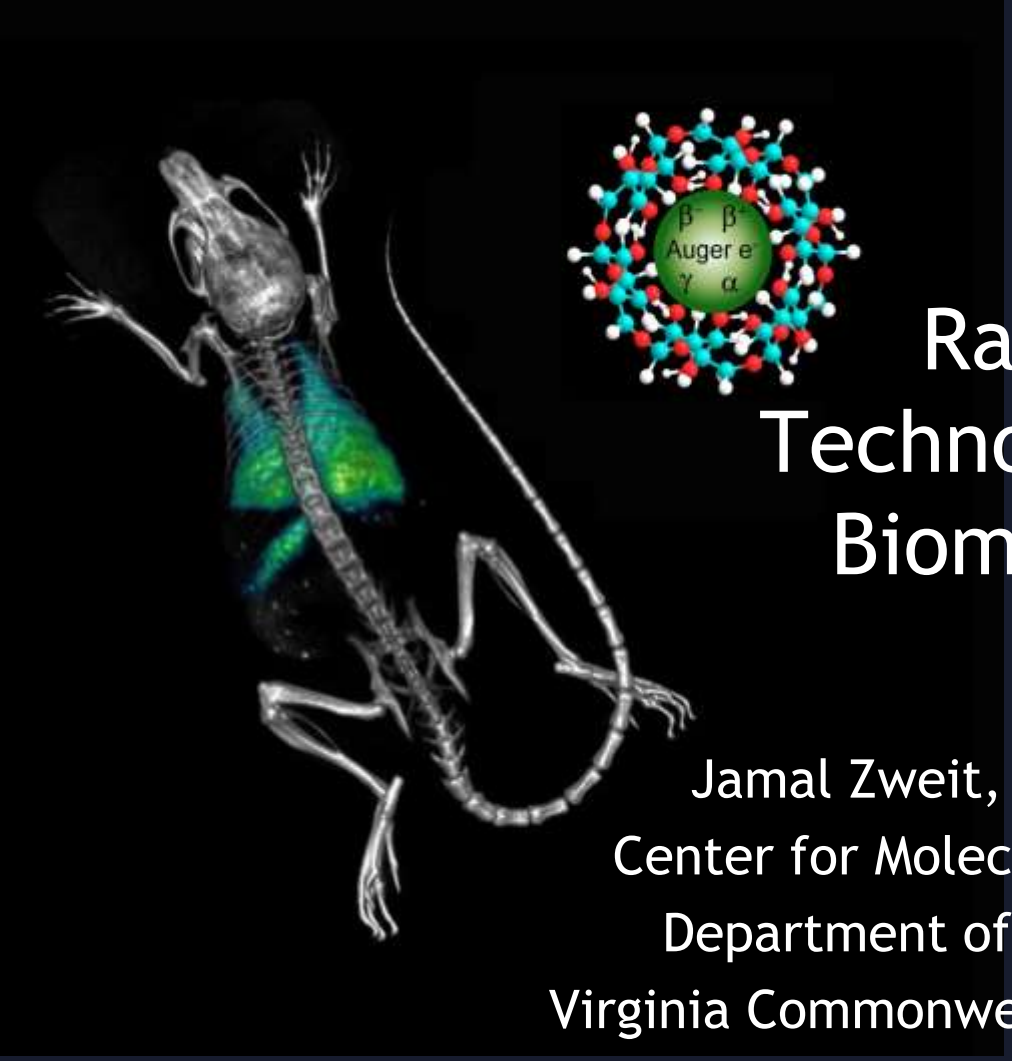
