TARGETED NANOTHERANOSTICS FOR FUTURE PERSONALIZED MEDICINE: RECENT PROGRESS IN CANCER THERAPY

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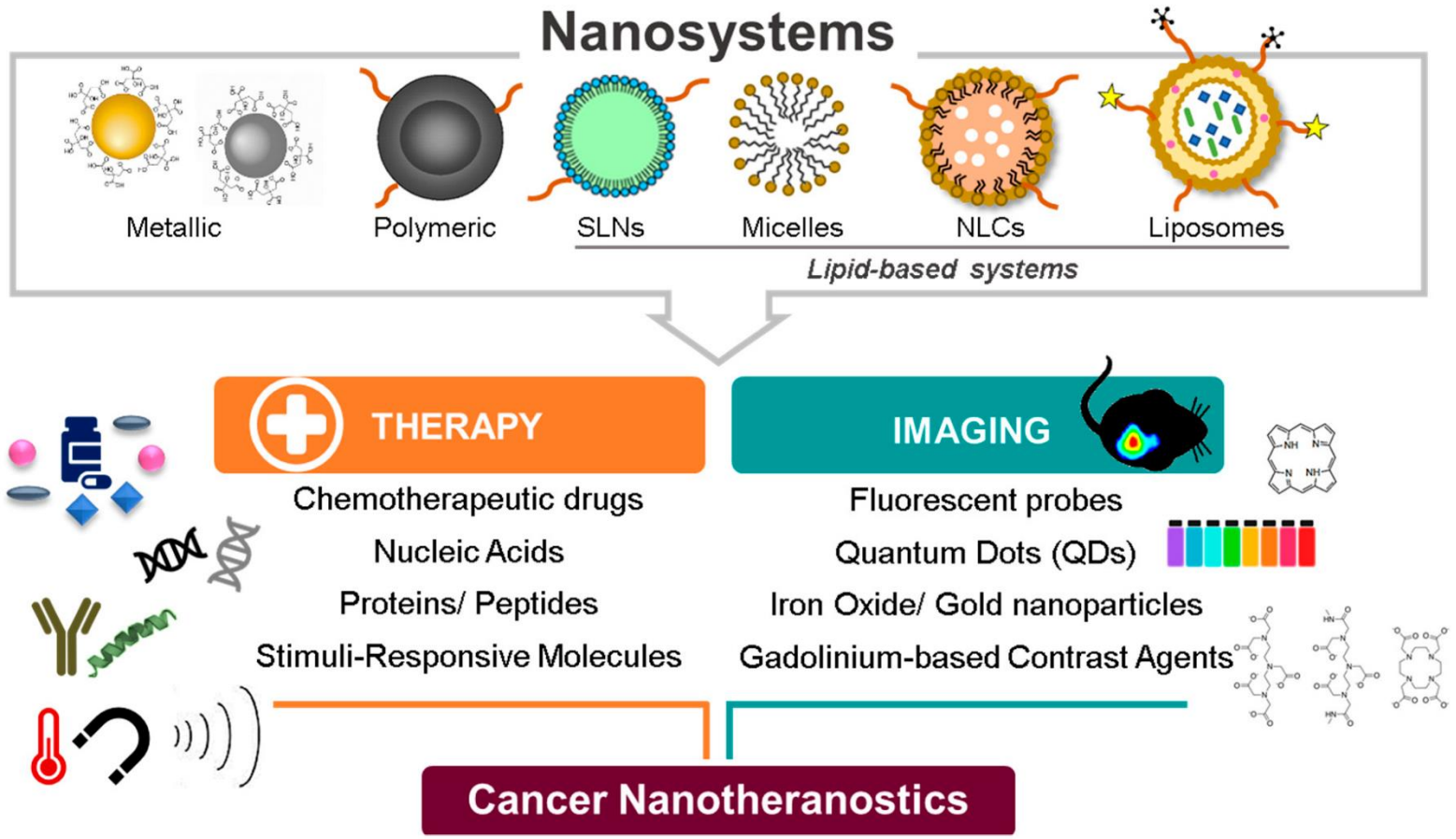
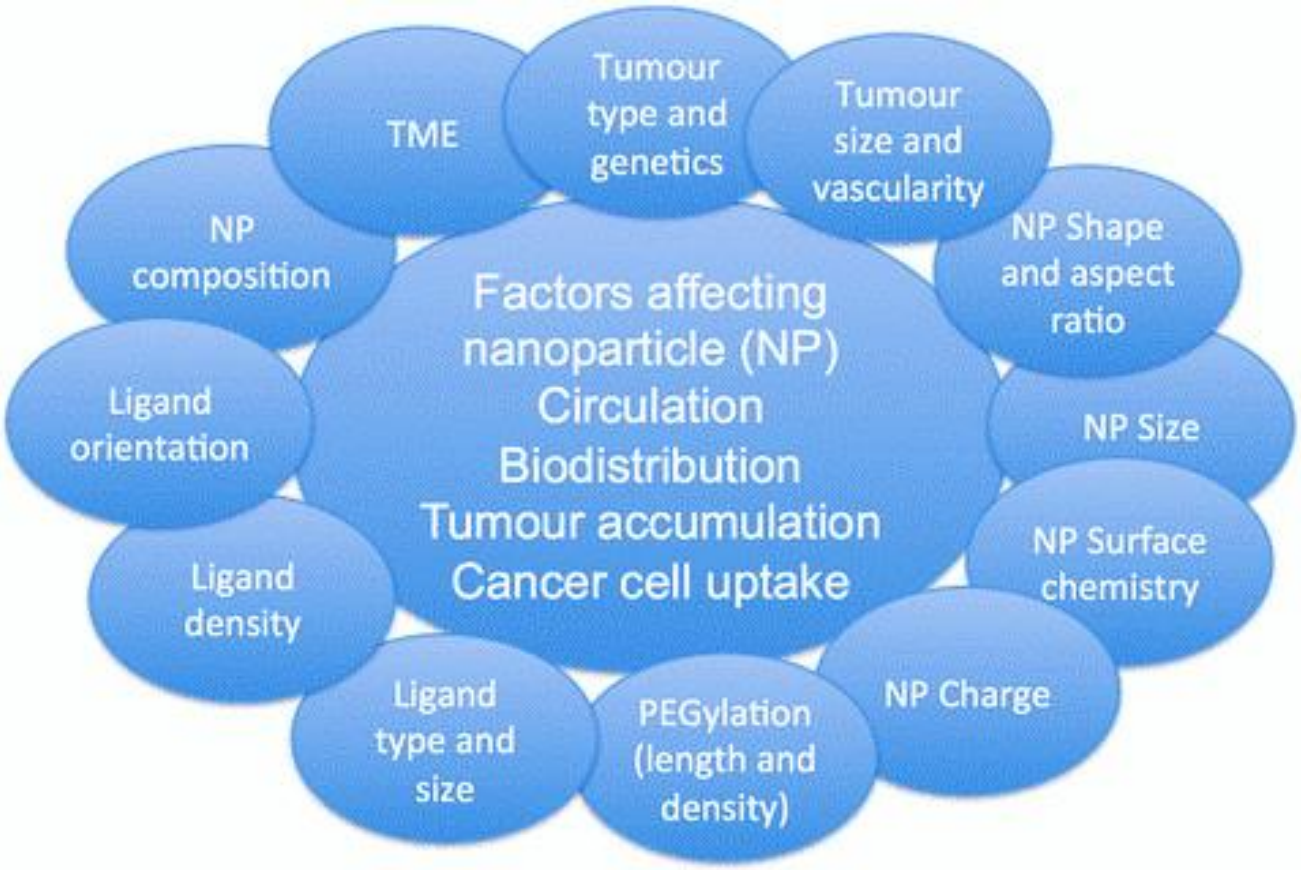
What is nanotheranostics?

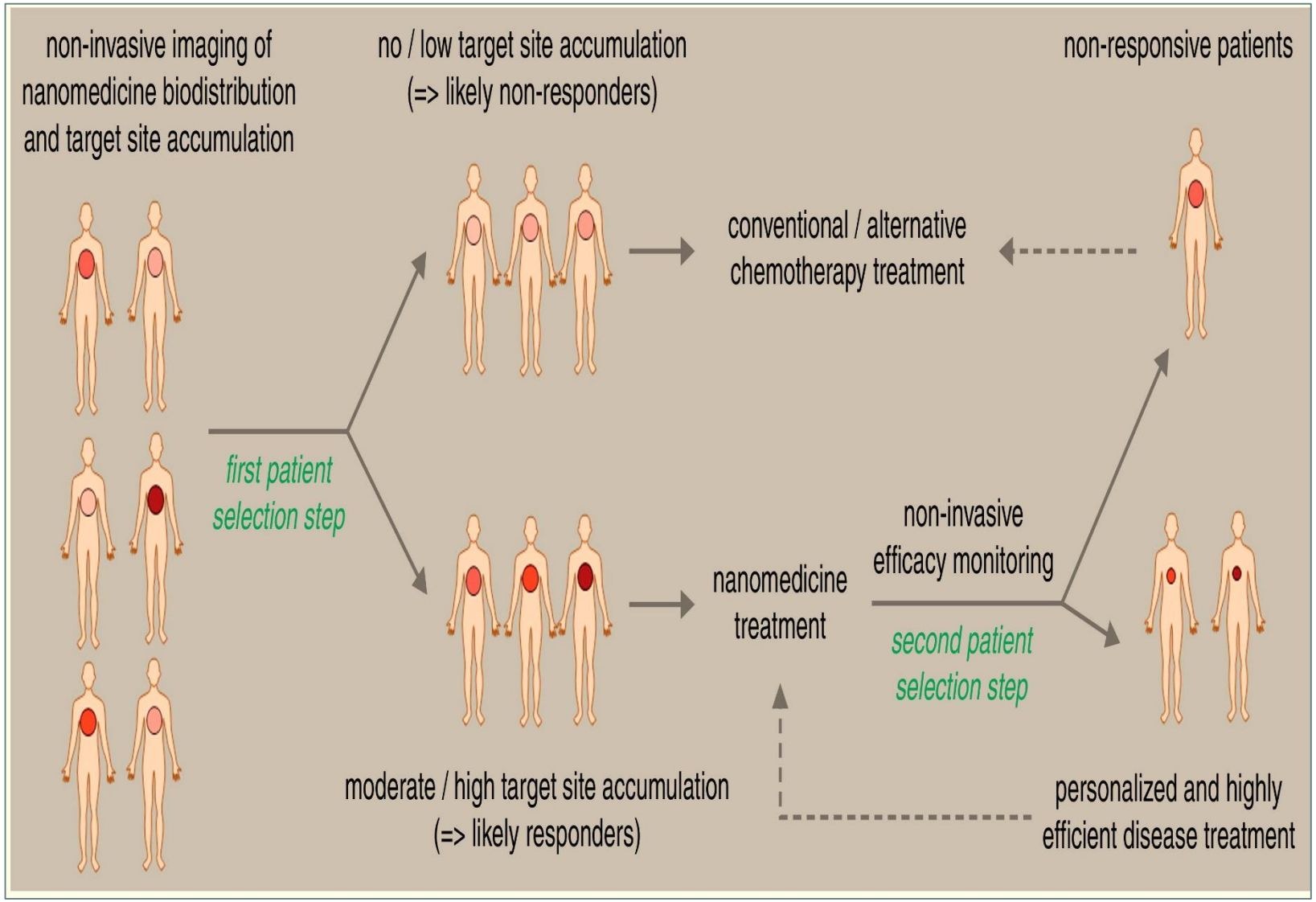
- Nanotheranostics contain both a drug and an imaging agent within a single formulation
- They provide real-time feedback on the drug delivery, drug release and drug efficacy

