and MRI



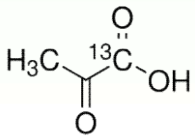
Transfer line for the sample



K. Golman et al. PNAS **103** (2006), 30, 11270-11275

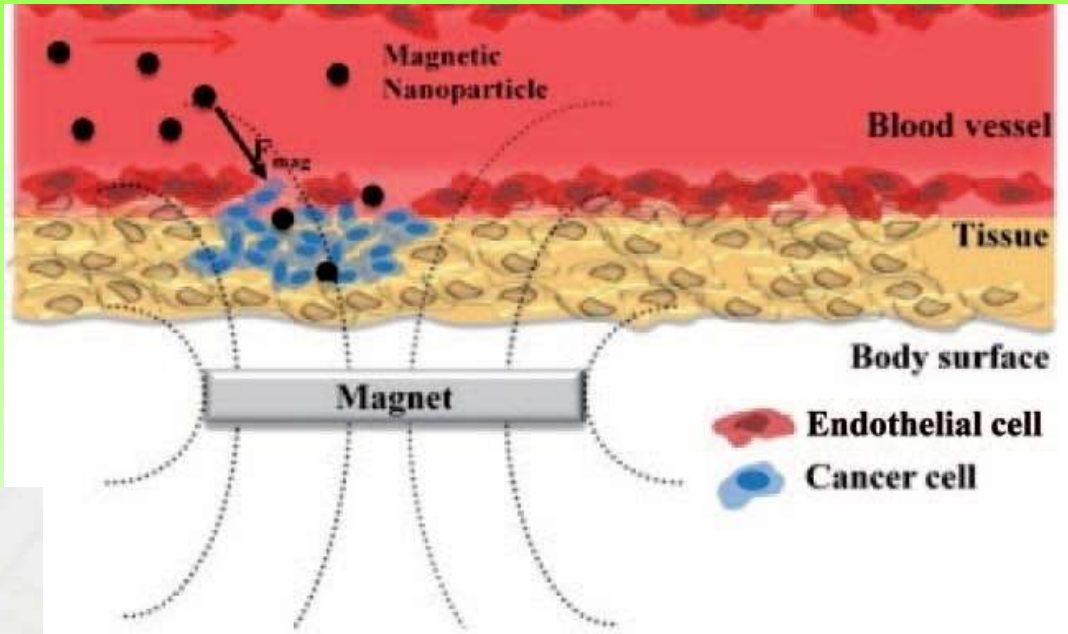
^{13}C Pyruvic Acid

- Endogenous molecule, important for the study of tumoral activity: NMR signal increased by a factor 100000



Trasporto magnetico- NON a livello clinico

Iniezione IV + rilascio di farmaco locale (cause : variazione pH o stimolo esterno)



Forces on a magnetic nanoparticle:

$$F_m = (m \cdot \nabla) B$$

$$F_m = V_m \Delta\chi \nabla(\tfrac{1}{2} B \cdot H)$$

Hydrodynamic drag force:

$$F_d = 6 \pi \eta R_m \Delta v$$

Equating the two:

$$\Delta v = \frac{R_m^2 \Delta\chi}{9\mu_0\eta}\nabla(B^2) \quad \text{or} \quad \Delta v = \frac{\xi}{\mu_0}\nabla(B^2)$$

Magnetic Particle Imaging – MPI (preclinico)

1st MPI system
(Bruker-Philips, 2013)

«Fornisce» le immagini della distribuzione di NP magnetiche nei tessuti biologici

http://www.philips.com/e/imalytics/productsnew/magneticparticle.html

SENTIMAG :
un suscettometro altamente sensibile

The Sentimag® is a Class IIa device, CE-approved for marketing and sales in Europe, and TGA-approved for Australasia.

Tecnica dei linfonodi sentinella

MNPs

Key features and benefits of Sienna+®:

- Particle size optimised for filtration and retention by sentinel lymph nodes
- Simple storage and handling procedure, and significantly improved workflow compared with radioactive tracers
- Localisation can start after only 20 minutes following injection†
- Natural dark brown colour eliminates the need for separate dye injections
- Non-toxic, aqueous suspension dissipates naturally in the body
- Long shelf life
- Uniquely designed and calibrated for use with Sentimag®
- Compatible with Sysmex's One-Step Nucleic Acid Amplification (OSNA) assay (http://www.sysmex-lifescience.com/OSNA-assay-for-lymph-nodes-175-2.html)

Caso clinico, tumore al seno

Senza utilizzo di
Radiofarmaci
Con NP magnetiche

Risonanza Magnetica per Immagini
Magnetic Resonance Imaging (MRI)

Typical MRI apparatus for clinical use, magnetic field H = 1.5 Tesla

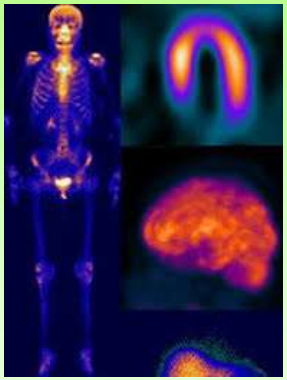
MRI Timeline

1946 MR phenomenon - Bloch & Purcell
1952 Nobel Prize - Bloch & Purcell
1950-70 NMR developed as analytical tool
1972 Computerized Tomography
1973 Backprojection MRI - Lauterbur
1975 Fourier Imaging - Ernst
1977 Echo-planar imaging - Mansfield
1980 FT MRI demonstrated - Edelstein
1986 Gradient Echo Imaging - NMR Microscope
1987 MR Angiography - Dumoulin
1991 Nobel Prize - Ernst
1992 Functional MRI
1994 Hyperpolarized ^{129}Xe Imaging
2003 Nobel Prize - Lauterbur & Mansfield

Alcune tecniche di Imaging

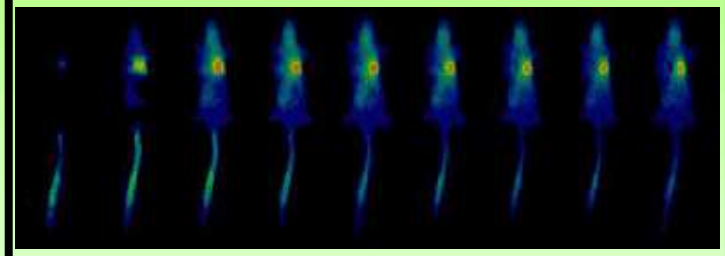
Nuclear Medicine:

- Poor spatial resolution
- Poor temporal resolution
- High sensitivity
- Reporters: radionuclides



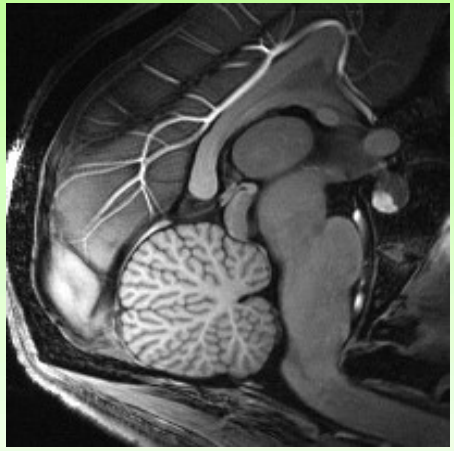
Optical Imaging:

- Poor spatial resolution
- Poor temporal resolution
- High sensitivity
- Reporters: luminescent probes



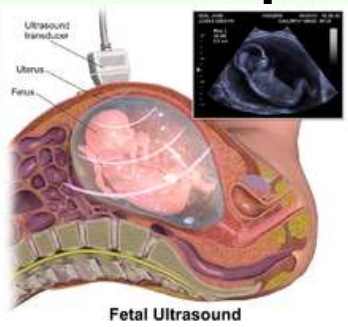
MRI :

- Non-invasive !!!
- Good spatial resolution
- Good temporal resolution
- Low sensitivity



Ultrasounds

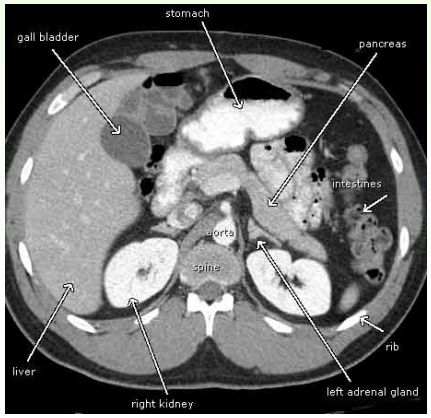
- Non-invasive
- Poor spatial resolution
- Good temporal resolution
- Low sensitivity
- Easy



Fetal Ultrasound

X-Ray (CT):