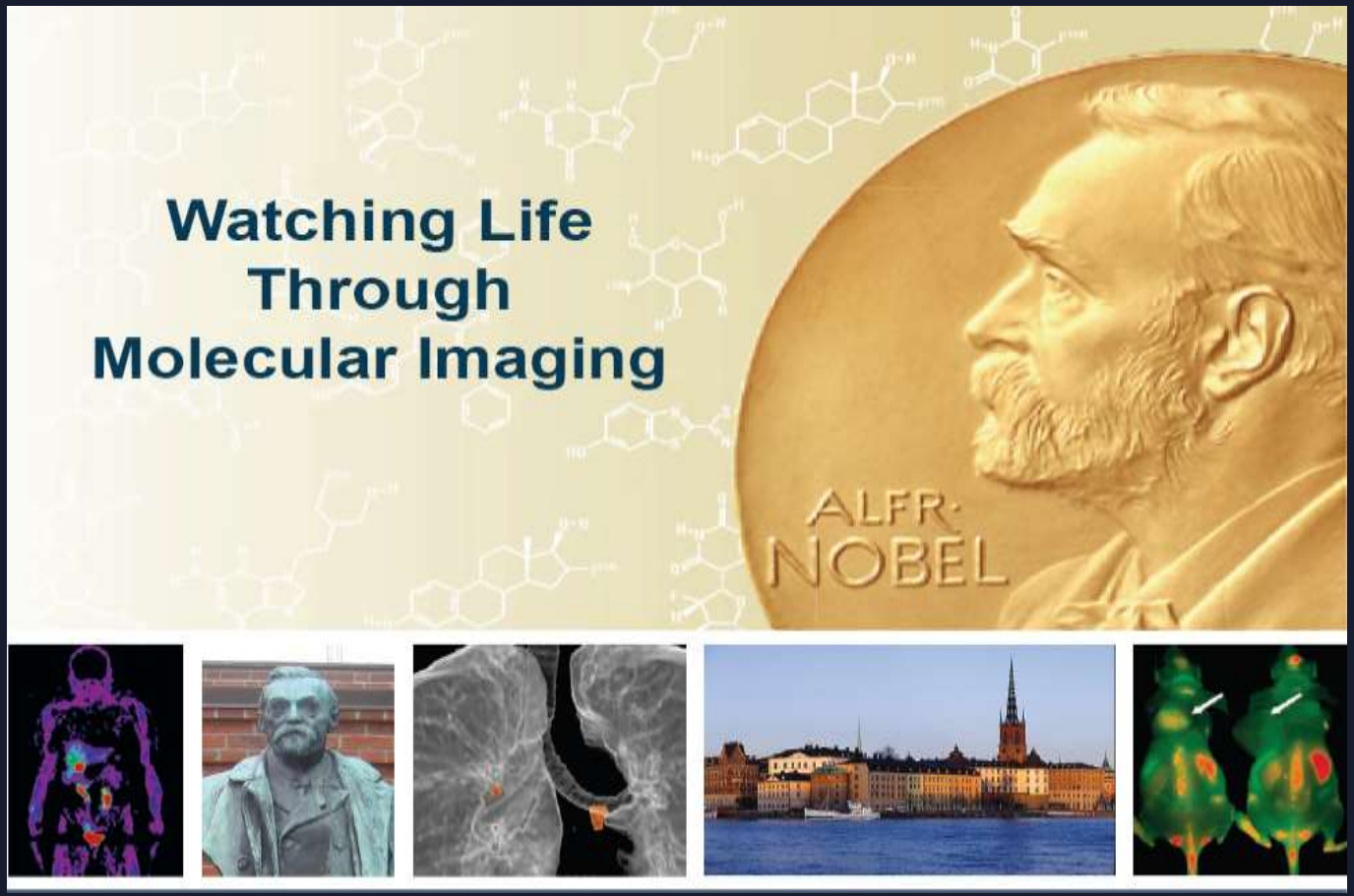