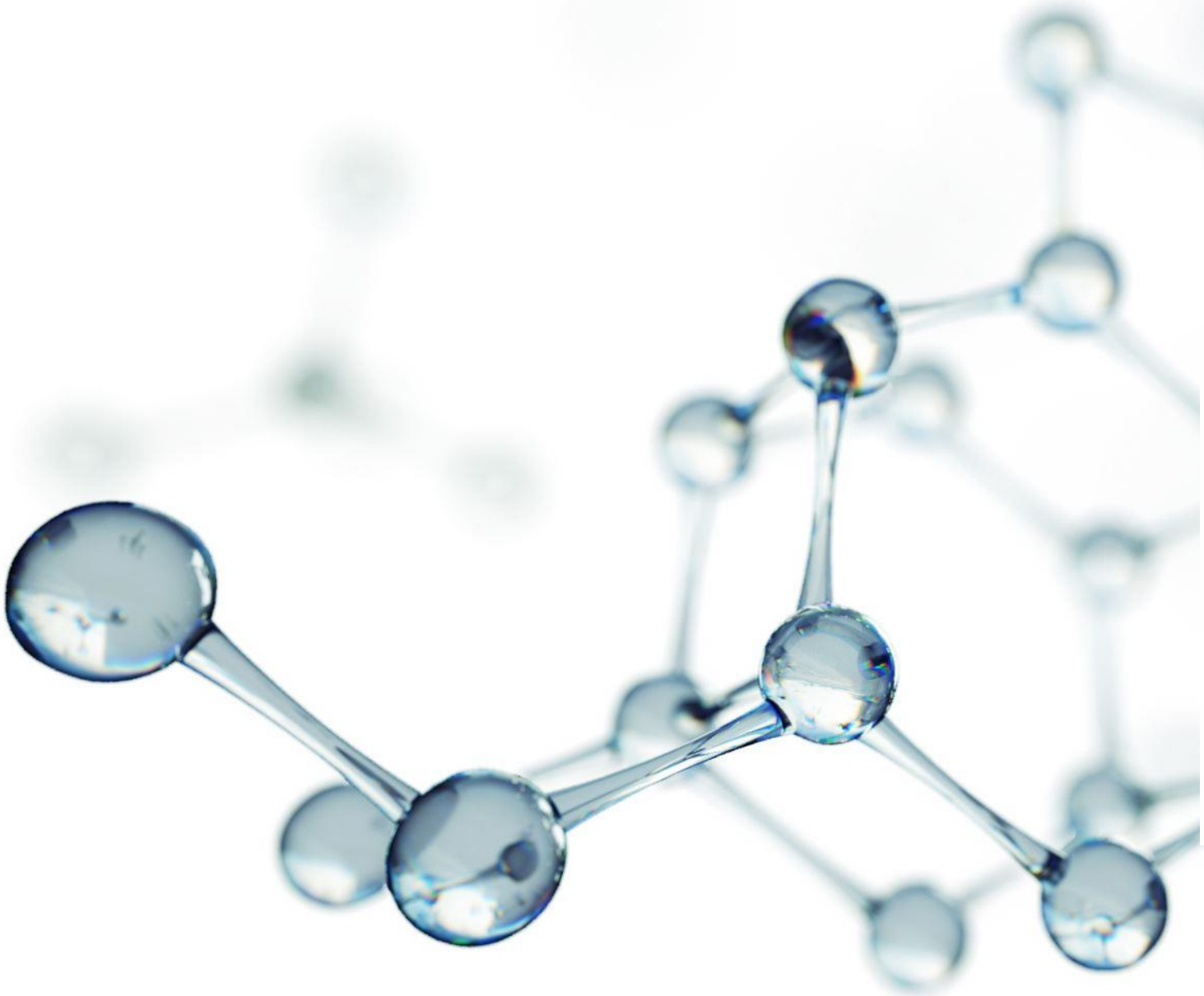


Nanotheranostics is used for validating and optimizing properties of drug delivery nanosystems in biological organisms



- Heterogeneous nature of cancer requires personalized approach in treatment
- Theranostics holds a great poterntial for personalized medicine.





NANOTHERANOSTIC OPTICAL IMAGING

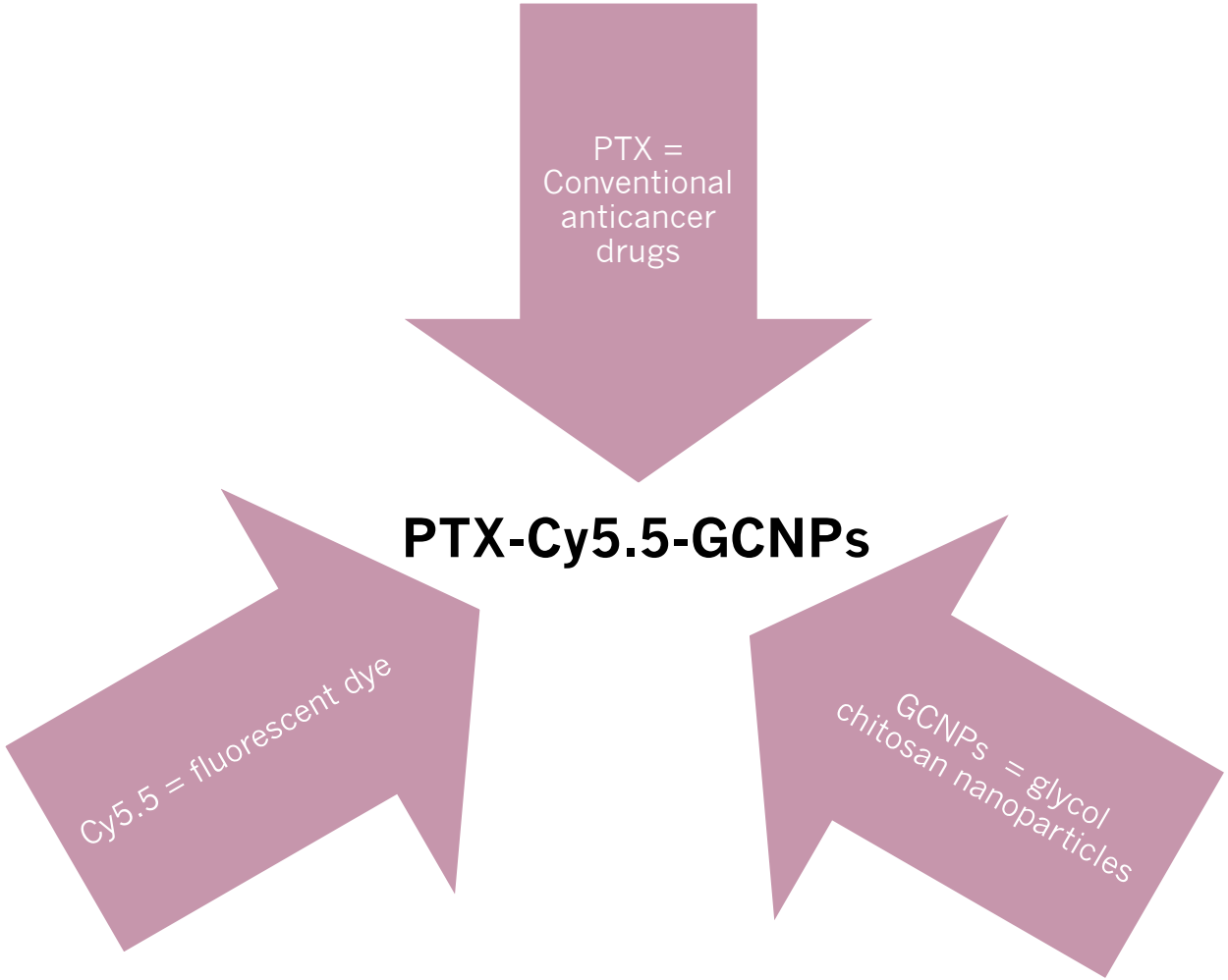
NANOTHERANOSTIC OPTICAL IMAGING

NIR(650-950 nm) Fluorescence Imaging.

NIR fluorescence dyes can be incorporated into nanoparticles.

enables non-invasive real-time measurements of biodistribution, drug pharmacokinetics and therapeutic responses against the disease.

OPTICAL IMAGING APPROACHES FOR MONITORING BIODISTRIBUTION



The tumor-homing characteristics of PTX-Cy5.5-GCNPs subsequently resulted in significant suppression of tumor growth (1,000 mm3 in treated mice vs. 8,400 mm3 in control mice), with significantly reduced levels of PTX toxicity in normal cells.

FLUORESCENCE RESONANCE ENERGY TRANSFER (FRET)

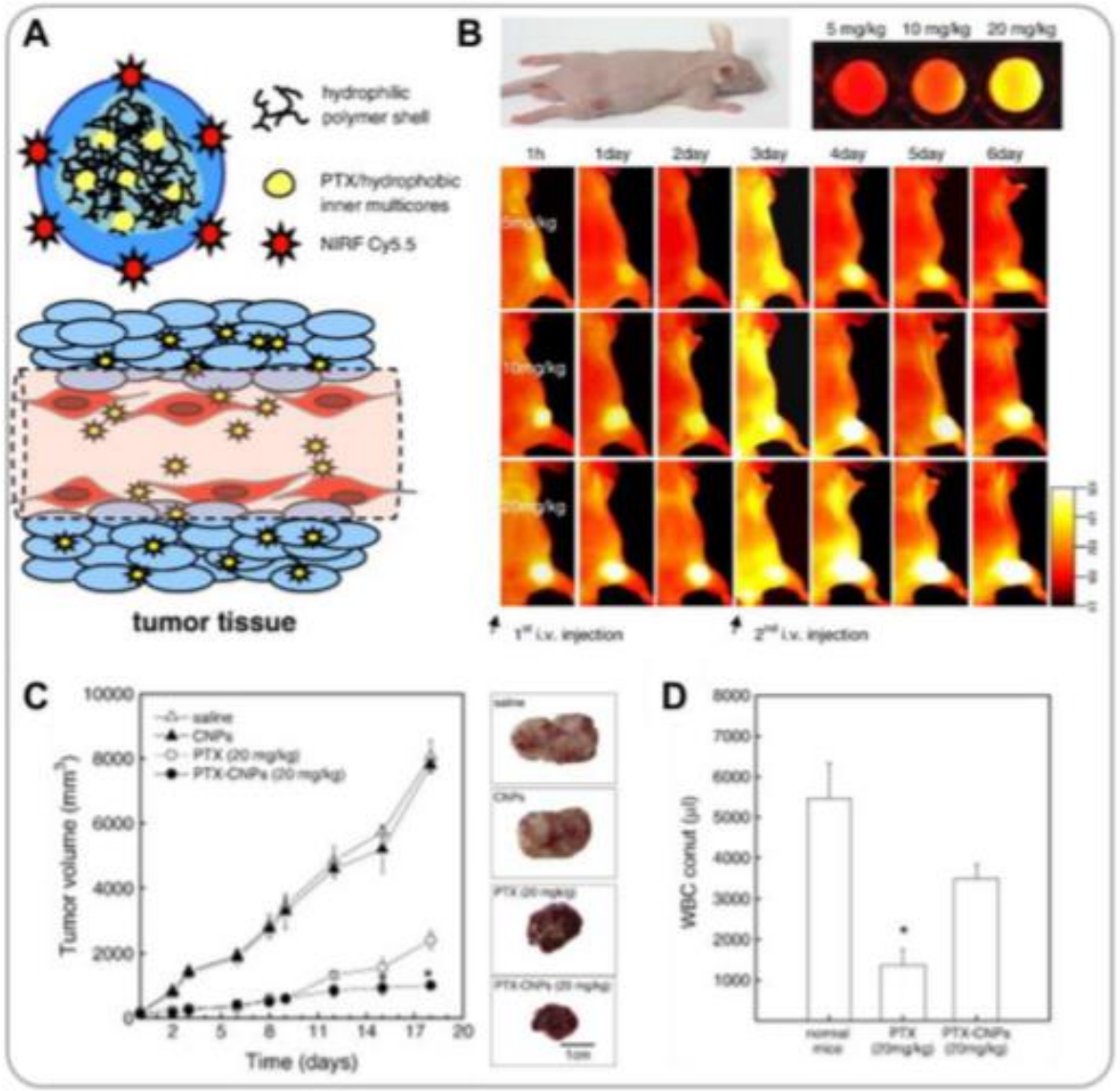


Figure 1. Glycol chitosan-based nanoparticles (GCNPs) for combining near infrared (NIR) fluorescence imaging and chemotherapy. (A) Schematic illustration of GCNPs labeled with Cy5.5 (for NIR optical imaging) containing physically loaded paclitaxel (PTX) (for chemotherapy) (PTX-Cy5.5-GCNP). (B) NIR images of tumor-bearing mice taken after i.v. injection of PTX-Cy5.5-GCNPs at different concentrations. (C) Tumor growth curves, and representative images of excised tumor tissues after repeated injections of saline, glycol chitosan nanoparticles, free PTX, and PTX-Cy5.5-GCNPs. (D) Acute toxicities of free PTX and