- Good spatial resolution
- Good temporal resolution
- Low sensitivity

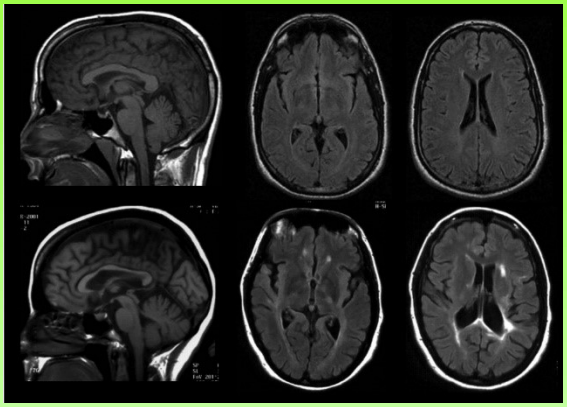


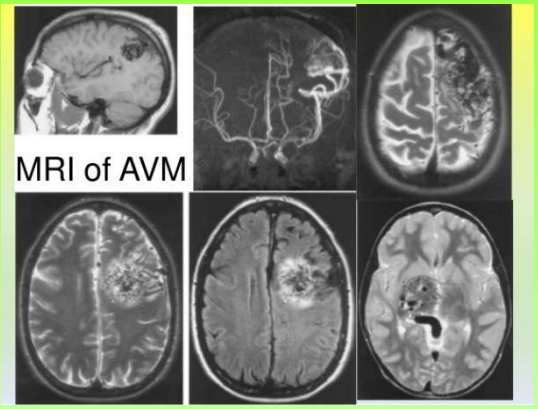
IEO
Istituto Europeo
di Oncologia

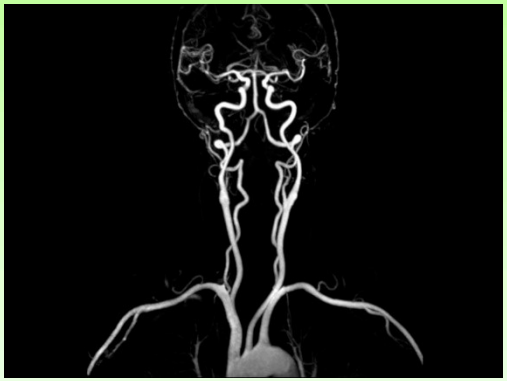
Milano, 09/04/2019

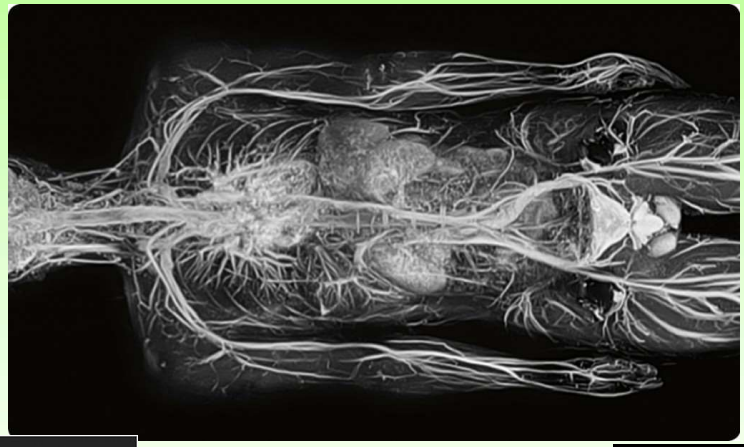
Cervello

Torino, 22/05/2018

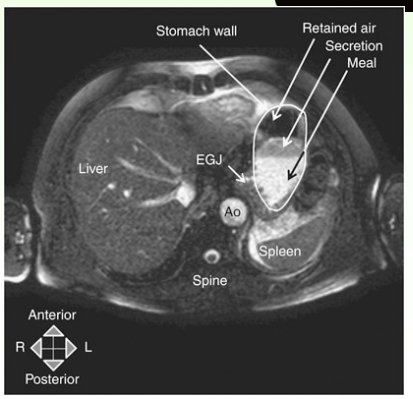






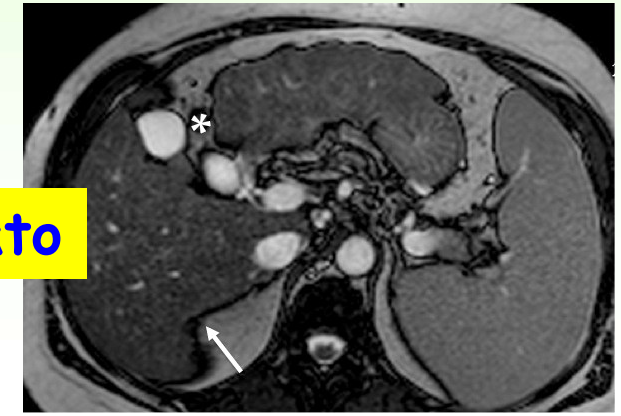


Angiografia



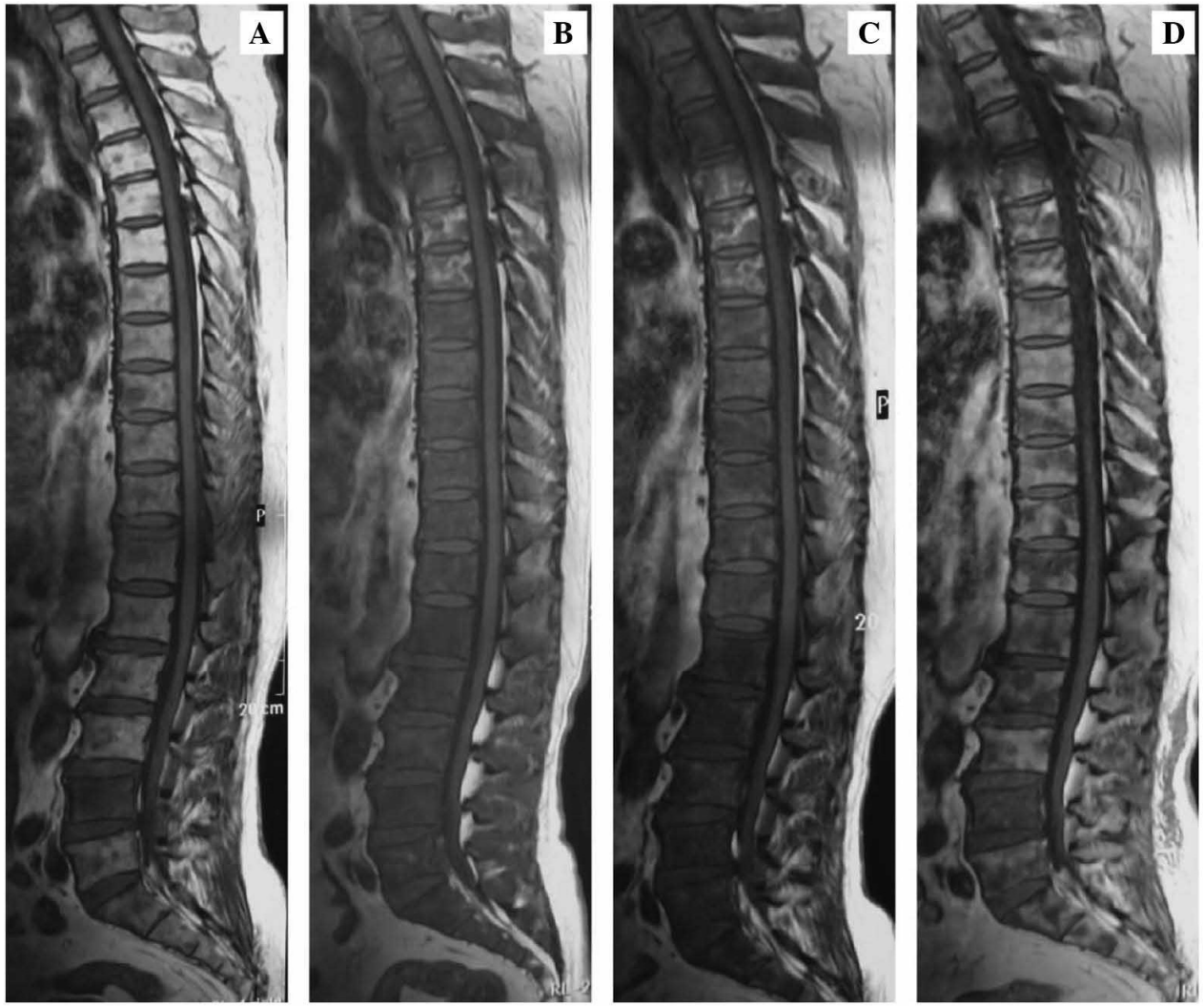
Addome

Fibrosi al fegato



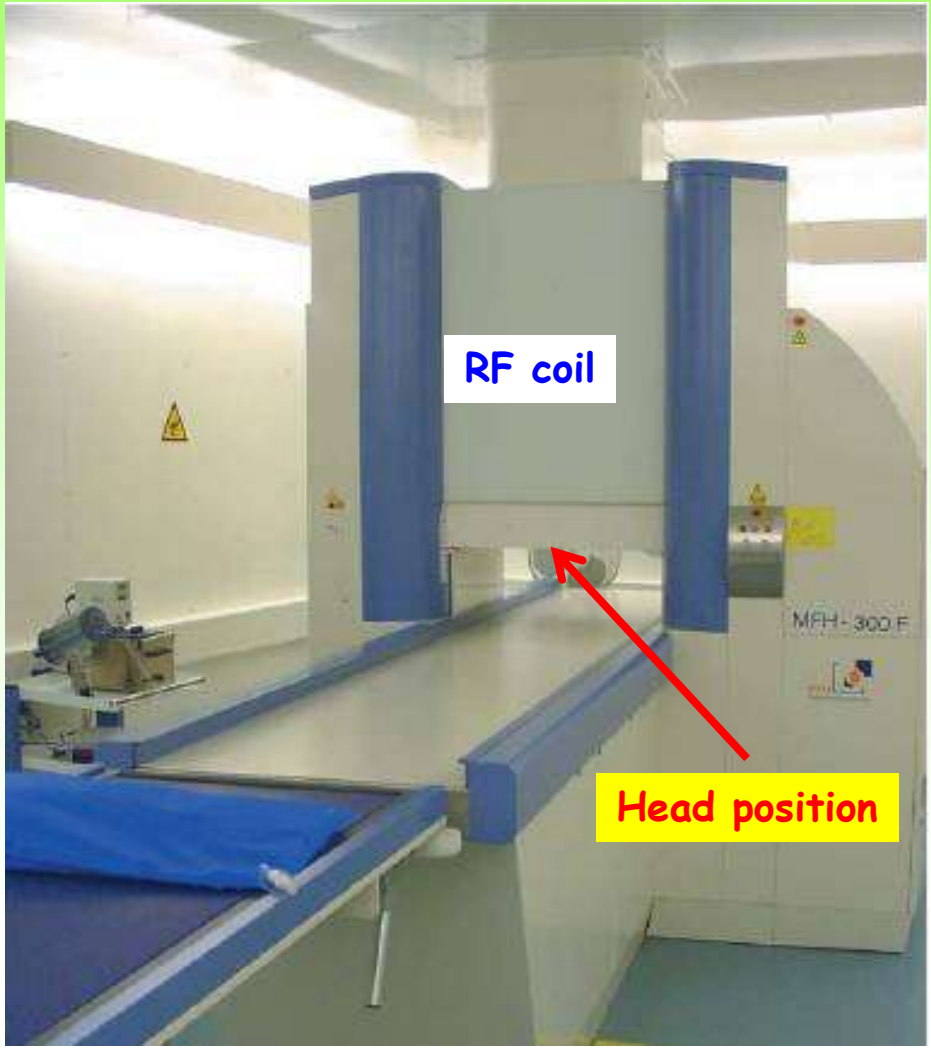
Midollo spinale

Torino, 22/05/2018



Ipertermia magnetica (MFH) : trattamento del tumore

Started a new study on glioblastoma multiforme in 2014, in USA and Germany Several german hospitals involved



· **Heating** through application of **AC magnetic field** via activation of 12 nm amino-silane coated Fe_3O_4 MNP directly implanted in the tumour mass at high doses (ca. 50 mg/cm^3)