Radio-Nanoparticle Technology and Imaging for Biomedical Applications

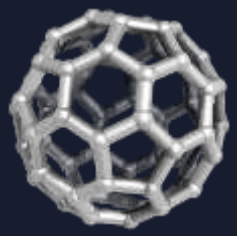
Jamal Zweit, PhD, DSc
Center for Molecular Imaging
Department of Radiology
Virginia Commonwealth University

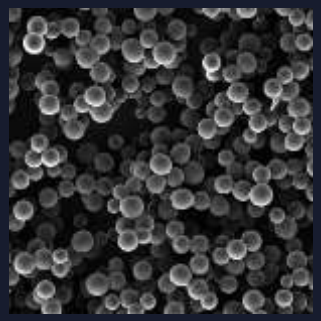
3rd International Workshop on Accelerator-Driven Sub-Critical Systems & Thorium Utilization

Virginia Commonwealth University



Molecular imaging is a rapidly emerging biomedical research discipline that may be defined as the visual representation, characterization, and quantification of biological processes at the cellular and sub-cellular levels within intact living organisms. This is a novel multidisciplinary field, where the images produced reflect cellular and molecular pathways and in vivo mechanisms of disease present within the context of physiologically authentic environments. The term 'molecular imaging' implies the convergence of multiple image-capture techniques, basic cell/molecular biology, chemistry, pharmacology, medical physics, biomathematics and bioinformatics into a new imaging paradigm.