OPTICAL IMAGING APPROACHES FOR VISUALIZING OF DRUG RELEASE

fluorescence resonance energy transfer (FRET)

redox-responsive DOX release from mesoporous silica nanoparticles (MSNPs)

REDOX-RESPONSIVE DOX RELEASE FROM MESOPOROUS SILICA NANOPARTICLES (MSNPS)

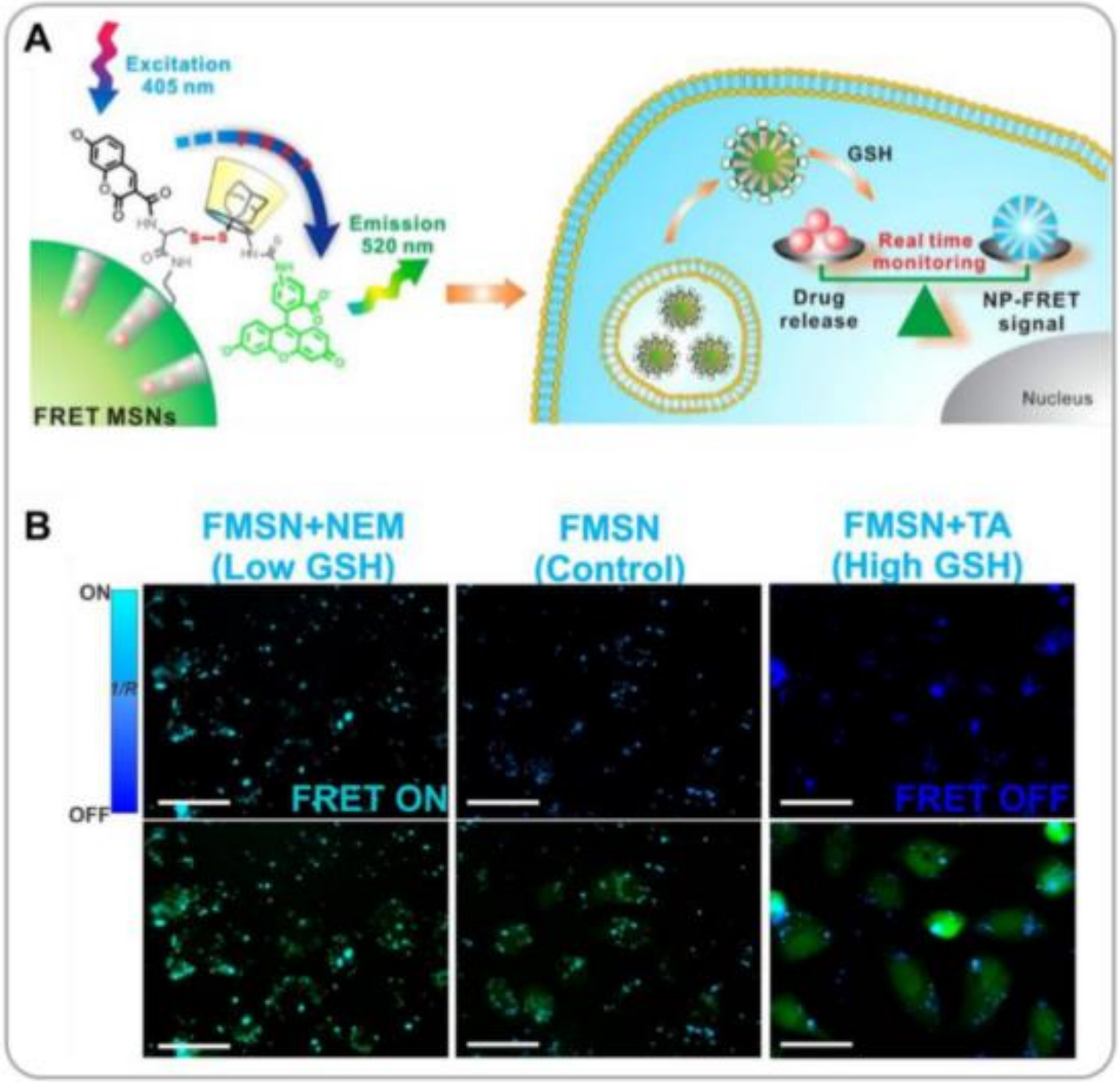


Figure 2. Mesoporous silica nanoparticles (MSNPs) for FRET-based drug release monitoring. (A) Schematic description of redox-responsisve drug release and FRET detection mechanisms. (B) Representative fluorescence images of MSNP-treated cancer cells with different glutathione concentrations, taken under FRET (λ_{ex} = 405 nm) and FITC (λ_{ex} = 488 nm) channels. Reproduced with permission from reference [26].

OPTICAL IMAGING APPROACHES FOR MEASURING THERAPEUTIC EFFICACY

A TUMOR'S RESPONSE TO CHEMOTHERAPY CAN BE MONITORED BY OPTICAL IMAGING METHODS.

1) MEASUREMENT INCLUDE THE DETECTION OF CHANGES IN THE COMPOSITION OF THE PLASMA CELL MEMBRANE

2) THE DETECTION OF OVEREXPRESSION OF CERTAIN ENZYMES DURING THE CELL DEATH PERIOD

MEASUREMENT INCLUDE THE DETECTION OF CHANGES IN THE COMPOSITION OF THE PLASMA CELL MEMBRANE

Phosphatidylserine (PS)

Annexin V-functionalized core-crosslinked polymeric micelles (A5-CCPMs) loaded with two types of imaging probes, Cy7 for NIR fluorescence imaging and 111In for SPECT/CT imaging .

confirms the apoptotic effect of the drugs in lymphoma xenografts.

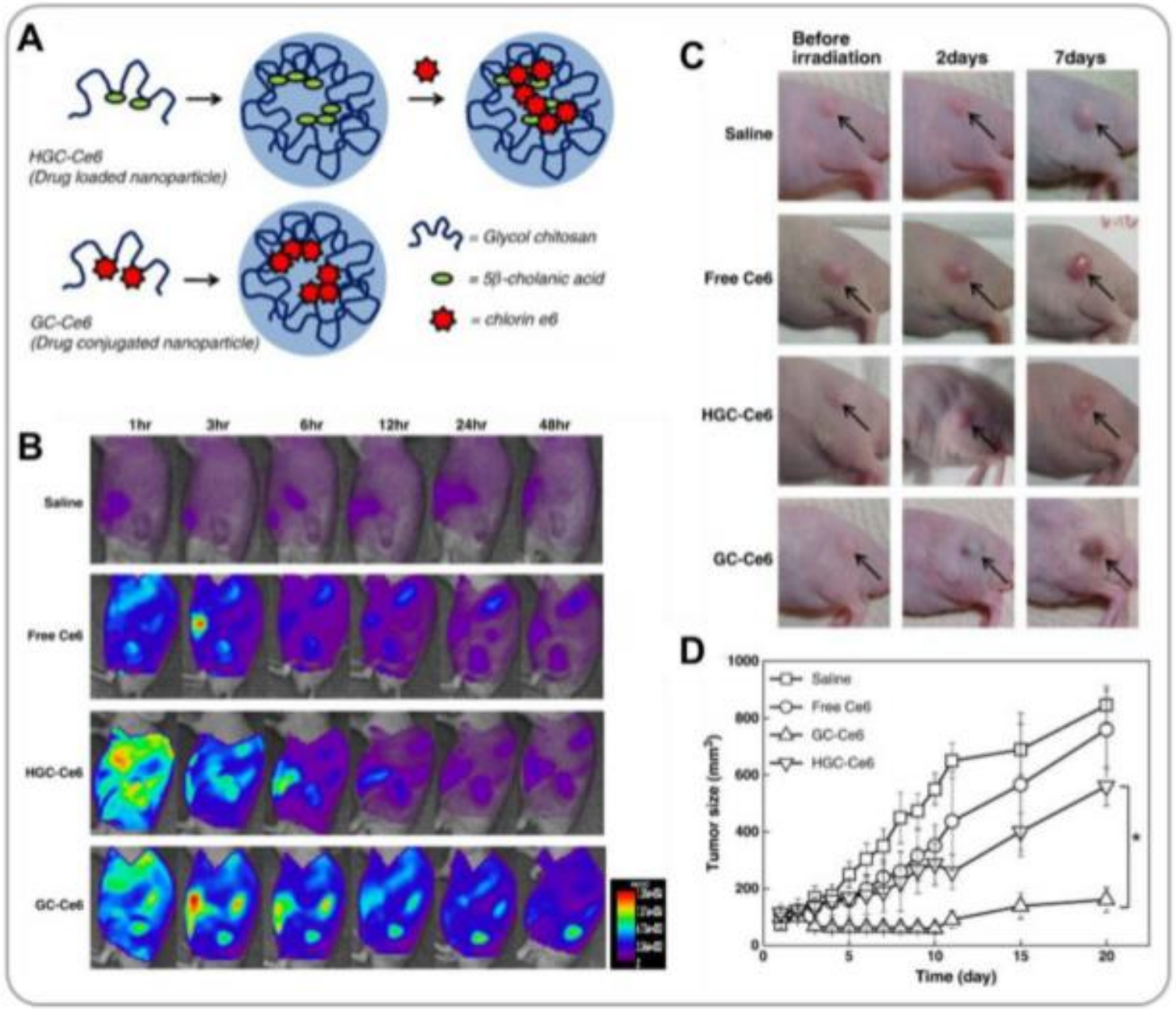
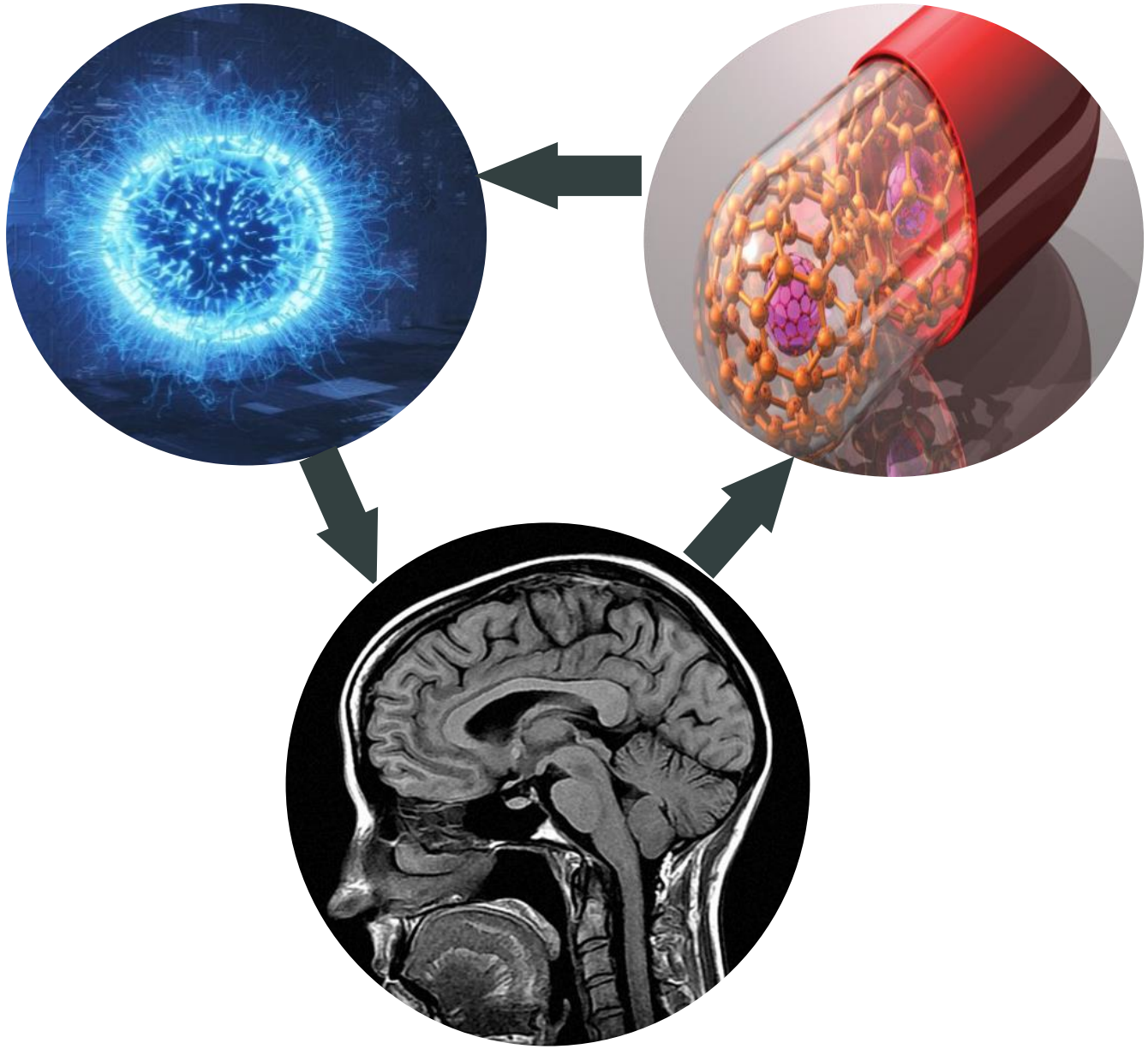


Figure 3. GCNPs for photodynamic therapy (PDT). (A) Schematic illustration of GCNPs containing physically encapsulated or chemically conjugated photosensizers. (B) Time series NIR images of tumor-bearing mice after i.v. injection of GCNPs. (C) Representative images of tumors, and tumor growth curves treatments with saline, free Ce6, GCNPs containing physically entrapped Ce6, and Ce6-conjugated GCNPs. Reproduced with permission from reference [36].