• Typically : $\nu \sim 100$ kHz, amplitude 10 kA/m

• Minor side effects

$H_0 f \leq 4\ 10^9\ Am^{-1}s^{-1}$ (*)

$50\ kHz \leq \nu \leq 1\ MHz$

(*) Depending on the radius of the exposed region

• Typical values of the reported **specific loss of power, SLP or SAR** (the energy converted into heat per mass unit) are : 10÷200 W/g [exceptions : 35 nm bacterial magnetosomes (960 W/g at 410 KHz and 10 kA/m); 16 nm γ-Fe_2O_3 N P (1650 W/g at 700 kHz and 24.8 kA/m, 300 W/g at 11 kA/m)]

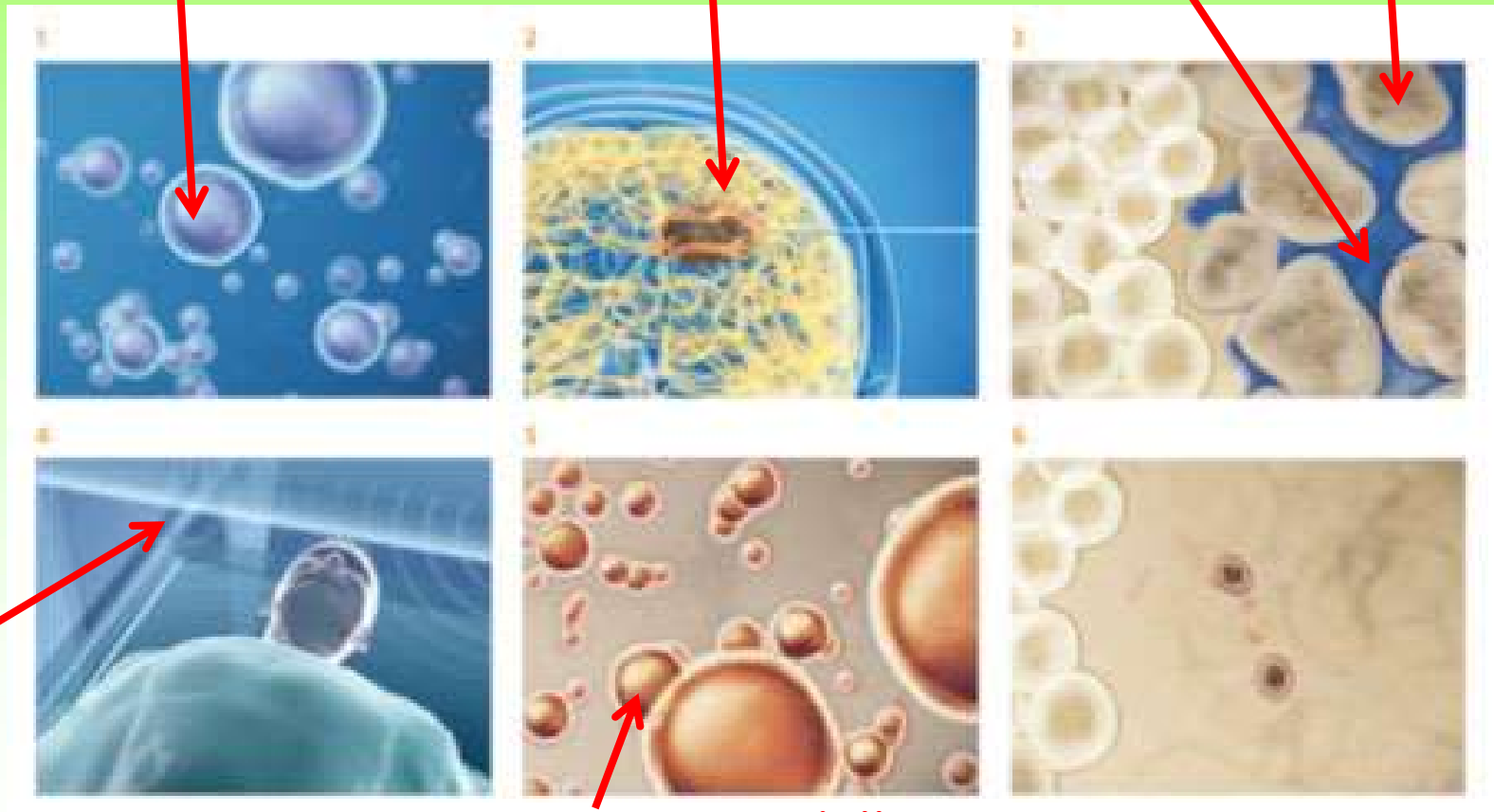
MFH – Applicazioni Cliniche

MNPs coated
With amminosilane

Direct injection in
the brain tumour

Tumour cells

ferrofluid



AMF

Heating – kill
tumour cells

Stato dell'arte della terapia ipertermica magnetica applicata in clinica (Magforce)

Started a new study on
glioblastoma multiforme in 2014,
in USA and Germany
Several german hospitals involved

Problems of "integrating" this therapy alongside the more conventional hospital therapies