Nanotechnology and Molecular Imaging in Cancer Therapy

- Nanotechnology combines the fields of chemistry, engineering, and medicine to develop unique therapies using carbon nanotubes, fullerenes, liposomes, metal oxides, quantum dots, and other nanoparticles (NPs)
- Multifunctional nanoparticles can be used as theranostic agents for both targeted therapy of cancer and as molecular imaging agents for advanced molecular diagnosis
- Through Molecular Imaging and Nanotechnology we can piece together the "jigsaw" of disease to reveal its key mechanisms:
  - how big it is
  - how fast it is developing
  - how many molecular processes are contributing simultaneously
  - what to treat it with
  - how it is responding to therapy
- Molecular targeting of therapies using NPs can increase efficacy and reduce toxicity
- The end point is non-invasive, individualized, and effective diagnosis and treatment of cancer

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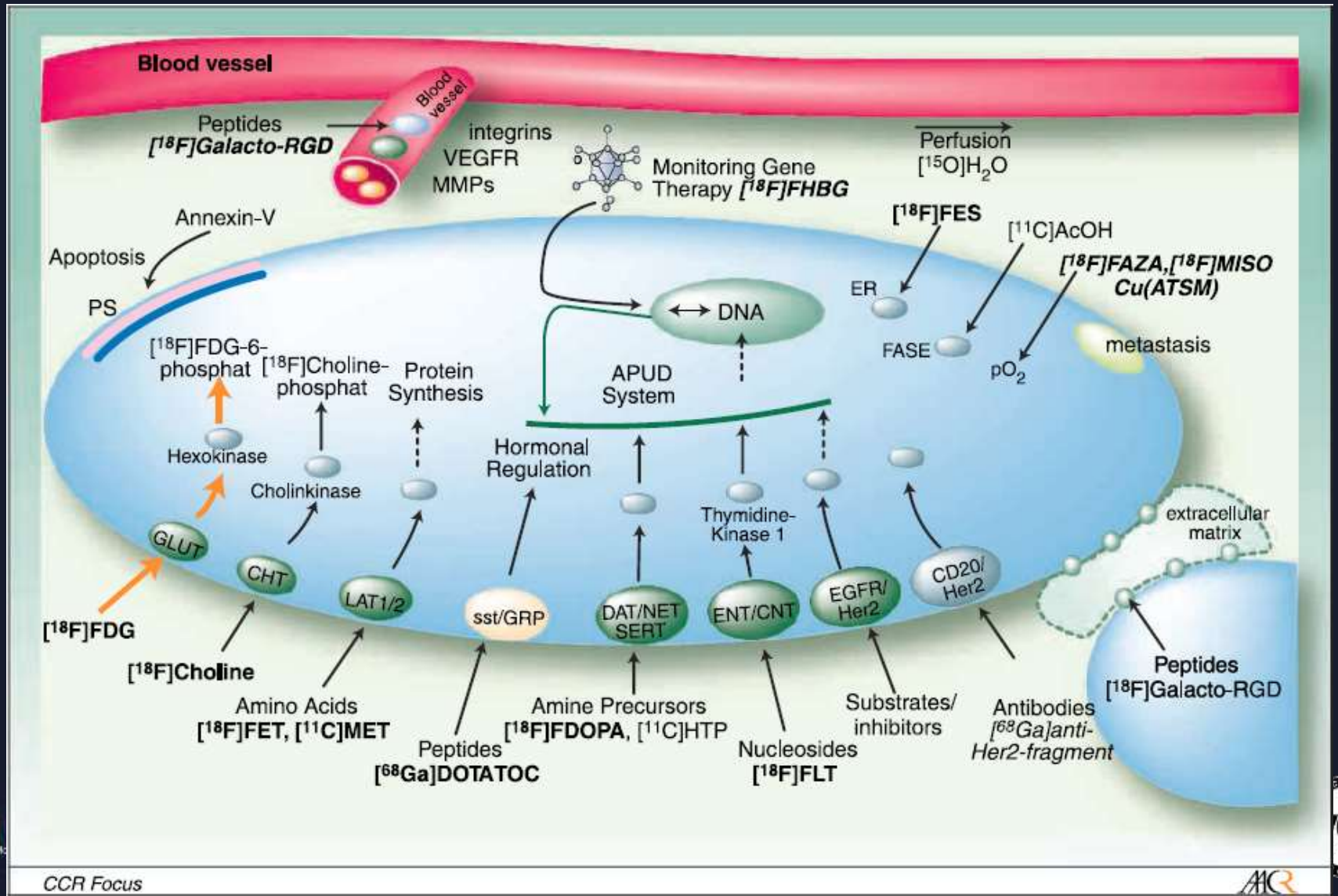
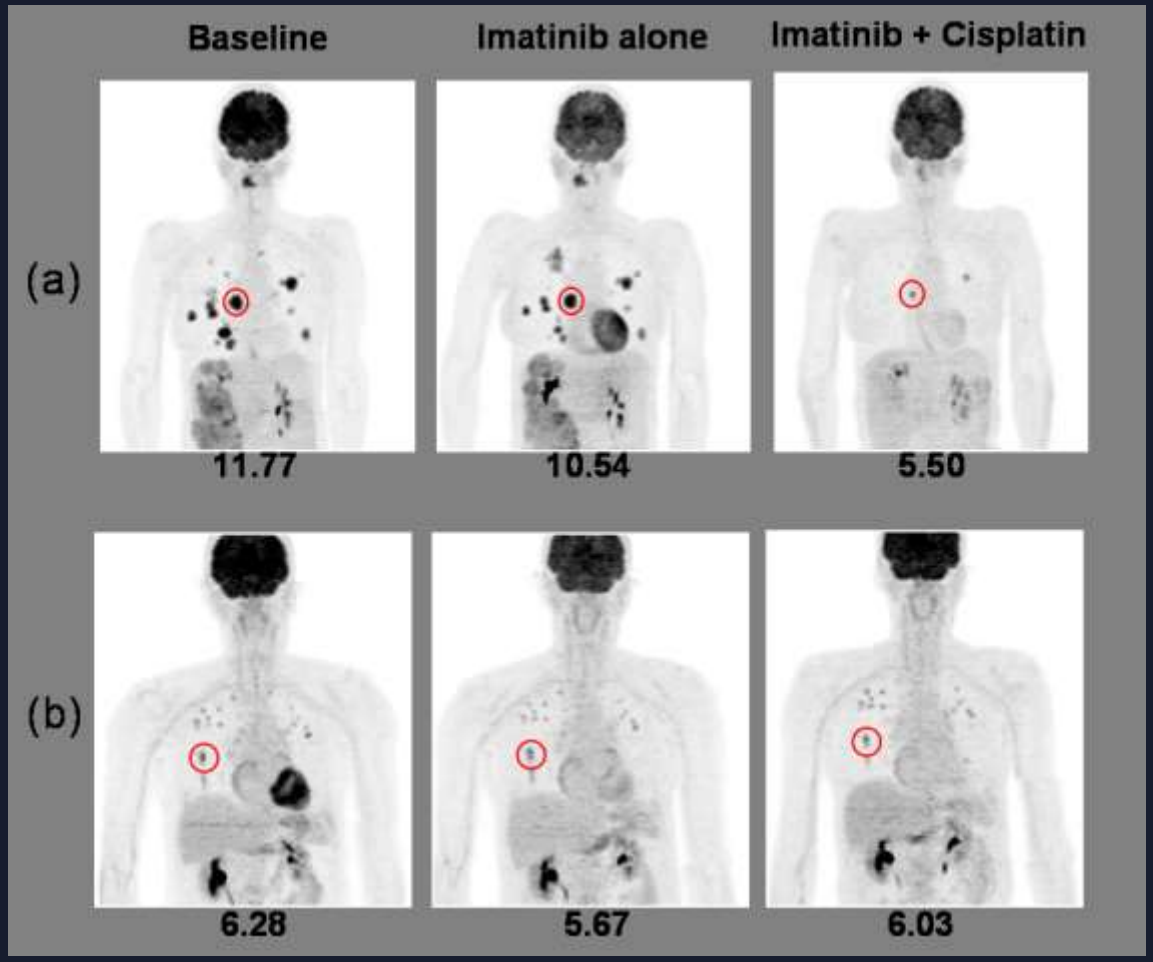
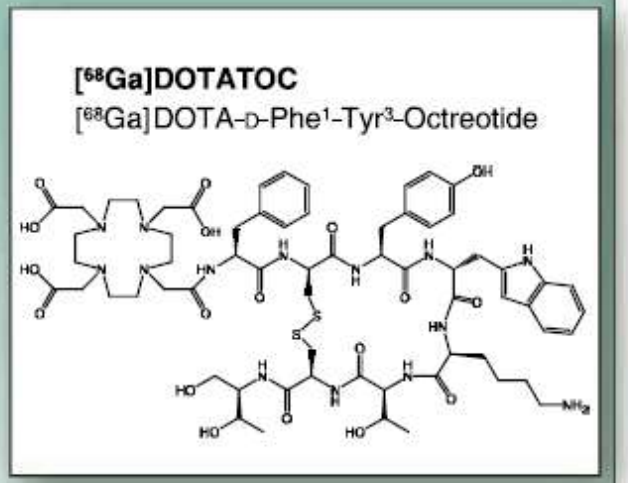
Targets and Molecular Imaging Probes