SIMULTANEOUS OPTICAL IMAGING AND PHOTODYNAMIC THERAPY

NANOTHERANOSTIC MAGNETIC RESONANCE IMAGING



What is MRI?

- Magnetic resonance imaging is a non-invasive imaging technique
- In order to obtain a cross-sectional image of a tissue,it uses strong magnetic fields and radio waves
- Advantages are:

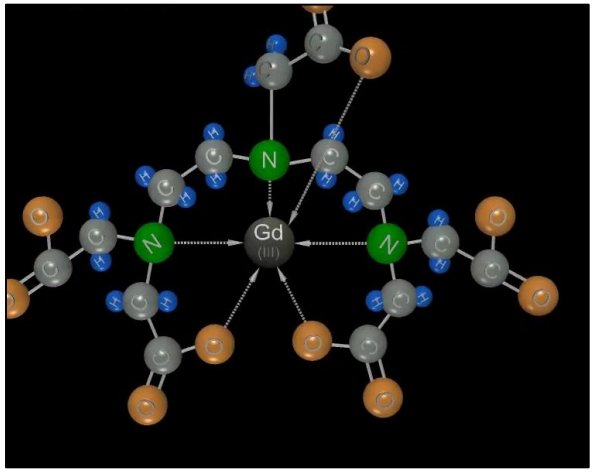
1.Usage of non-ionizing radiation

2.High spatial resolution

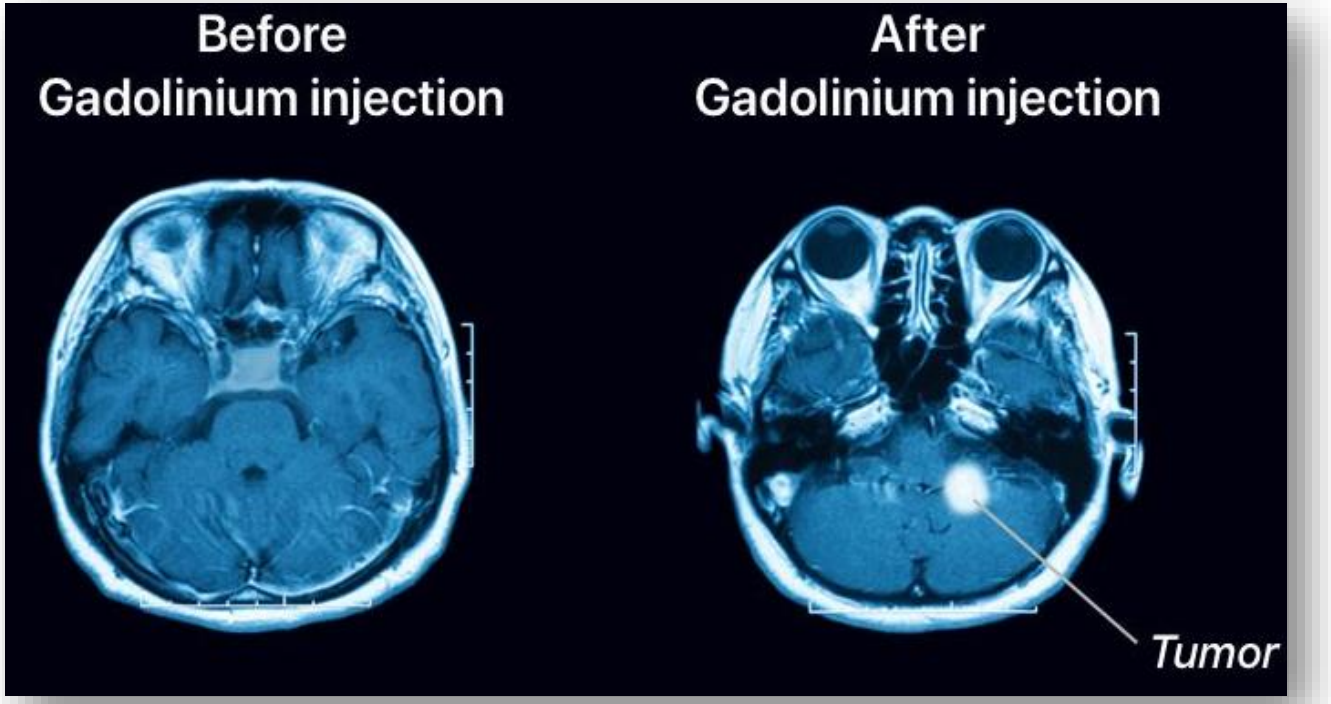
3.Deep tissue penetration

MRI contrast agents

- Low sensitivity of MRI images can be improved by using contrast agents
- The most widely used contrast enhancing agents are chelated gadolinium and magnetic nanoparticles(MNPs,such as iron oxide)
- Gadolinium is used as T1 contrast agents

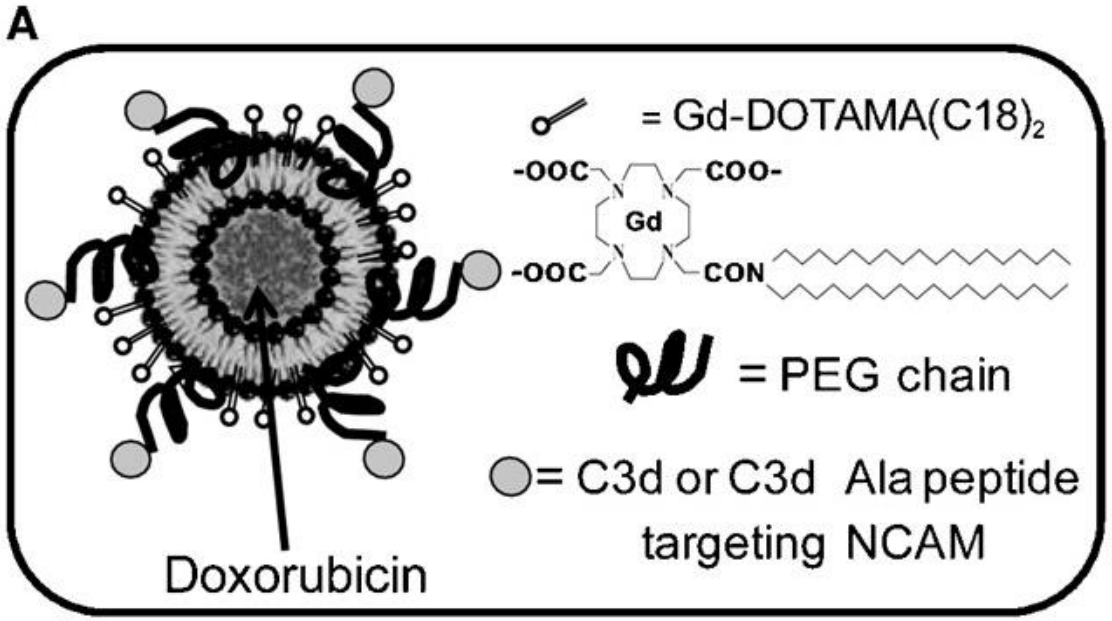


Chelated gadolinium



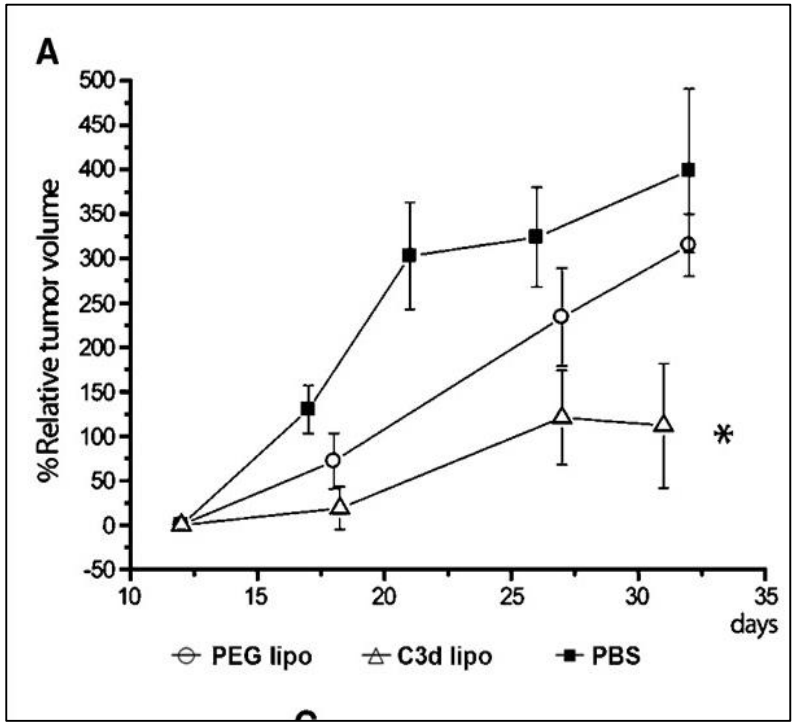
Gadolinium-based theranostic agents

- The PEG-coated liposomes were functionalized with the neural cell adhesion molecule (NCAM)-binding peptide (C3d) for targeting NCAM-positive Kaposi's sarcoma cells.
- The C3d-functionalized PEGylated liposomes were loaded with Gd(Gadolinium) and DOX (Doxorubicin).Will be called C3D-lipo afterwards.