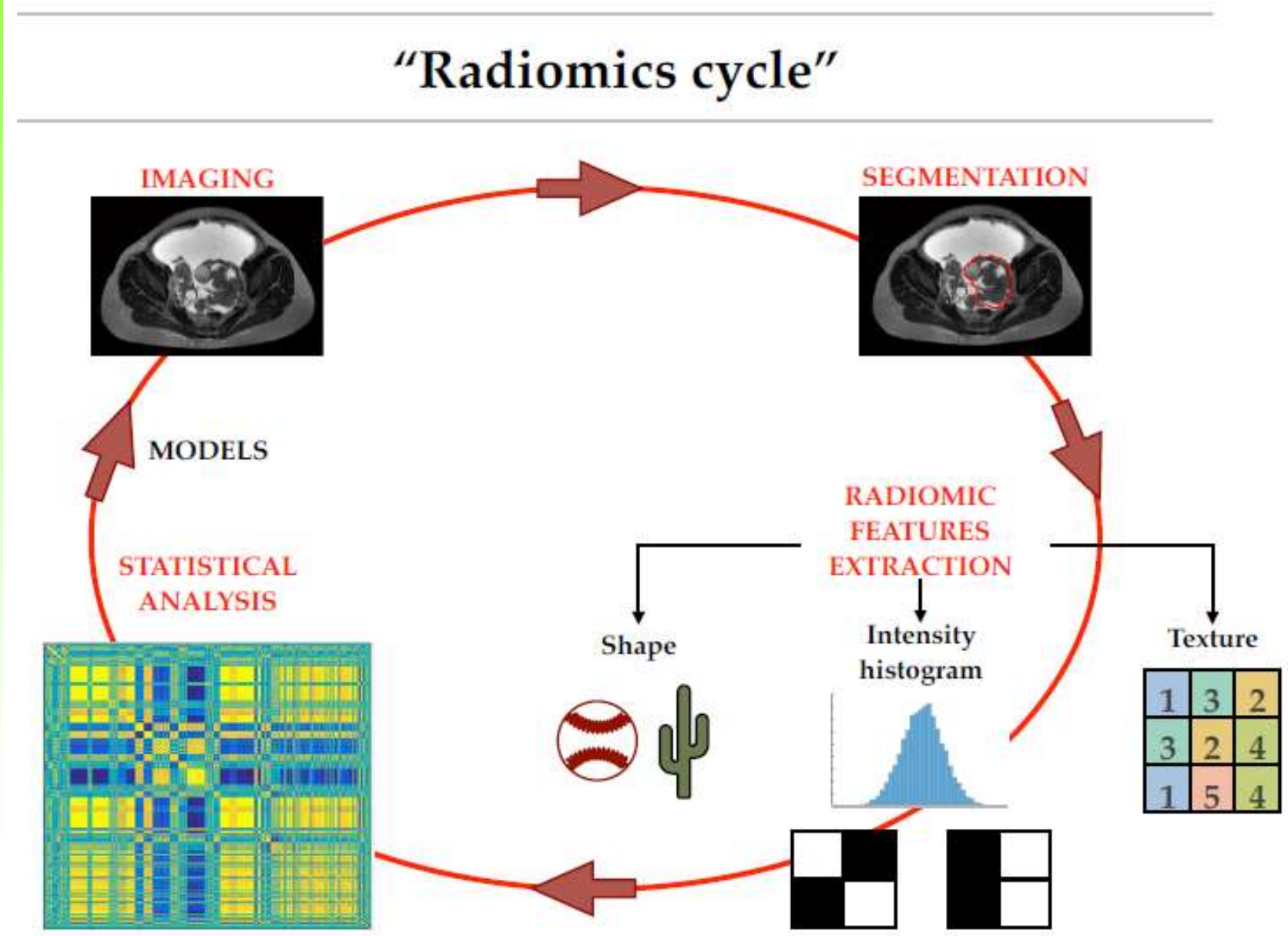
Fine 1^ parte

Thanks

Any questions ??

Magnetic Resonance Imaging
&
Radiomica

Diagnostica e radiomica



Modelli per la radiomica

Repeatability and robustness of radiomic features extracted from Magnetic Resonance images of pelvic district: a phantom study

L. Bianchini[1], F. Botta[2], D. Origgi[2], M. Cremonesi[2], P. Arosio[1], A. Lascialfari[1]

[1]Dipartimento di Fisica and INSTM, Università degli Studi di Milano
[2]IEO, Istituto Europeo di Oncologia IRCCS, Milano

GIDRM XLVII NATIONAL CONGRESS ON MAGNETIC RESONANCE
Torino, 19th-21st September 2018

From scratch
First : phantom development for MRI

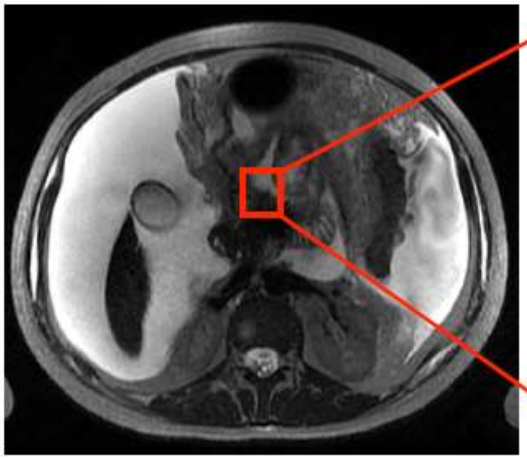
1. Need for phantom studies

2. Data from standard phantom

3. Development of "ad hoc 3D phantom"

What is radiomics?

512 x 512 matrix



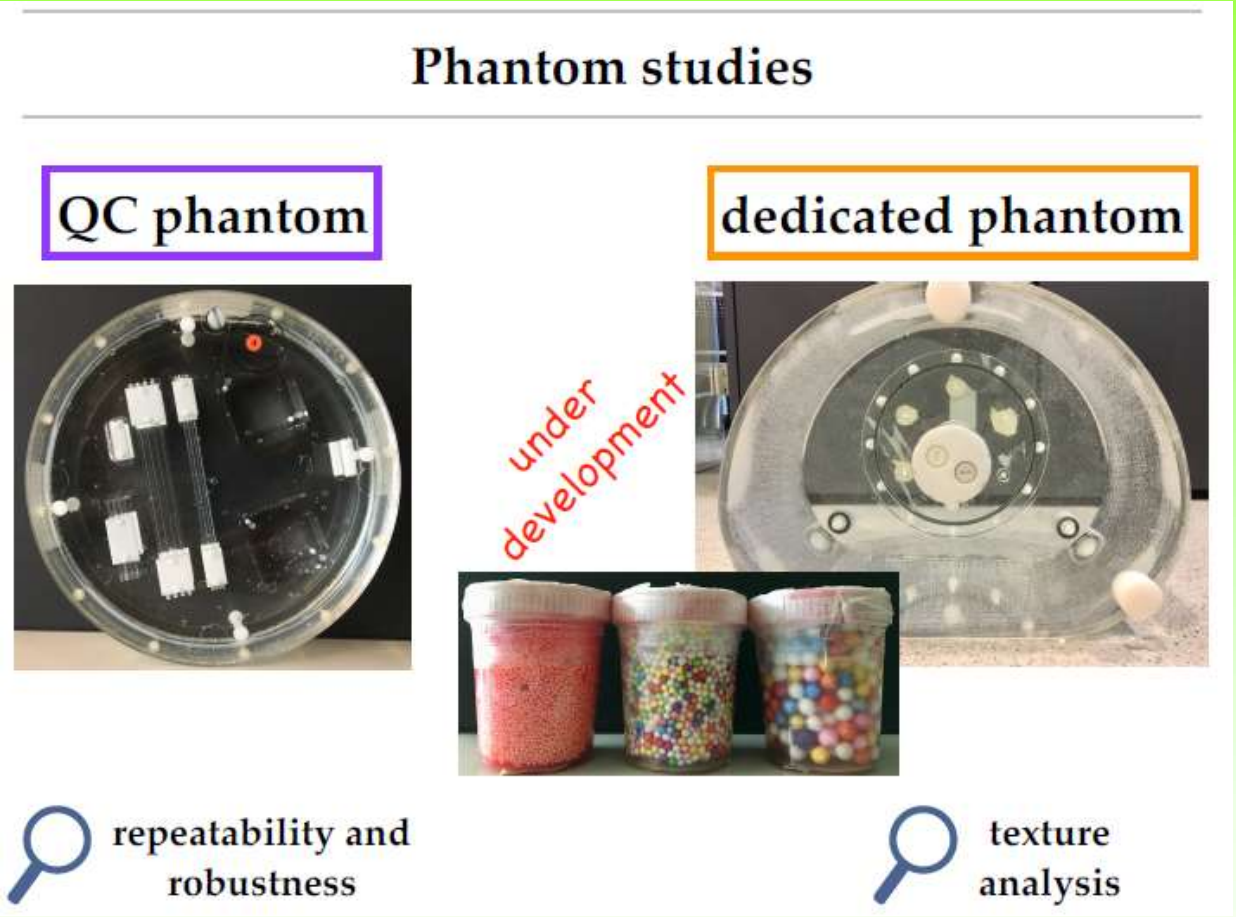
313	289	305	293	266	312	407
302	279	293	271	228	270	376
285	265	274	252	205	236	340
271	255	264	250	209	227	318
267	257	268	264	231	239	315
273	264	278	281	248	248	313
285	267	280	288	255	244	297
295	265	266	283	260	239	271
301	261	245	275	276	250	254
300	259	232	269	296	276	256
293	262	232	265	302	292	266
282	265	241	261	287	283	269
262	251	242	252	261	260	266
231	219	228	241	242	248	269
195	183	211	236	244	260	283
169	165	207	243	260	279	289
169	176	225	261	275	281	274
194	213	258	281	277	265	246
223	252	287	291	270	247	230
239	276	299	291	264	243	233
242	284	295	281	261	246	240