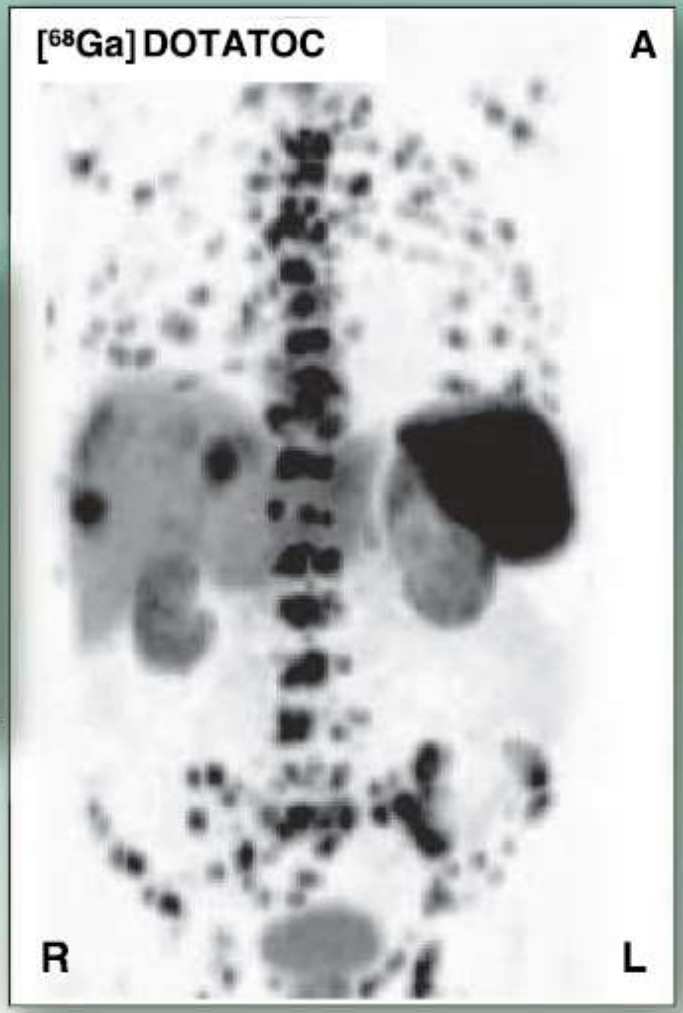


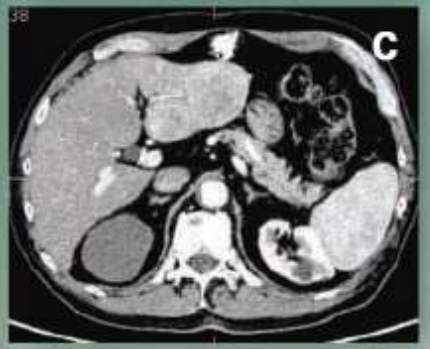
Monitoring Response to Therapy