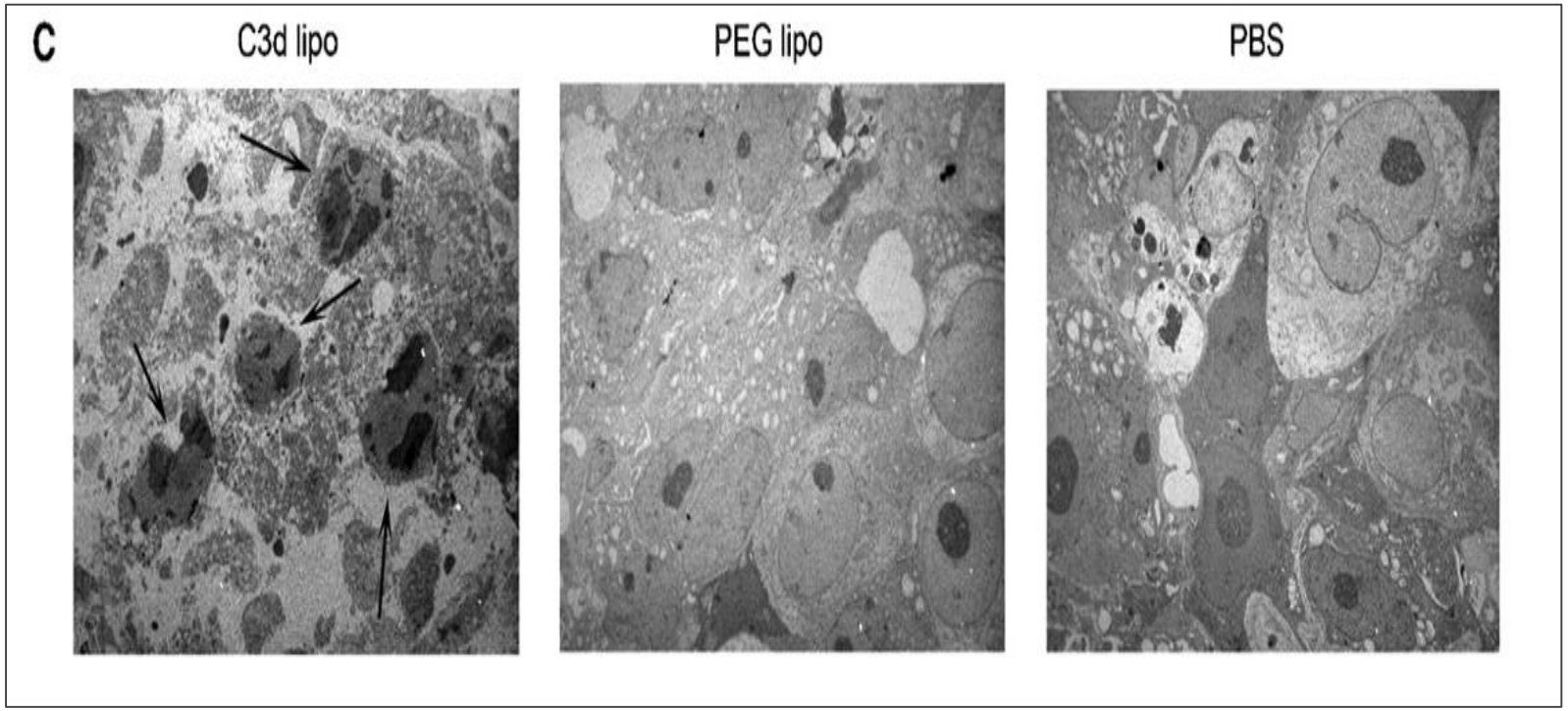


A. schematic representation of liposomes loaded with both doxorubicin and the lipophilic Gd-DOTAMA(C18)2 MRI contrast agent.

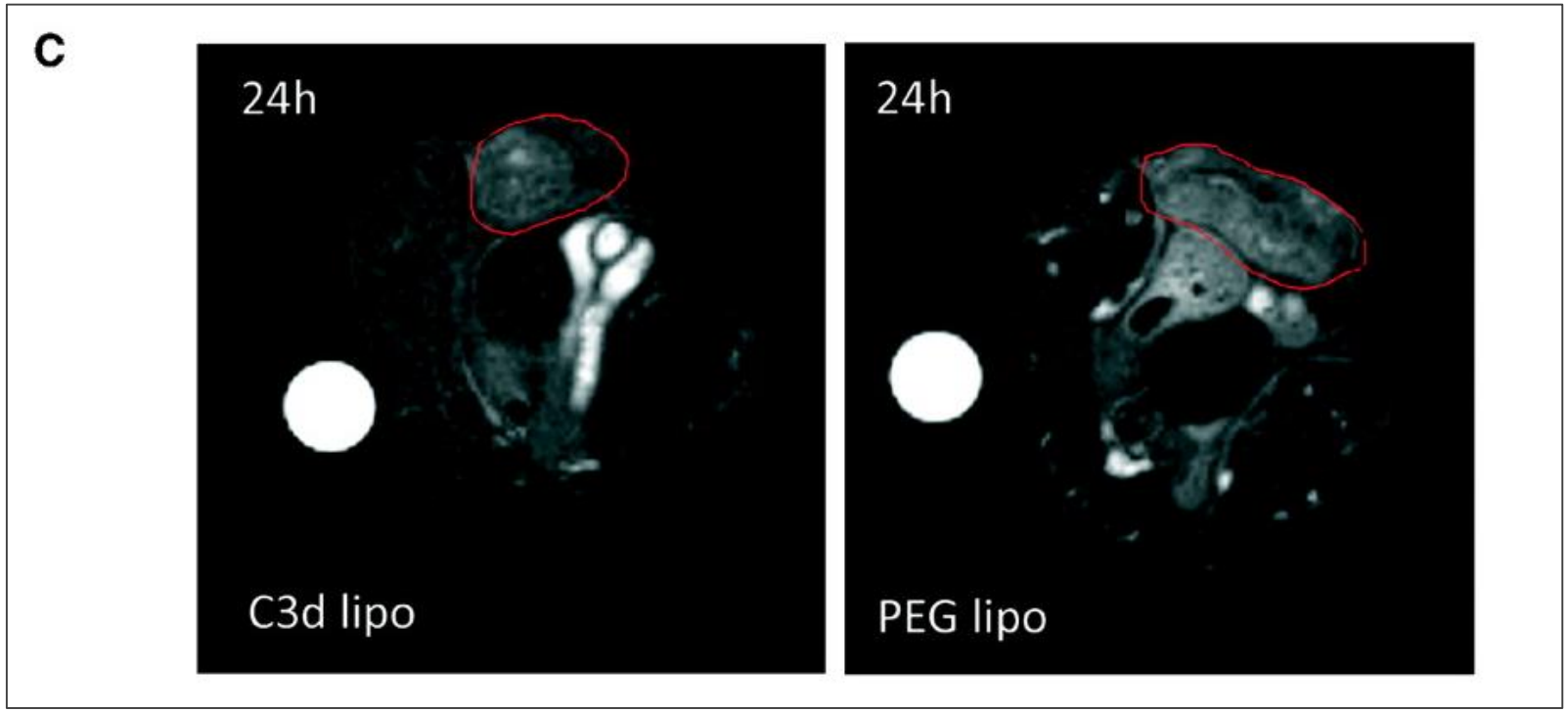
Results



A.C3d lipo induced a significant reduction of tumor volume compared with PEG lipo or PBS alone, measured weekly by MRI



C.Representative micrographs showing transmission electron microscopy of Kaposi's sarcomas developed in SCID mice treated with C3d lipo, PEG lipo, or PBS.



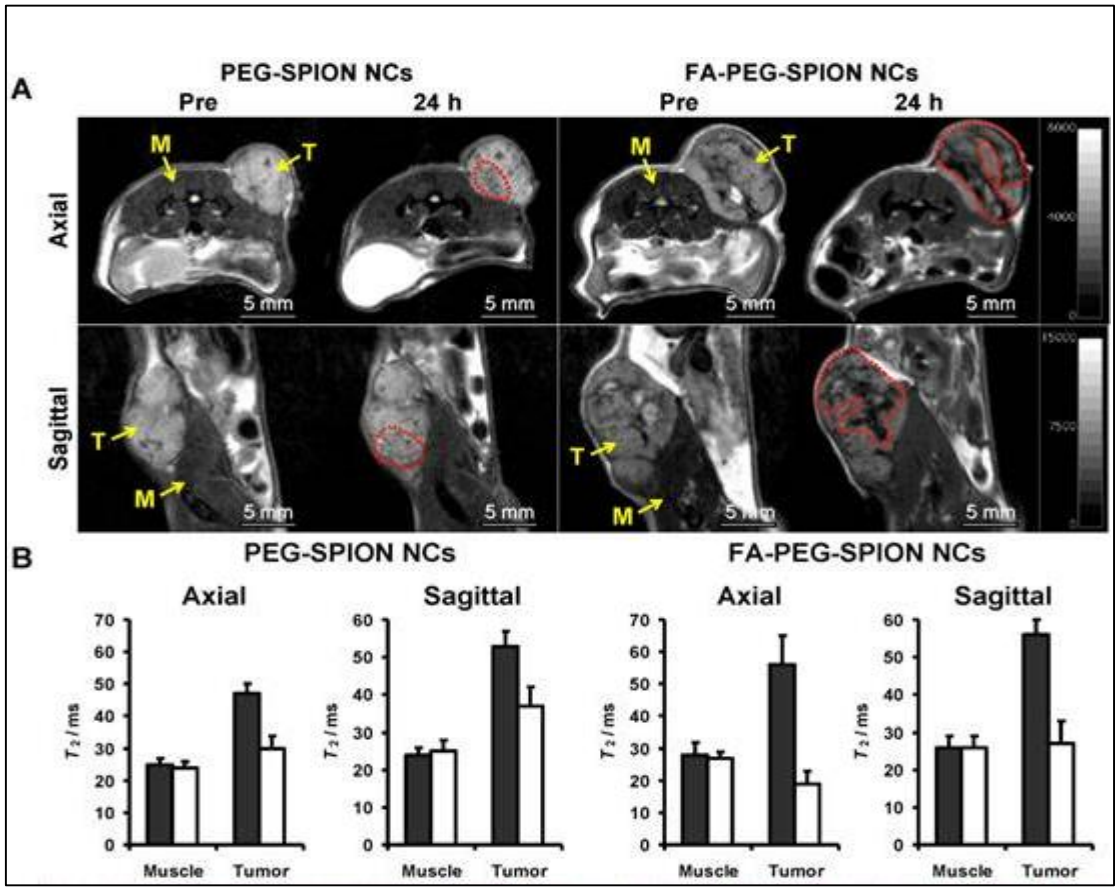
C.Representative T_1-weighted MRI of Kaposi's sarcomas acquired 24 h after the administration of C3d lipo and PEG lipo at a DOX dose of 5 mg/kg

Magnetic nanoparticle-based theranostic agents

SPIONS(superparamagnetic iron oxide nanoparticles)

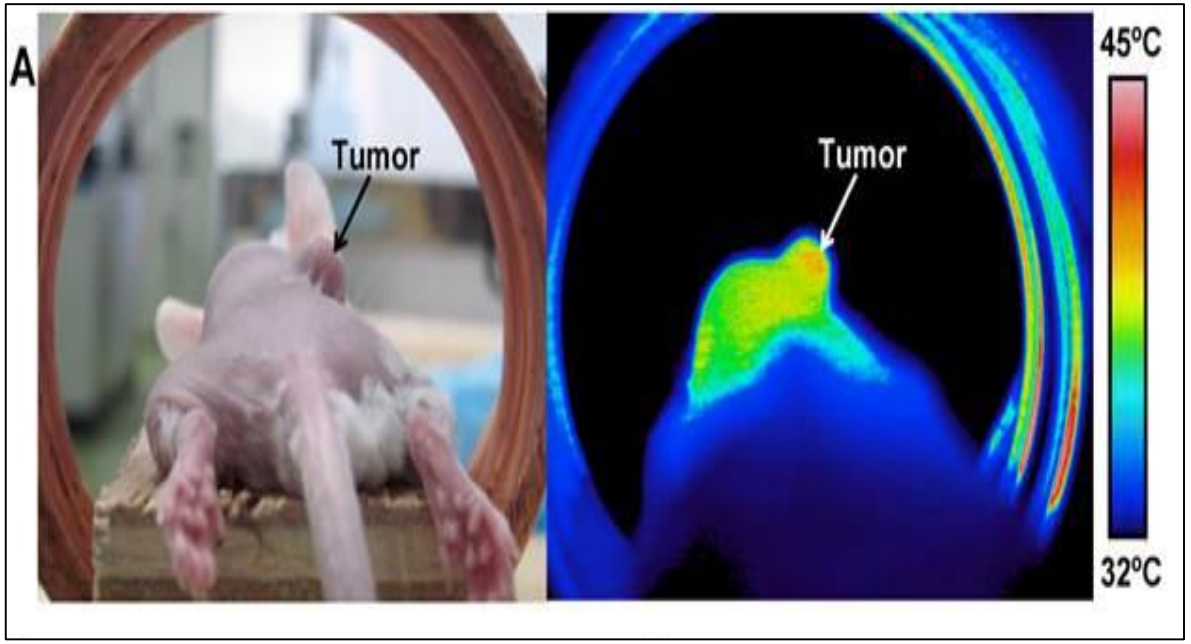
- Can be visualized by MRI
- Can be heated to provide hyperthermia for cancer therapy
- Are degraded into nontoxic iron ions in vivo.
- Guided to target sites by external magnetic field

Example of combination of MRI imaging with hyperthermia for multiple myeloma treatment