Slides from
Linda Bianchini,
PhD, UNIMI

IEO members
F. Botta, D. Origgi
M. Cremonesi

UNIMI
P. Arosio
F. Orsini

Modelli per radiomica MRI : un fantoccio



QC phantom

Dedicated one

Fundamentals :
Choice of phantom : 3D printing !
Data choice and collection
Data analysis

Primo tentativo di fantoccio

Texture phantom

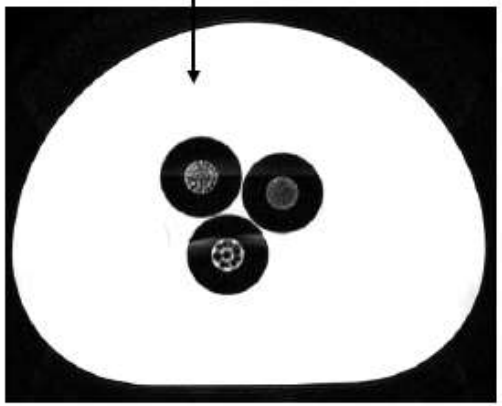
Phantoms for texture analysis of MR images. Long-term and multi-center study

Daniel Jirák,[a] Monika Dezortová, and Milan Hájek
Department of Diagnostic and Interventional Radiology, Institute for Clinical and Experimental Medicine, Videnska 1958/9, Prague, Czech Republic 140 21, Czech Republic

(Received 18 April 2003; revised 17 December 2003; accepted for publication 17 December 2003; published 26 February 2004)

Simulation of human body (pelvis)

next: $MnCl_2$



Advanced phantoms :

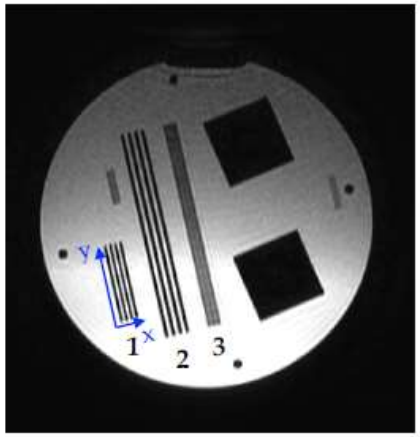
Problem of simulation of human body "granularity", tissues heterogeneity, and so on

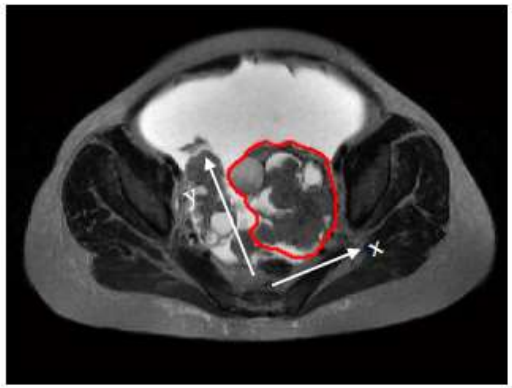
Fundamentals :
Choice of phantom : 3D printing !
Data choice and collection
Data analysis

Modelli per radiomica : scelta dei dati e raccollta

Which volumes?

	R1-B	R1-M	R1-S	R2-B	R2-M	R2-S	R3-B	R3-M	R3-S	tumour
x (cm)	1.1	1.1	1.1	1.4	1.4	1.4	0.7	0.7	0.7	7.0
y (cm)	4.7	2.4	1.2	12.0	6.0	3.0	12.0	6.0	3.0	8.0
z (cm)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.5

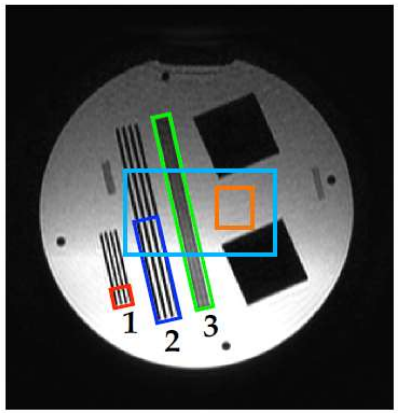




⚠ SMALL TUMOUR VOLUMES

Fundamentals :
Choice of phantom : 3D printing !
Data choice and collection
Data analysis

Materials & Methods



	Region Of Interest (ROI)
1	R1-Big
2	R1-Med
3	R1-Sma
4	R2-Big
5	R2-Med
6	R2-Sma
7	R3-Big
8	R3-Med
9	R3-Sma
10	R-All
11	R-Hom

Volume selection
(crucial influence of 3D phantom choice)

Analisi dati

Software:

IBEX: An open infrastructure software platform to facilitate collaborative work in radiomics

Lifei Zhang
Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

David V. Fried, Xenia J. Fave, and Luke A. Hunter
Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030 and The University of Texas Graduate School of Biomedical Sciences at Houston, Houston, Texas 77030

Jinzhong Yang
Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

Laurence E. Court[a]
Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030 and The University of Texas Graduate School of Biomedical Sciences at Houston, Houston, Texas 77030

(Received 27 October 2014; revised 15 January 2015; accepted for publication 2 February 2015; published 25 February 2015)

Pre-processing: "3σ normalization"

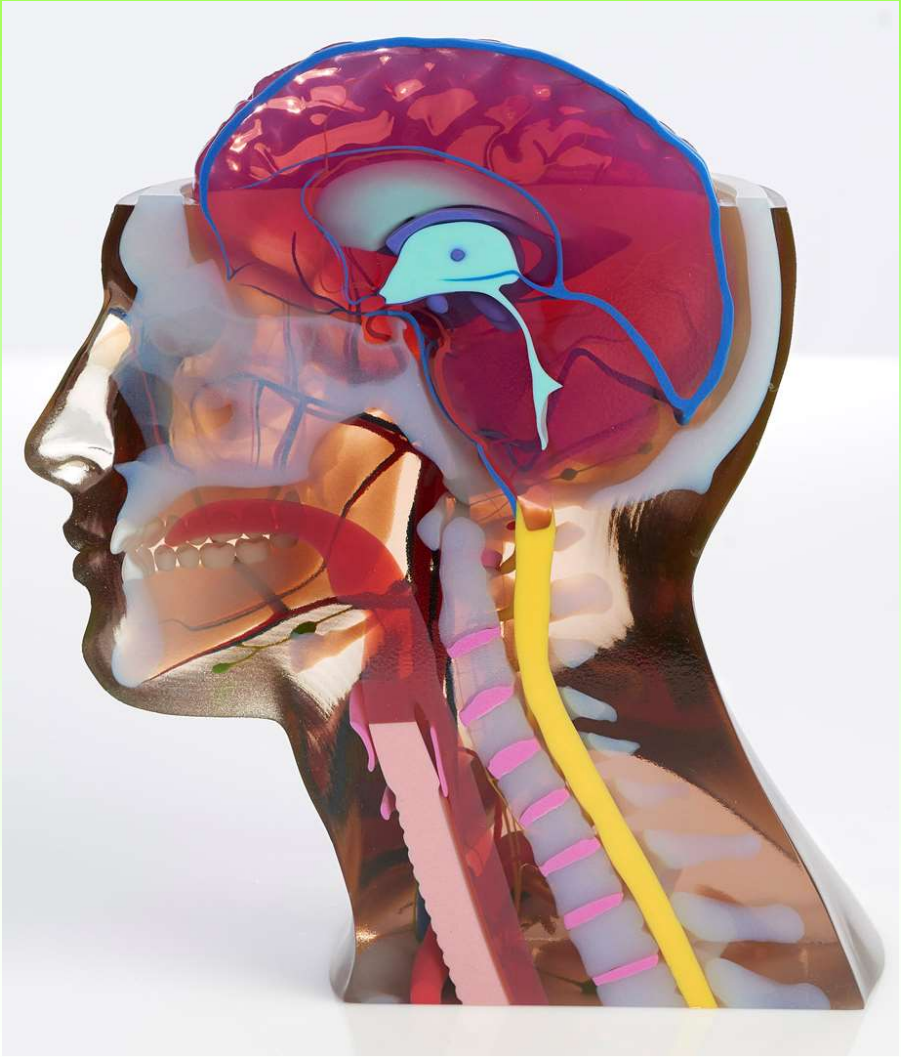
7 categories of features → shape, intensity histogram, texture

- Software
- Pre-processing
- Features selection

Machine learning
Deep learning
Artificial intelligence

Fundamentals :
Choice of phantom : 3D printing !
Data choice and collection
Data analysis

Modelli per radiomica : molto ambizioso, prossimo fantoccio 3D !!