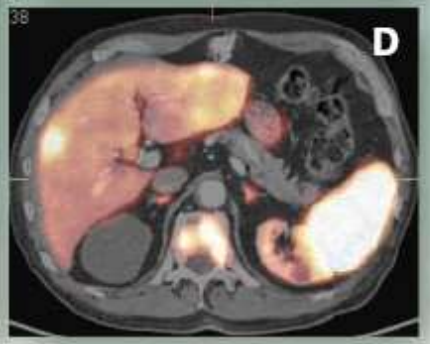


[^{68}Ga]DOTATOC-PET/CT Neuroendocrine Cancer

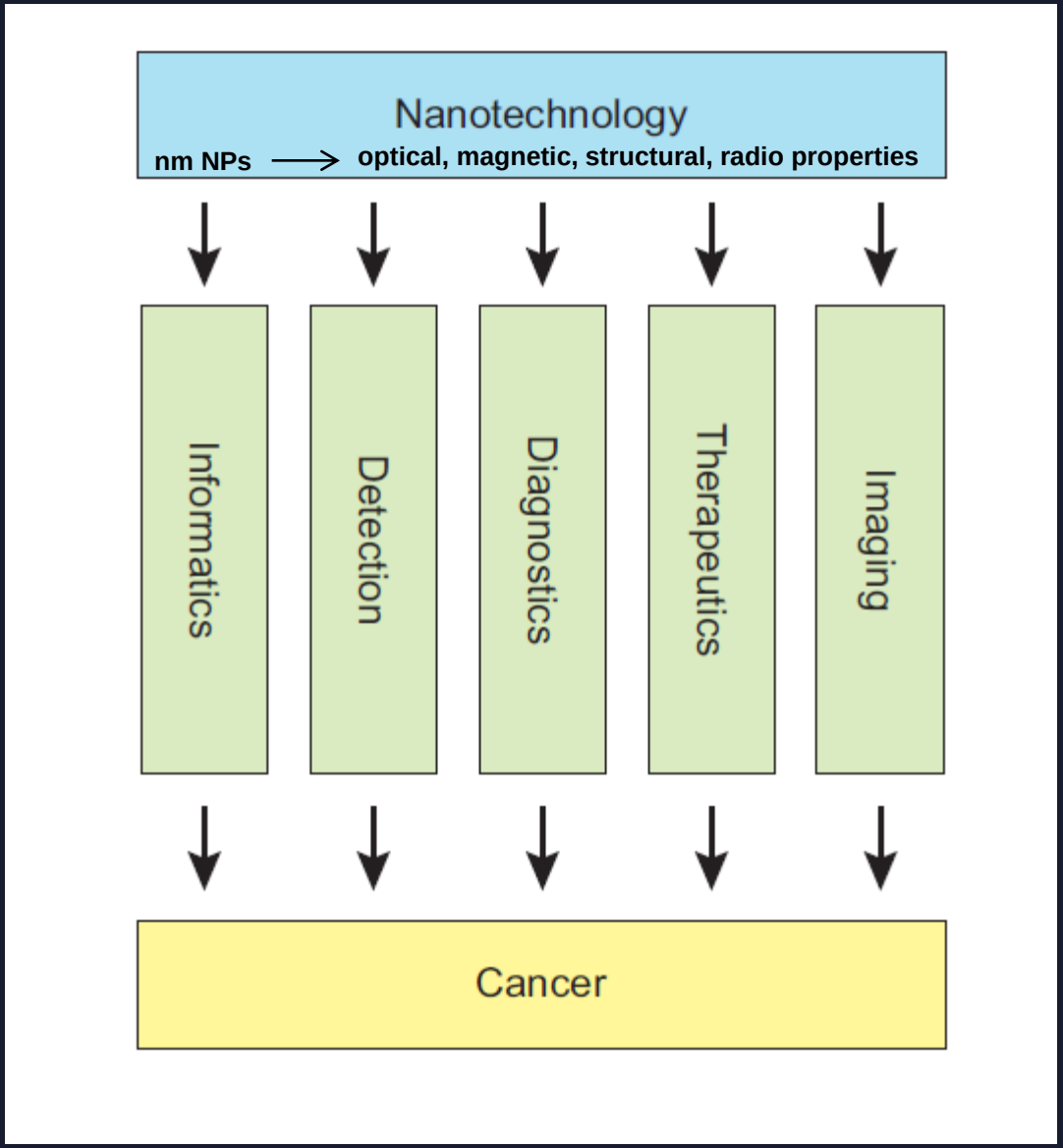