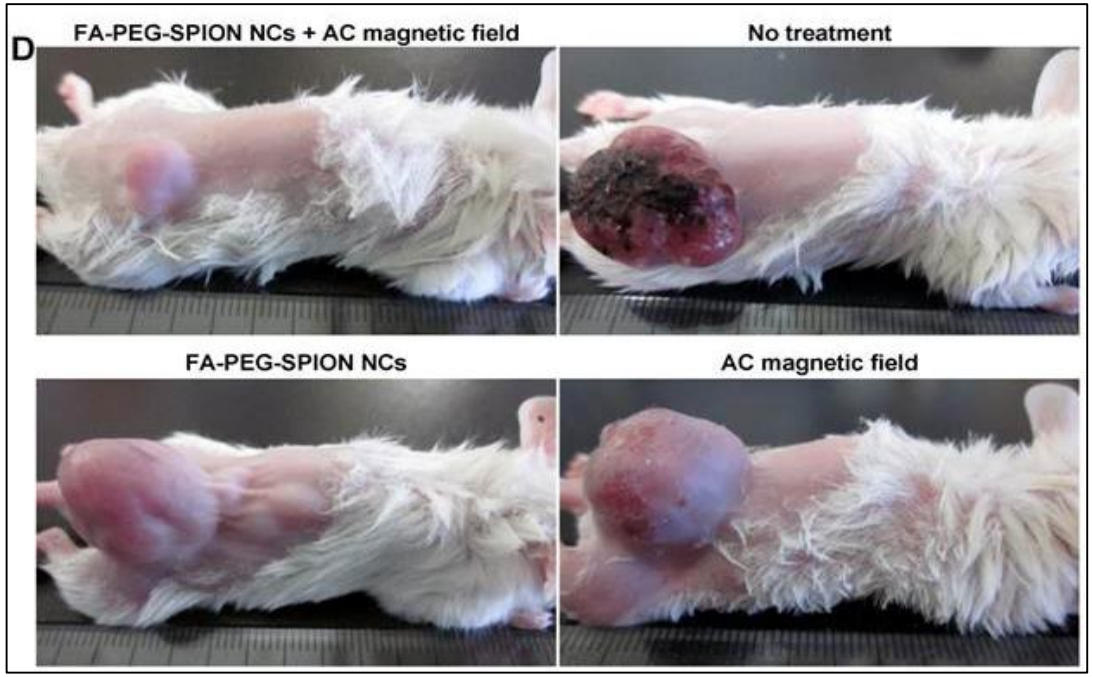


A) *In vivo* T_2 axial and sagittal maps of mice before and 24 h after intravenous injection of PEG-SPION NCs and FA-PEG-SPION NCs: M and T indicate muscle and tumor, respectively. (B) Changes in T_2 values in the tumors and muscles of mice before and 24 h after intravenous injection of PEG-SPION NCs and FA-PEG-SPION NCs

Application of AC magnetic field and hyperthermia effect



A.Photograph (left) and thermal image (right) of a mouse 24 h after intravenous injection of FA-PEG-SPION NCs under an AC magnetic field with f = 230 kHz



(D) Photographs of mice 35 days after treatment.

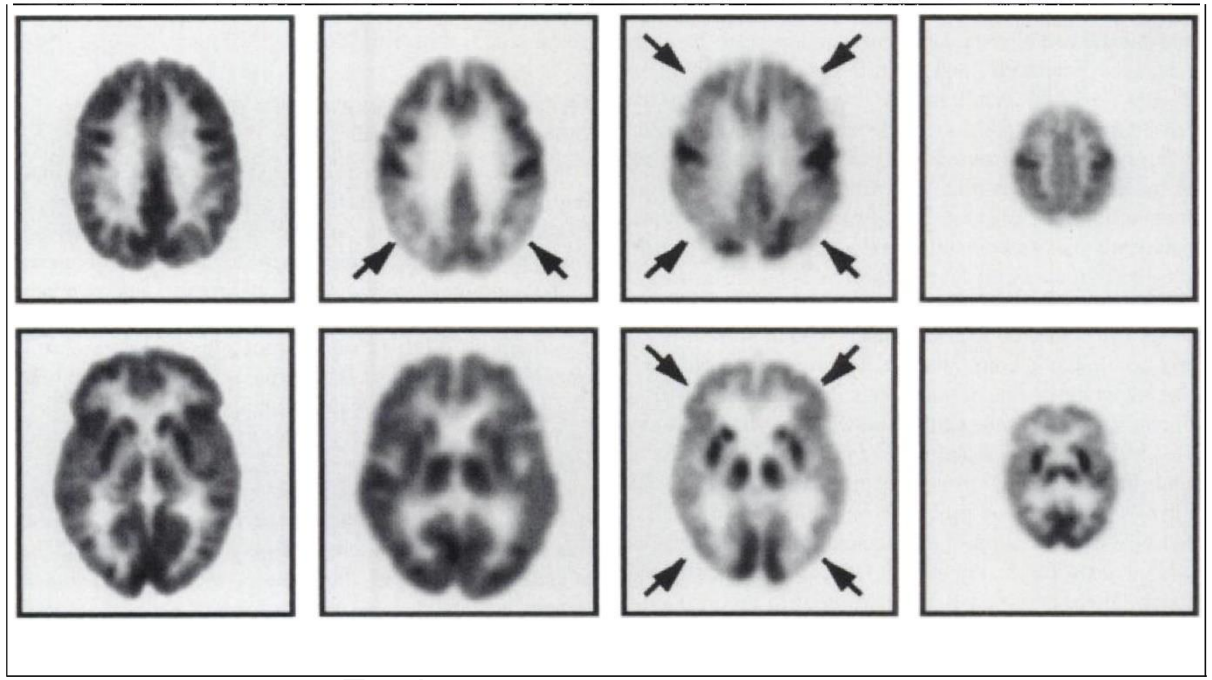
PET SCAN

- Positron emission tomography (PET) scans are used to produce detailed 3-dimensional images of the inside of the body.
- They are used most often to detect cancer, heart problems, brain disorders and other central nervous system disorders.

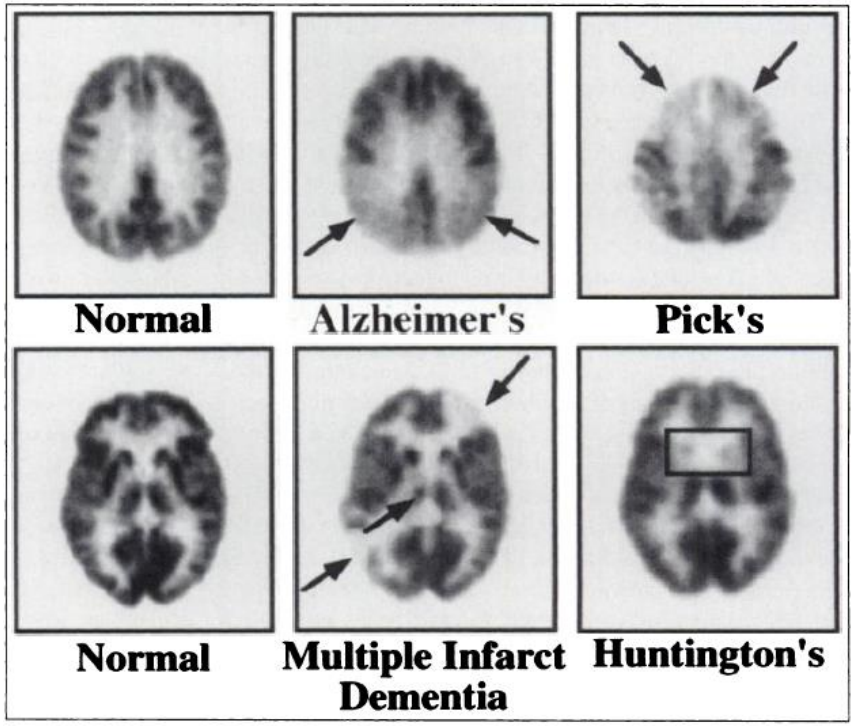
A PET SCAN CAN:

- Measure vital functions
- Detect tumor cells
- Evaluate how well a patient's treatment plan is working, allowing the care to be adjusted, if necessary.

IMPORTANCE OF PET IN THE DEVELOPMENT AND ASSESSMENT OF THERAPIES FOR DEMENTIA



Normal | Early Alzheimer's | Late Alzheimer's | Child

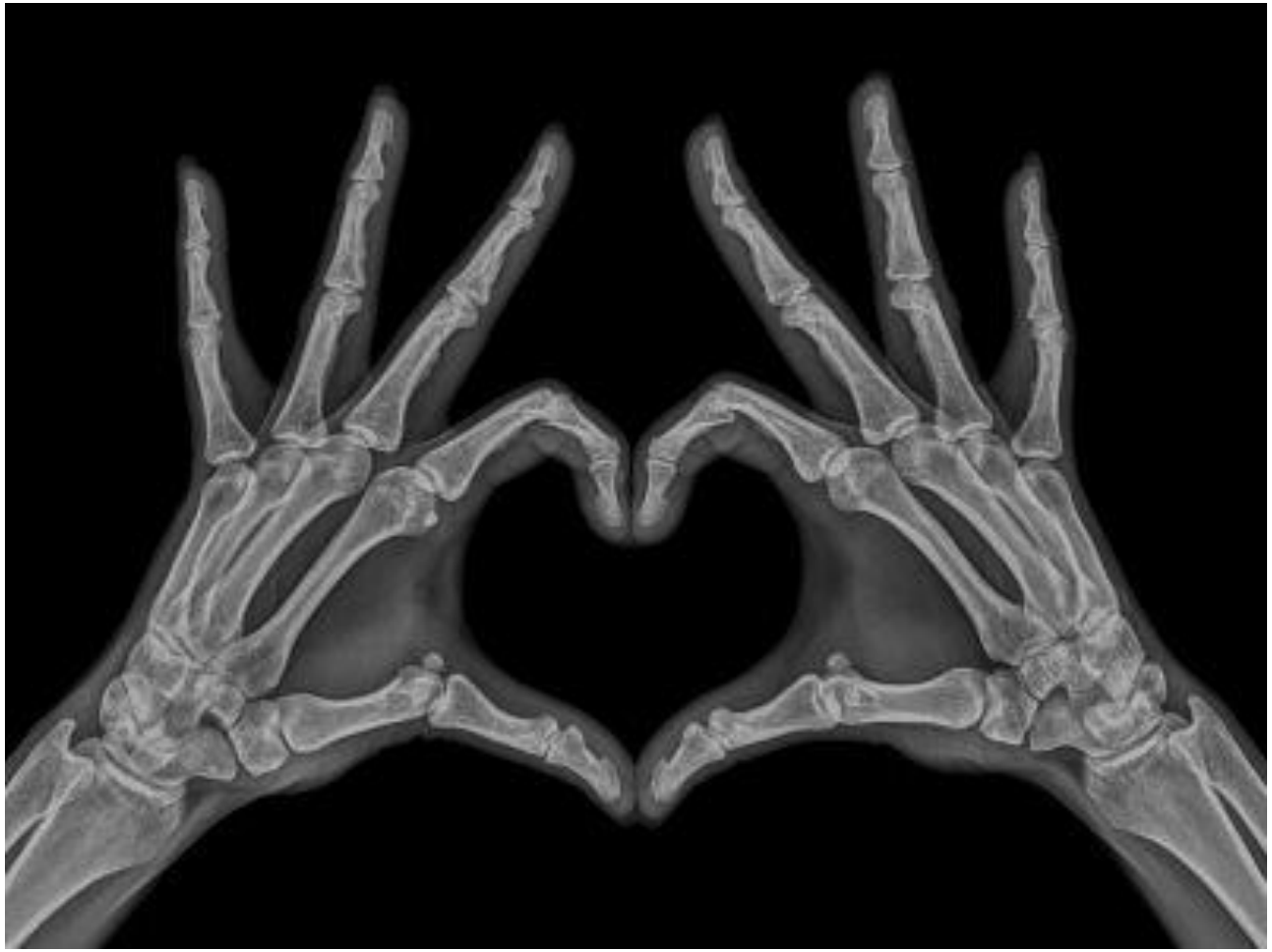


X-RAYS

- A quick, painless test
- Called electromagnetic waves
- It shows the parts of your body in different shades of black and white.