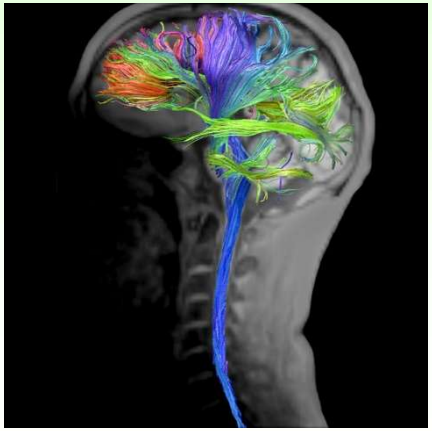
For all techniques :
CT, MRI, PET, US, …..

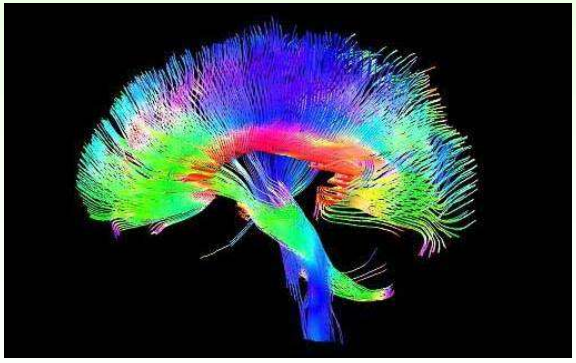
Also : radiotherapy !

Advices for MRI :

- Same sequences and field (and Imager)
- Quality of 3D phantom
- Materials : T_1 and T_2 simulation for different tissues (bio-inks)
- Data analysis : multiexpontial behaviour !
- …….

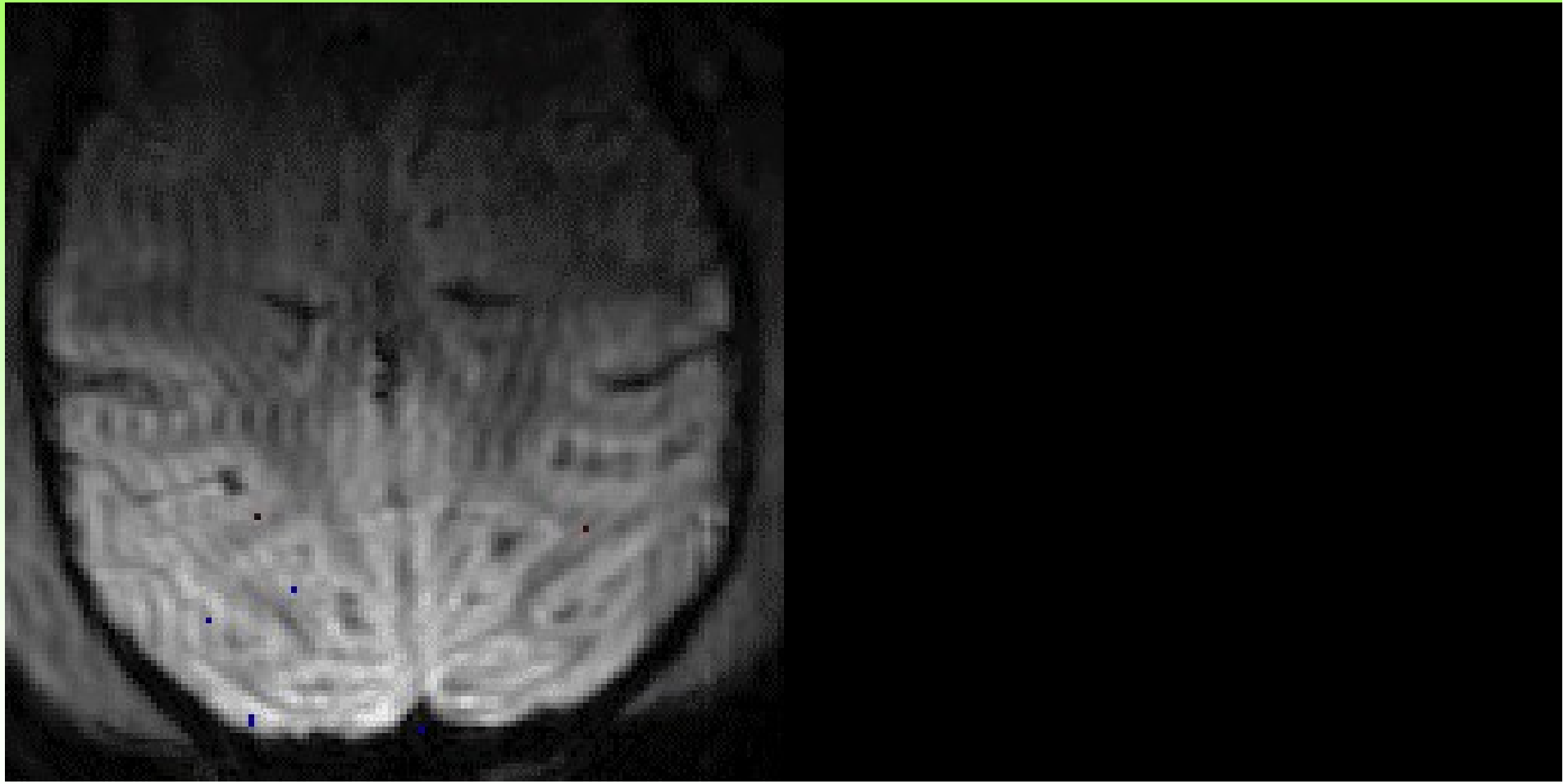
MRI : Imaging con tensore di diffusione, MRI-funzionale, connettomica





MRI funzionale

Real-time
Monkey's brain



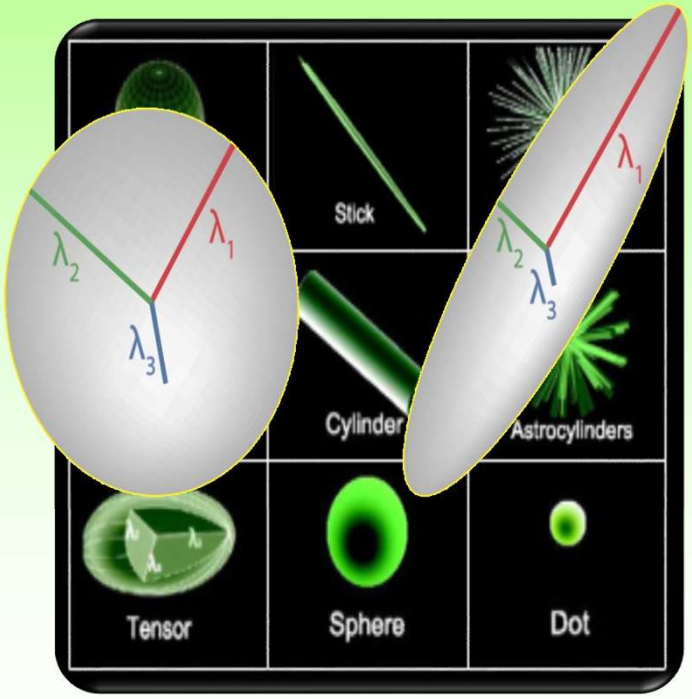
MRI & microstruttura del cervello

Diffusion MRI can be used to probe the microstructure (i.e. barriers, obstacles, membranes…) that surrounds water molecules randomly moving in the brain.

Many models of the diffusion signal were and are currently proposed:

From the "simple" symmetric tensor

To more complicated multi-compartment models



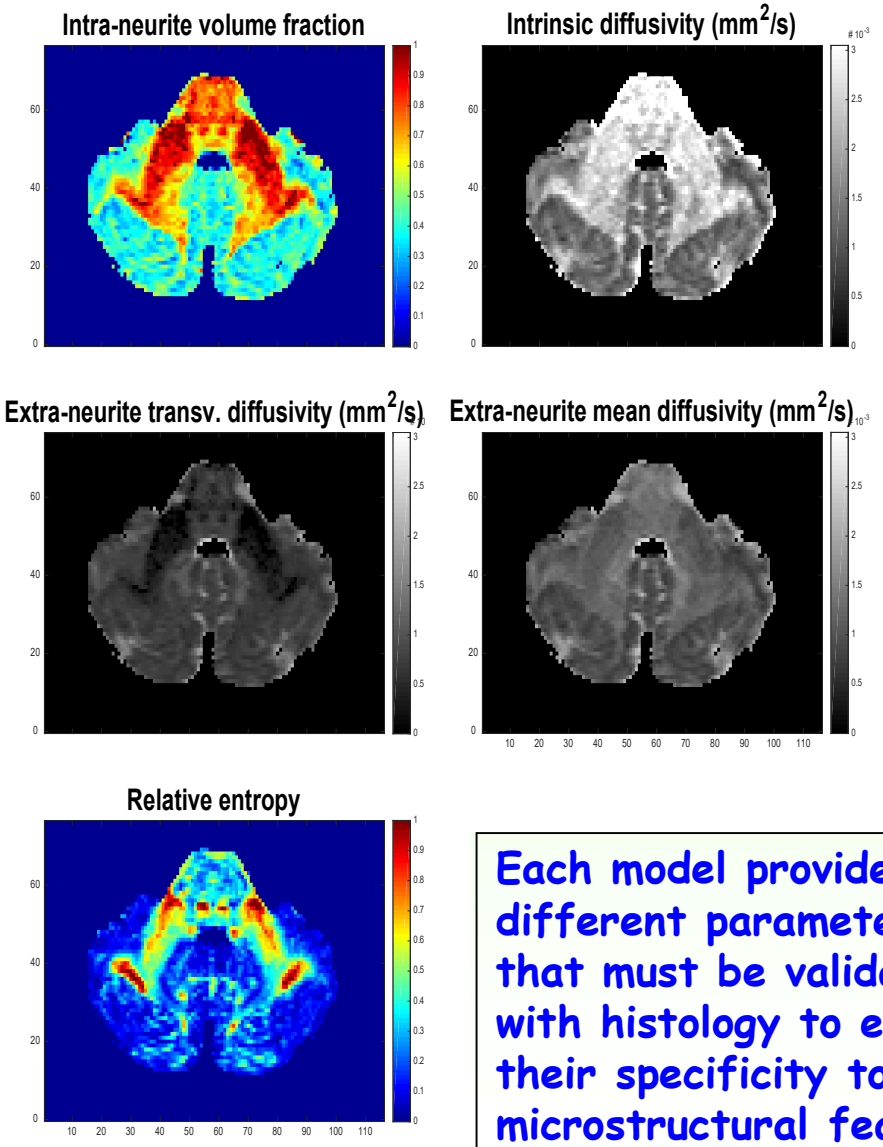
Isotropic diffusion

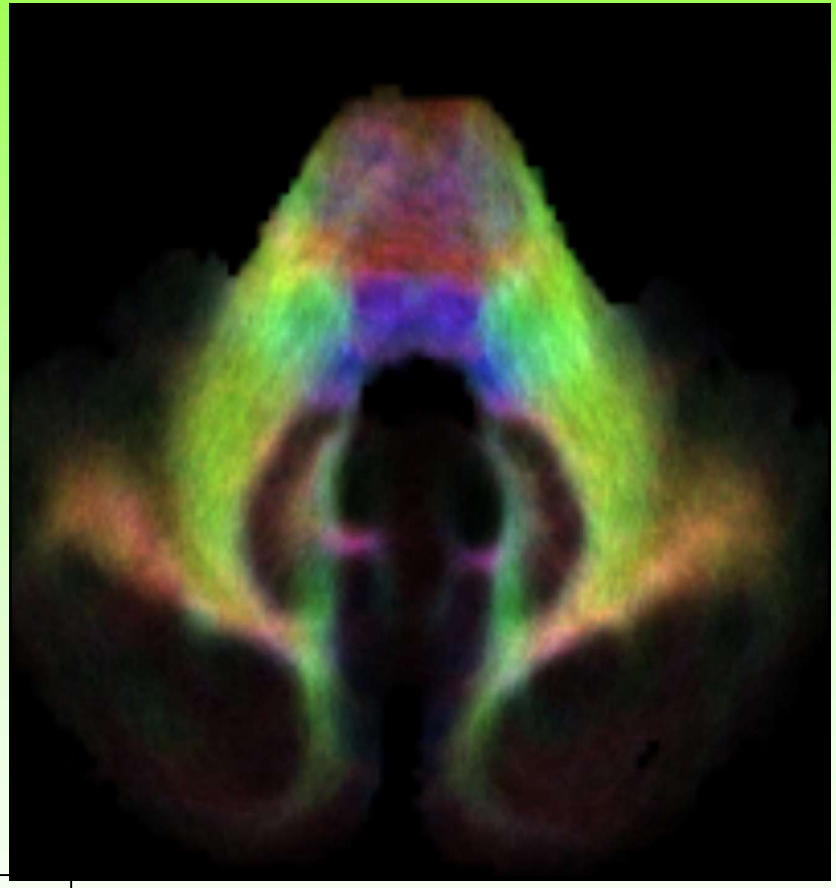
Anisotropic diffusion

G. Savini – PhD activity - UNIMI

Microstruttura cerebellare

Two-compartment model

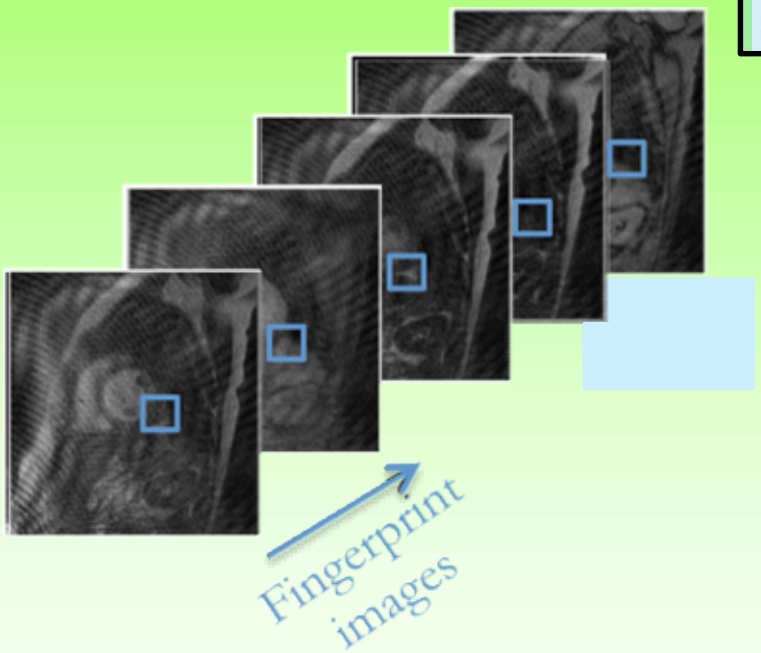




Each model provides different parameters that must be validated with histology to evaluate their specificity to real microstructural features.

Here, diffusion MRI is used to investigate the microstructure of the cerebellum.

MRI fingerprinting (impronte digitali)