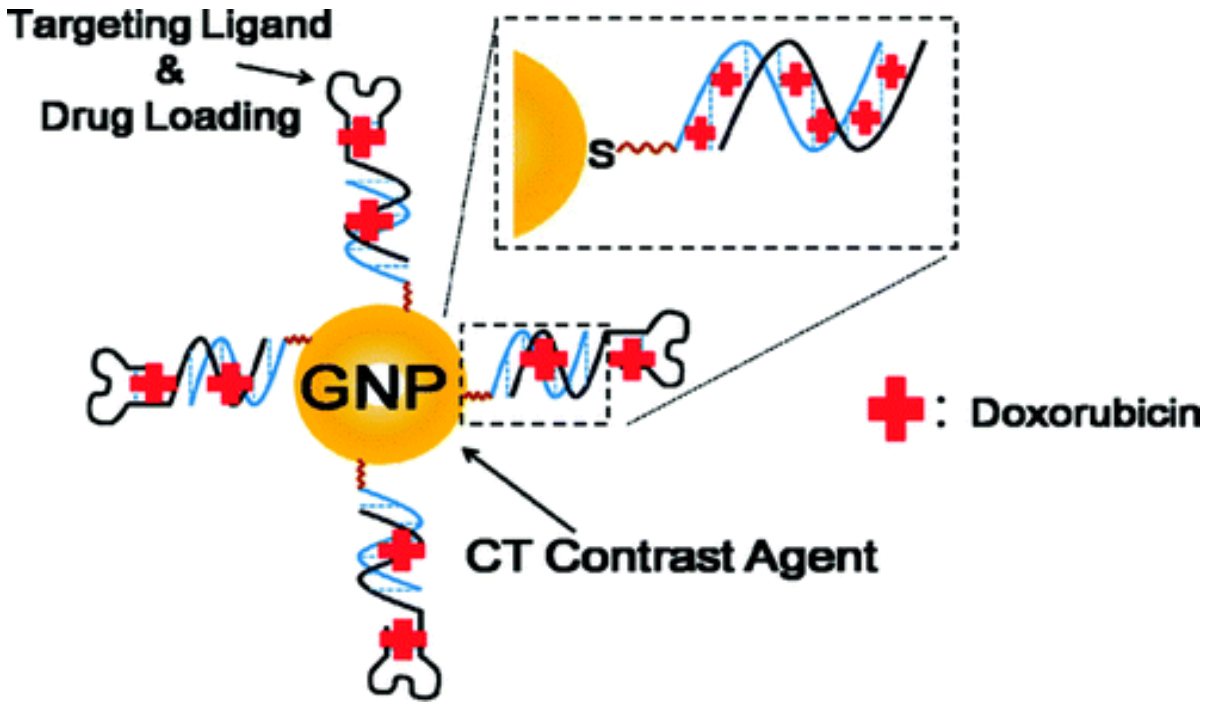
WHY IT'S DONE?

- Bones and teeth
- Chest
- Abdomen



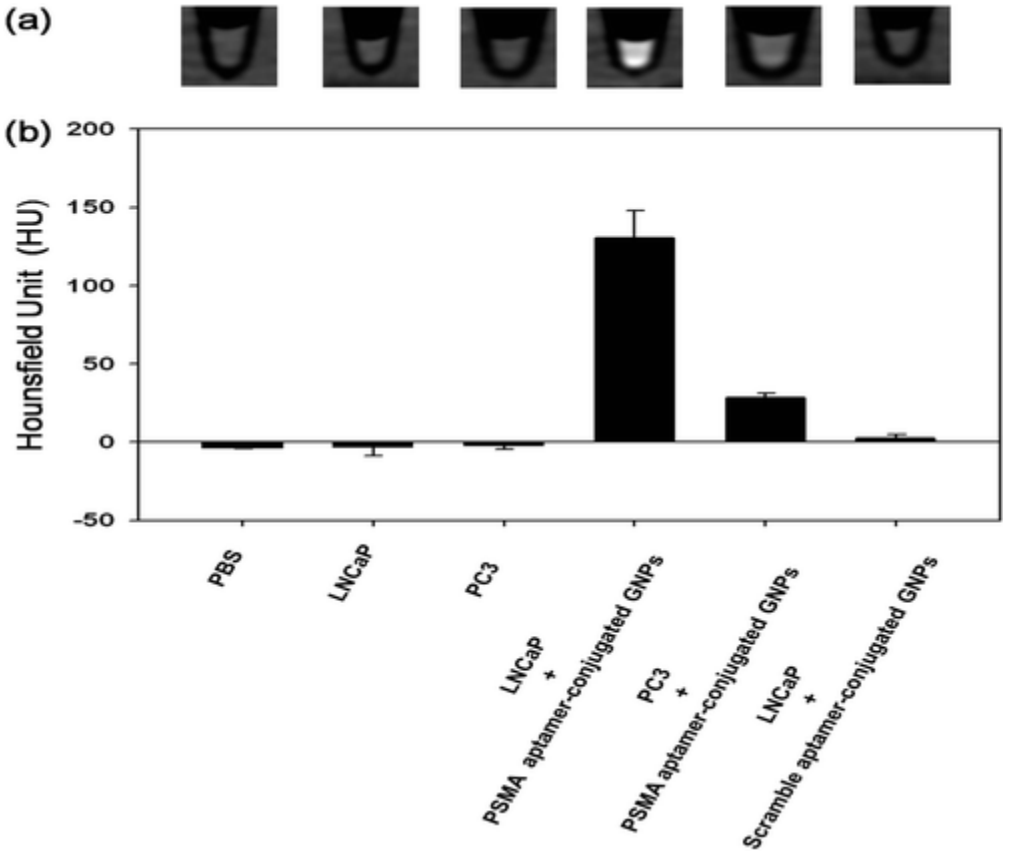
GOLDEN NANOPARTICLES

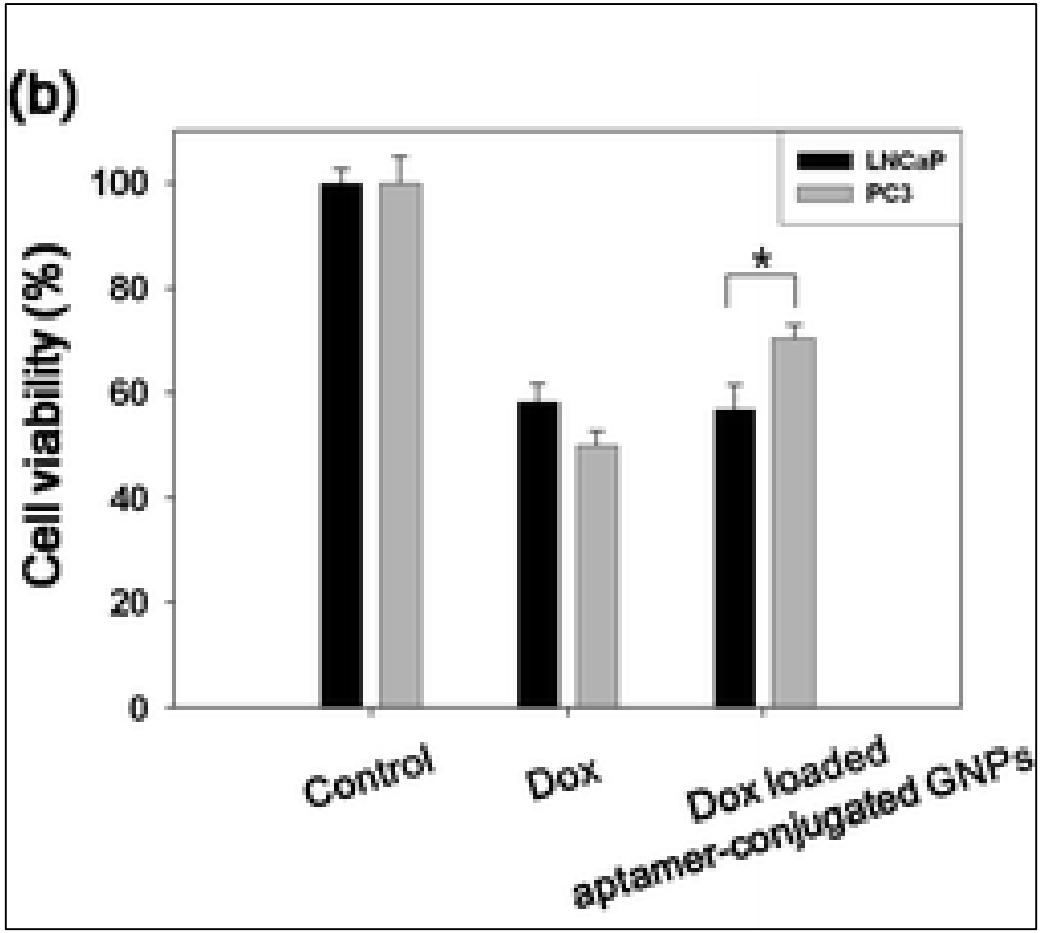
- **Golden nanoparticles can be used to enhance contrast in X-ray images.**
- **nanosystem had both prostate cancer cell binding domain, imaging domain made of Golden nanoparticles and DOX which was able to kill cancer cells.**



TESTING

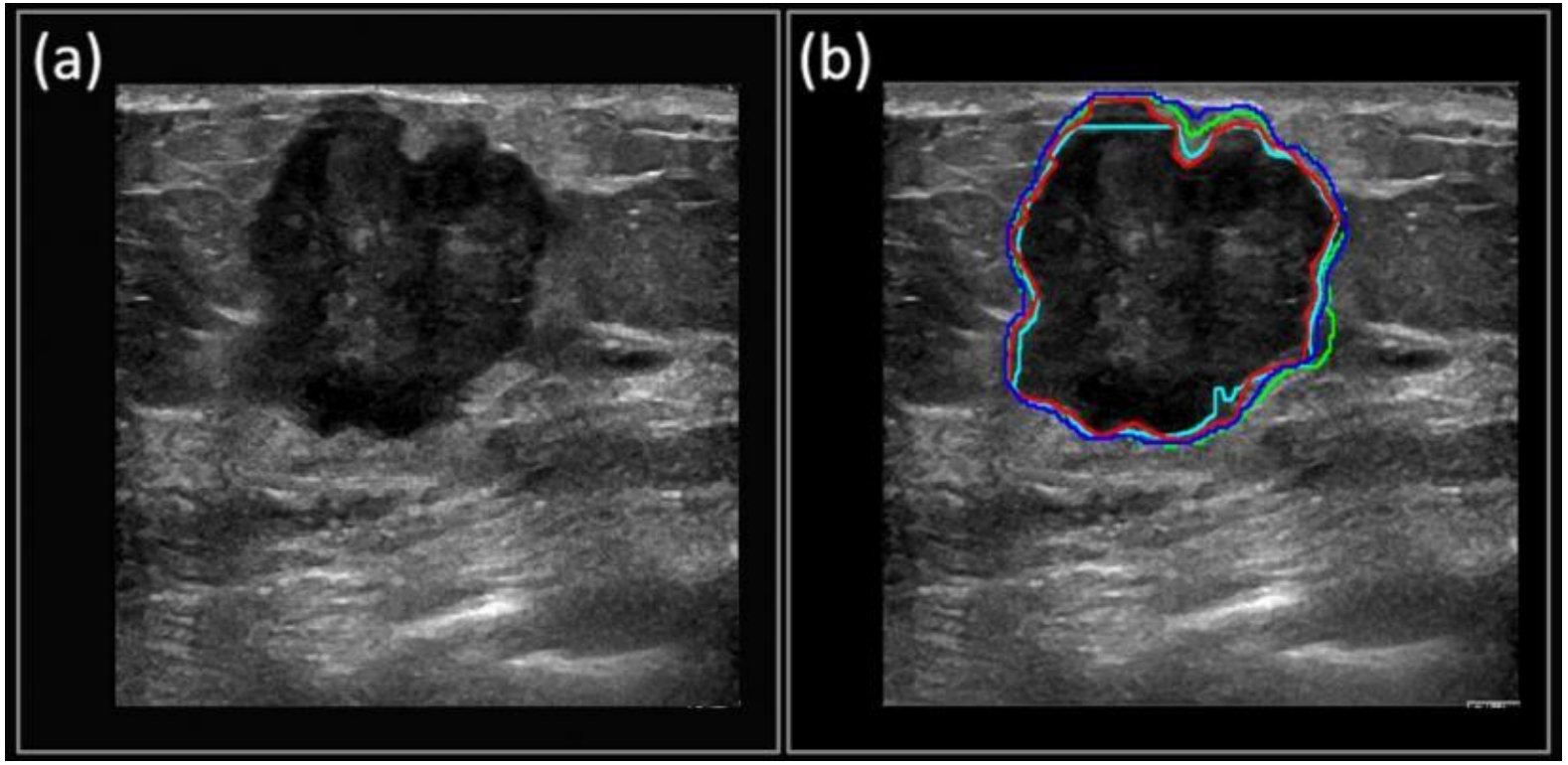
They tested this nanosystem in two types of cancer cells, one expressing that PSMA antigen and the second non-experssing, called pc3.