Magnetic resonance fingerprinting

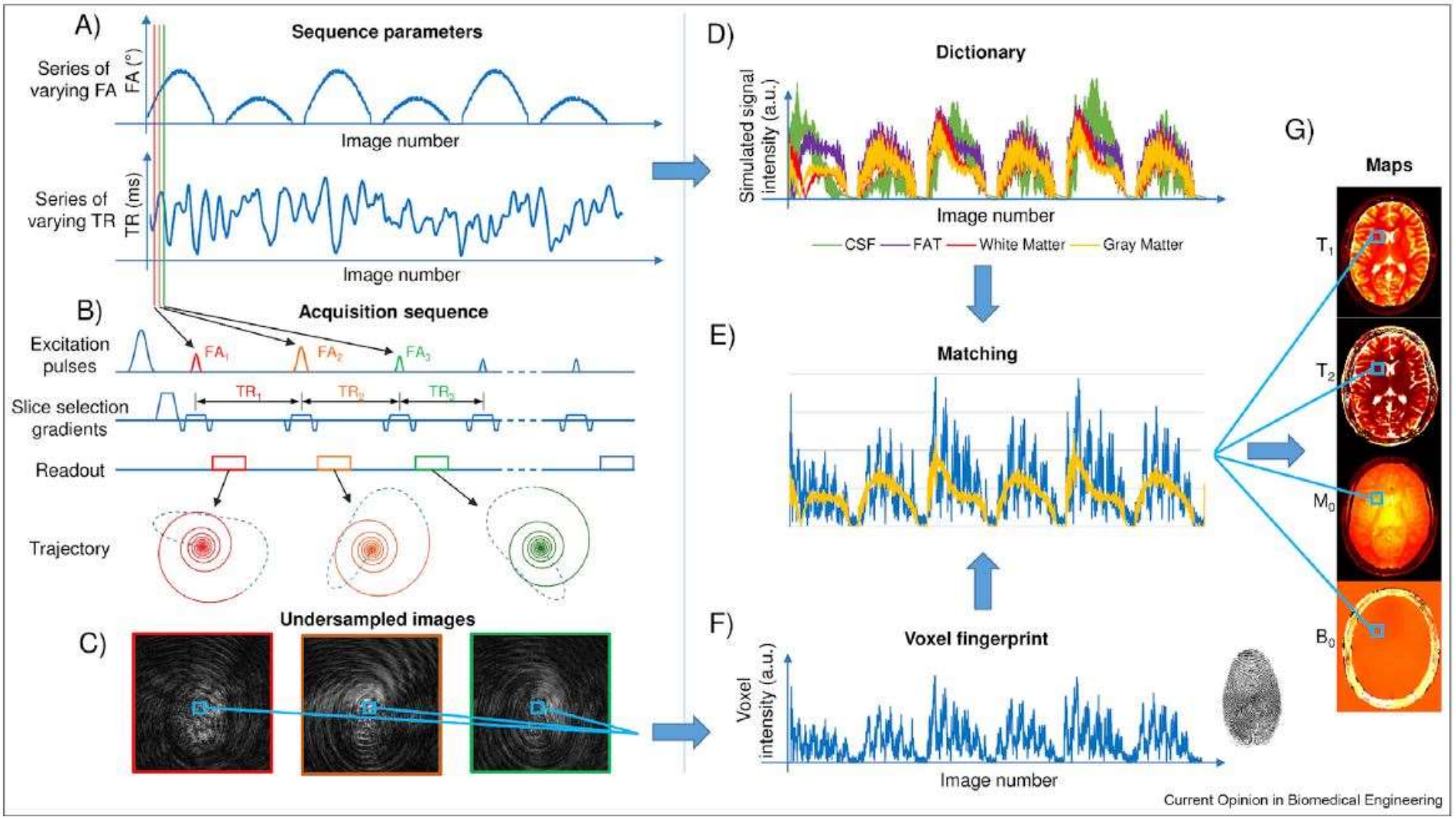
14 MARCH 2013 | VOL 495 | NATURE

Dan Ma[1], Vikas Gulani[1,2], Nicole Seiberlich[1], Kecheng Liu[3], Jeffrey L. Sunshine[2], Jeffrey L. Duerk[1,2] & Mark A. Griswold[1,2]

«One-scan, multiple-properties»

- **Misura SIMULTANEA di più parametri in un'unica e breve acquisizione**
- **Fino a 48 immagini in meno di un quarto di secondo**
  Hamilton et al., 2015

MRI fingerprinting (impronte digitali)



Presso il Dipartimento di Fisica di Pavia – NMR group – biomed research

University researchers of NMR group, Dip. Fisica, UNIPV:

Seniors : *Carretta P., Corti M. (retired), Filibian M. Lascialfari A., Mariani M., Moscardini M., Prando G.*

PhD and postdoc students *: Avolio M., Bianchini L., Brero F., Charlaftis S., Cicolari D., Cobianchi M. (ex), Rinaldi L.*

UNIMI personnel*: Arosio P., Basini M. (ex), Orsini F., Veronese I.*

MAIN RESEARCH LINES

NOT EXHAUSTIVE

- ***Applications of magnetic techniques and magnetic nanoparticles to biomedicine – DIAGNOSIS AND THERAPY : MRI, CT, Hadron Therapy and magnetic hyperthermia, DNP***

- ***Magnetic techniques for fundamental magnetism : NMR, SQUID magnetometry, EPR, muSR, MRI, calorimetry (Hyperthermia), Dynamic nuclear polarization - DNP***

- ***Magneto therapy – THERAPY (just begun)***

Suggested book : Magnetism in Medicine, eds. W. Andrä and H. Nowak, Wiley-VCH

Thanks are due to Q. Pankhurst and C. Sangregorio for contributions to slides

Hospitals/companies involved

Hospitals :

- **Pavia ospedali :** Policlinico S. Matteo, Ist. Neurologico "Mondino", Fondazione Maugeri

- **Pavia** : CNAO

- **Milano :** Ospedale Niguarda, IEO, Ist. Mario Negri, Istituto Europeo di Oncologia,

Istituto Neurologico Besta

Companies :

Bracco SpA, Bruker Italia srl, Stelar srl

Actual main collaborations

(magnetism, MRI, synthesis, hyperthermia)

- Dipartimento di Chimica, Università di Roma, gruppo prof. G. Ortaggi
- Dipartimento di Chimica, Università di Cagliari, Dr. M.F. Casula
- Dipartimento di Chimica, Universita' di Modena, gruppo prof. A. Cornia
- Dipartimento di Chimica, Universita' di Firenze, gruppo prof. D.Gatteschi
- Dipartimento di Chimica Fisica, Universita' di Pavia, gruppo prof. P. Ghigna
- Dipartimento di Chimica, Università di Pisa, Prof. E. Chiellini
- Dipartimento di Chimica, Università di Bologna, Prof. M. Comes Franchini
- Dipartimento di Chimica, Università degli studi di Milano, prof. P. Ferruti e E. Ranucci
- Dipartimento di Chimica, Università degli studi di Milano, prof. G. D'Alfonso
- Dipartimento di Scienze Chimiche, Università degli studi di Padova, Dr. V. Amendola
- Dipartimento di Scienze Chimiche, Università degli studi di Catania, Prof. G. Vecchio
- Dipartimento di Fisica, Università di Milano Bicocca, gruppo prof. C. Riccardi
- Dipartimento di biologia e biotecnologie "L. Spallanzani", Università degli studi di Pavia, Prof. R. Nano
- Dipartimento di Chimica, Università di Pavia, Prof. Vidari
- Facoltà di Medicina, Università di Pavia, Prof. Dionigi
- Dipartimento di Fisica, Università di Pavia, Prof. Altieri
- Dipartimento di Scienze Farmacologiche, Universita' di Milano, Prof. R. Paoletti, Prof. E.Tremoli, Dr.U.Guerrini, Dr.G.Sironi
- Dipartimento di Scienze Morfologiche-Biomediche, Università degli studi di Verona, Prof. P. Marzola, Prof. A. Sbarbati
- Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli studi di Milano, Prof.ssa V.F. Sacchi, Dr.ssa A. Rizzo
- Dipartimento di Chimica, Università degli studi di Milano, Dr. M. Scavini
- INFM-CNR,National Nanotechnology Laboratory, Dr. T. Pellegrino, Dr. D. Cozzoli, Dr. L. Manna, Prof. R. Cingolani
- Department of Chemistry, Humboldt Universitat – Berlin (Germania), Prof. N. Pinna

Regional Center of Advanced Technology and Materials, Olomouc (Repubblica Ceca), Dr. G. Zoppellaro

- FORTH (Foundation for Research and Technology – Heraklion, Greece), Prof. A. Lappas
- Dept. Chemistry, Università di Bordeaux, Prof. S. Lecommandoux
- Dept. Of Physics, University of Zaragoza (Spagna), Prof. F. Palacio e Dr. A. Millan
- Departamento de Química Inorgánica, Universidad de Granada (Spagna), Dr. J.M. Dominguez-Vera
- CNRS and University of Montpellier (Francia), Dr. J. Larionova, Dr. Y. Guari
- Pasteur Institute of Tehran (Iran), Dr. M. Mahmoudi
- Phillips Marburg University (Germany), Dr. W. J. Parak
- Policlinico S. Matteo, Pavia, Dr. R. Di Liberto (direttore Fisica sanitaria)
- Istituto Neurologico "Mondino", Pavia, Prof. E. D'Angelo (anche Università degli studi di Pavia) e Dr.ssa F. Palesi
- Ospedale Niguarda, Milano, Dr. A. Torresin (direttore Fisica Sanitaria)
- Istituto Europeo di Oncologia (IEO), Milano, Dr.ssa D. Origgi
- Bracco SpA, Milano (Italia), dr. V. Lorusso
- Centro Ricerche Colorobbia, Vinci (FI) (Italia), Dr. G. Baldi, Dr.ssa L. Niccolai
- Stelar srl, Mede (PV) – Italia, Ing. G. Ferrante

Experimental techniques at NMR group

Universita' degli studi di Pavia

- **MRI Bruker** B = 7 Tesla, **Esaote , Artoscan**, B = 0.2 Tesla
- **NMR : broadband spectrometers** (Bruker, Tecmag, Mid-Continent) covering a frequency range 4-400 MHz. Magnetic field 0-9 Tesla. Temperature : 0.3-1000 K.
- **Quantum Design SQUID magnetometer**. Temperature: 1.7-800K.
  Magnetic Field : -7 ÷ 7 Tesla.
- **Adiabatic calorimeter,** 1.5 < T < 300 K
- **"Wide-band" EPR**

Universita' degli studi di Milano

- **Atomic Force Microscopy** / Scanning Tunneling Microscopy / Magnetic Force Microscopy - Autoprobe CP Research System - Veeco. Working temperature range 0-60°C.
- **NMR : broadband spectrometer** Stelar Spinmaster. 5-70 MHz. Temperature : 4.2-350 K. Magnetic field 0-1.4 Tesla.
- **NMR relaxometer**, 10 KHz < f < 10 MHz. Temperature 150 < T < 350K
  (**MRI : Bruker AMX200**, 4.7 Tesla, super-wide-bore, rats and mice coils. Physiological parameters' control)

Available equipments : broad-band NMR, magnetometry and relaxometry

SMART Tracer
Frequency : 10KHz – 10MHz

FT-spectrometers
and electromagnets

9 Tesla magnet
for broad-band NMR

Esaote Artoscan 0.2 Tesla
MRI Imager

Cryogenics

SQUID magnetometer

Bruker 7 Tesla
MRI Imager

Thank you !

Any questions ??