(b)
Cell viability (%)
100
80
60
40
20
0
LNCaP
PC3
*
Control
Dox
Dox loaded
aptamer-conjugated GNPs

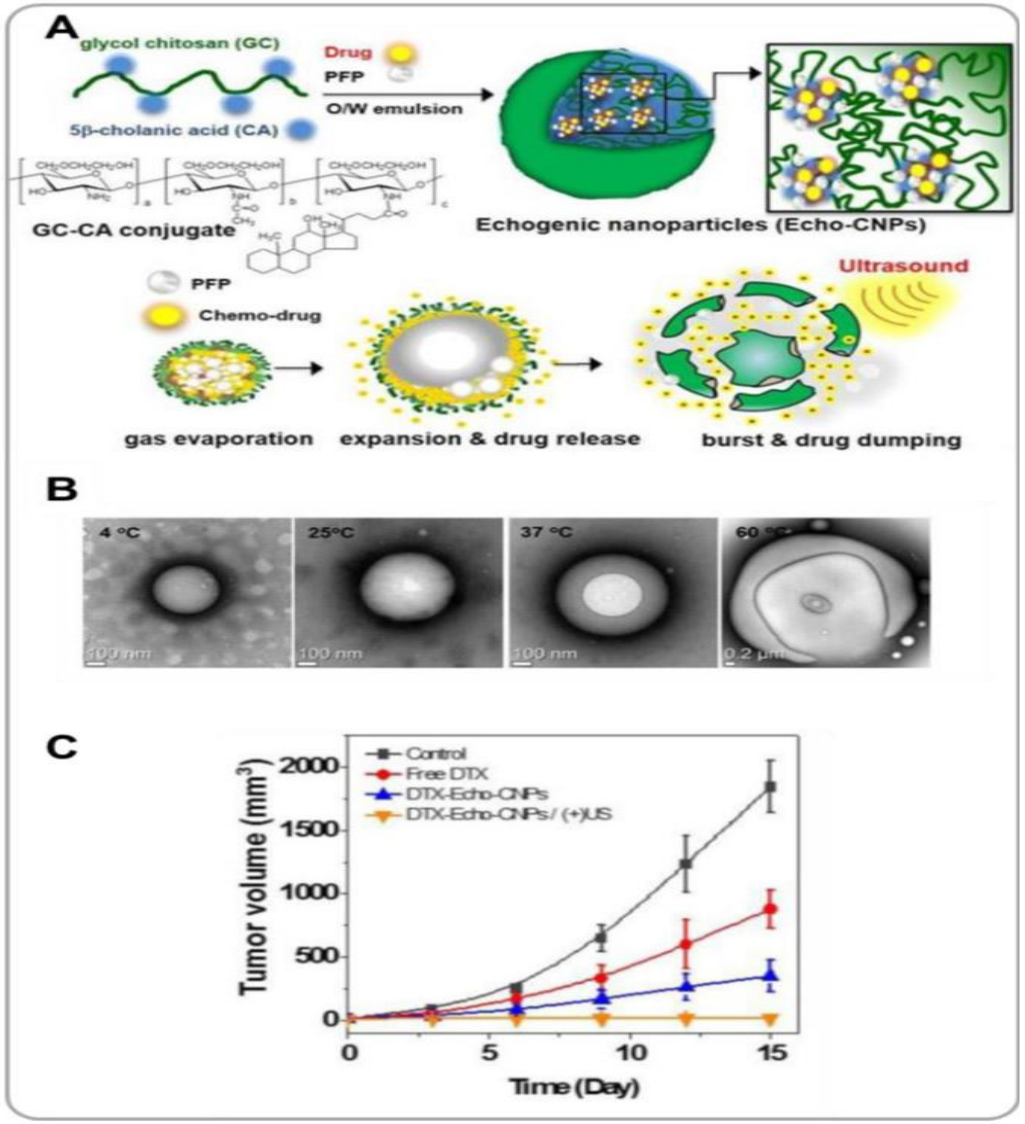
NANOTHERANOSTIC ULTRASOUND IMAGING

- Widely used
- Low cost
- Image in real time
- No ionizing radiation



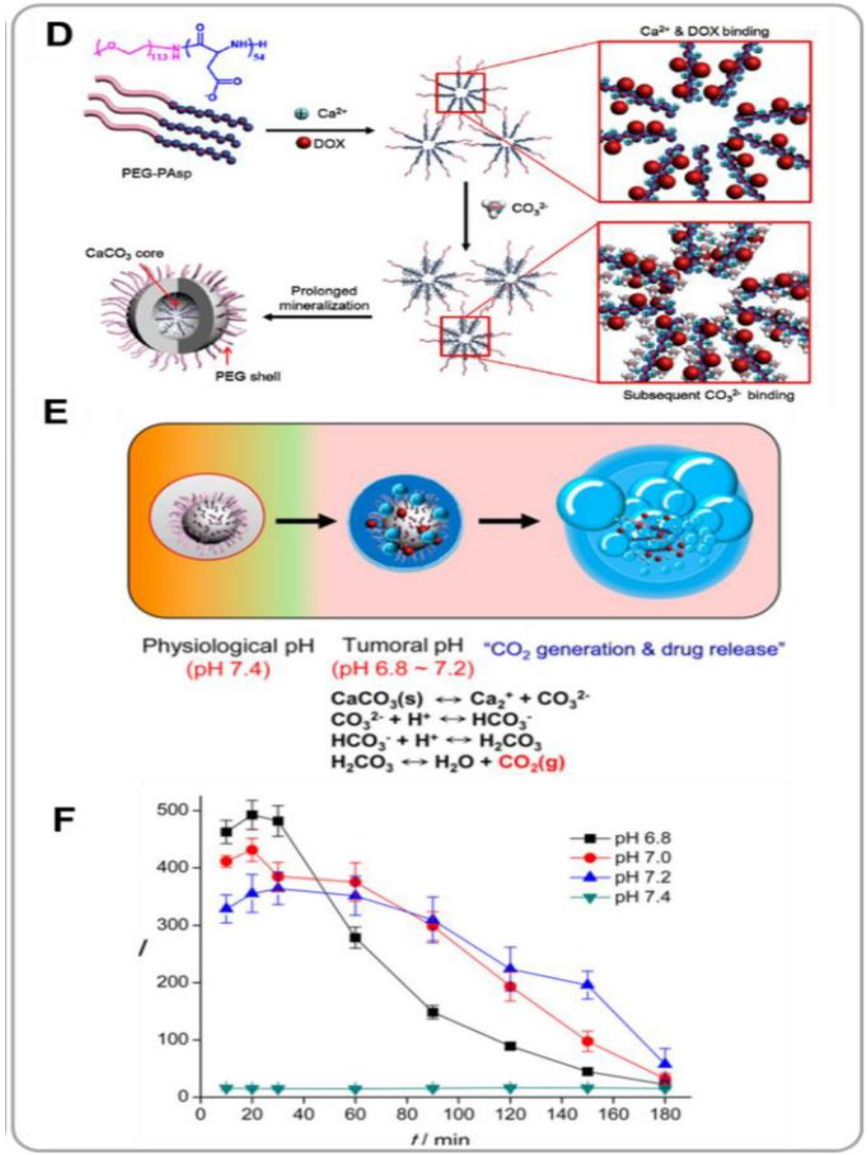
The red outline shows the manually segmented boundary of a carcinoma

IN SITU GAS-GENERATING MATERIALS



- Echo Signal Intensity ↑ Size↓
- Glycol Chitosan (5b-cholonic) + PFP + Drug → Echogenic nanoparticles (Echo-CNPs)
- EPR EFFECT
- Acoustic cavitation enhances extravastion of nanoparticles into tumor tissue.

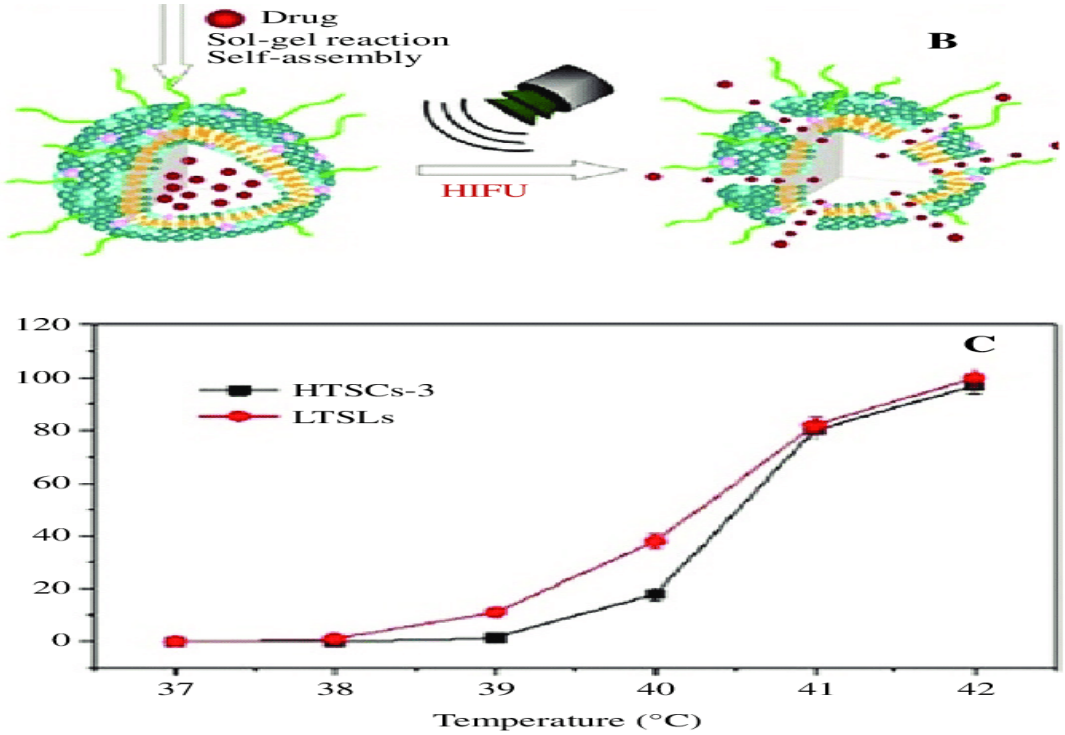
- PEG-Pasp + Ca^{2+} + DOX $\rightarrow$ +CO_3 $\rightarrow$ DOX-CaCO-MNPs
- Acidic pH
- Cargo space which drug molecules loaded



HIGH-INTENSITY FOCUSED ULTRASOUND-TRIGGERED CONTROLLED DRUG RELEASE

Silica(PFOB + CPT + PLGA)→CPT/PFOB@SNCs

- Prevent premature release
- Tumor ablation under HIFU



Stimulus-responsive liposomes as smart nanoplatforms for drug delivery applications · Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Ultrasound-sensitive-drug-loaded-liposomal-cerasome-A-Schematic-of-the-formation-of_fig10_320300849 [accessed 30 Nov, 2019]

TO SUM UP

TUMOR-HOMING ABILITY AND SELECTIVITY(CAUSED BY EPR EFFECT)

SURFACE MODIFICATION

SURFACE FUNCTIONALIZATION

ALL-IN-ONE

(THERAPEUTIC-IMAGING-TARGETING-CONTROLLED RELEASE)

IMAGE-GUIDED CANCER THERAPY

PERSONALIZED CANCER CARE

LIMITATIONS

- OPTIMAL COMBINATION
- OPTIMIZE DOSE LEVELS AND FREQUENCIES
- PREMATURELY RELESE

THANKS FOR LISTENING