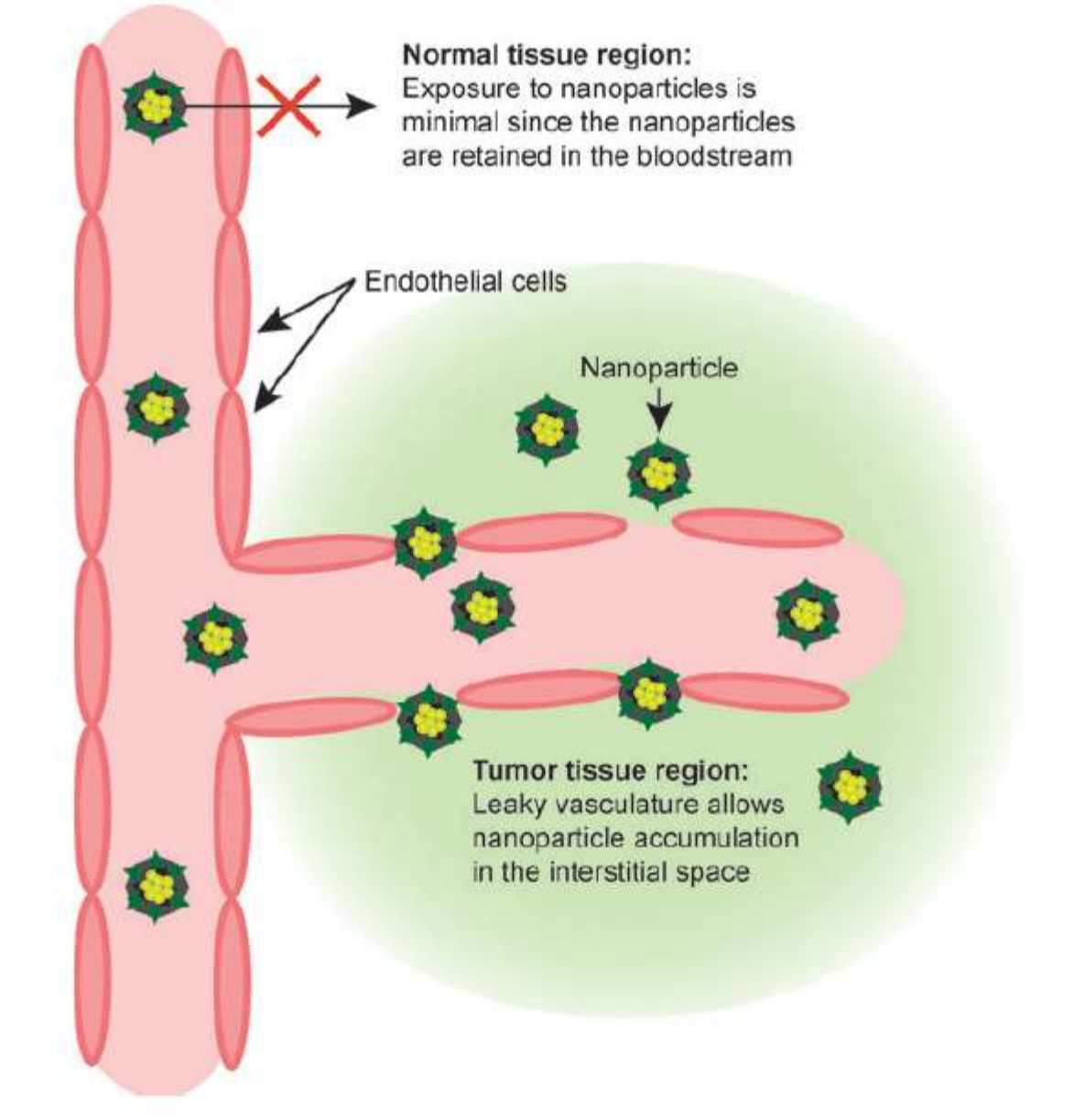




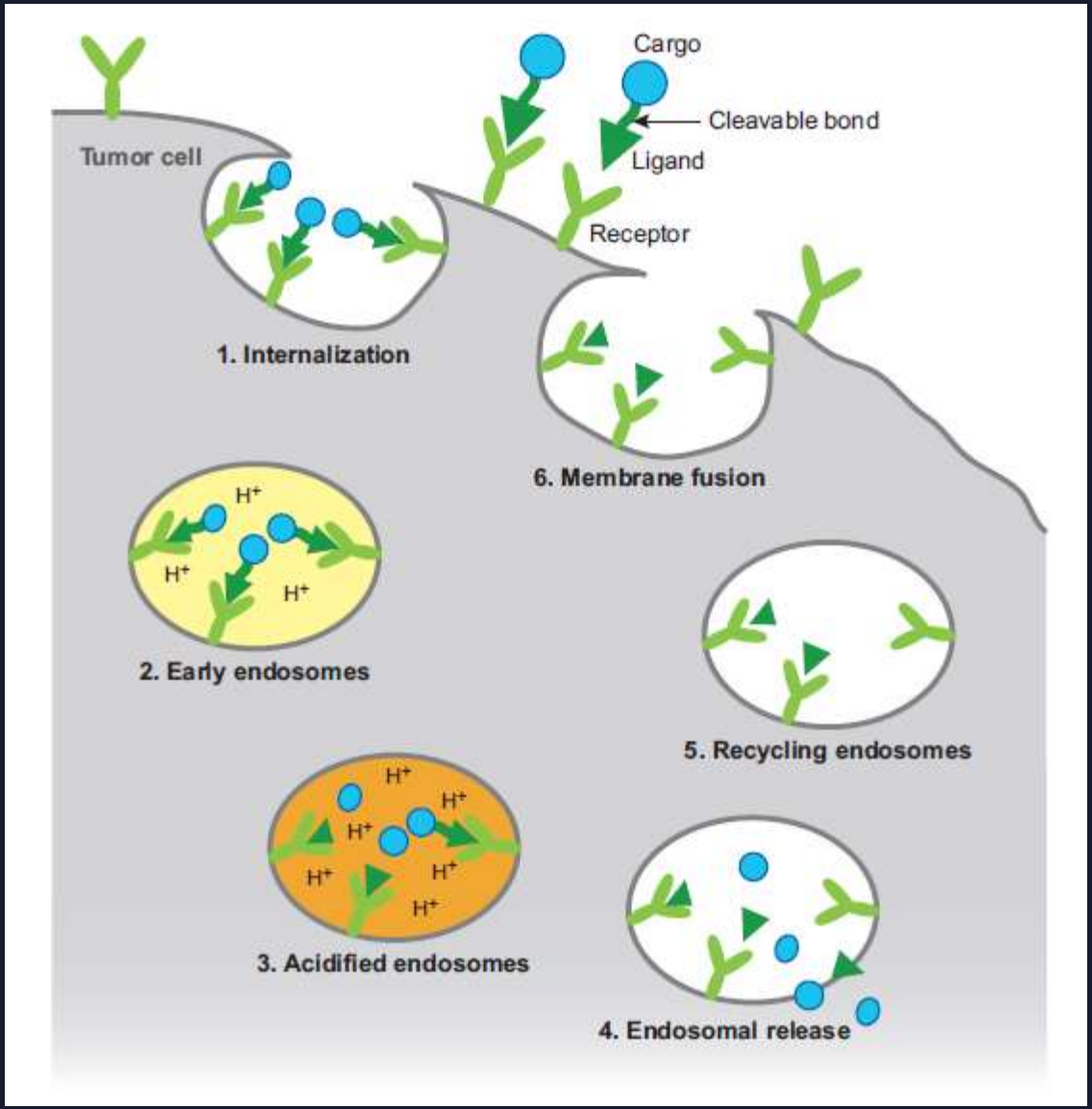
Nanotechnology applications in cancer



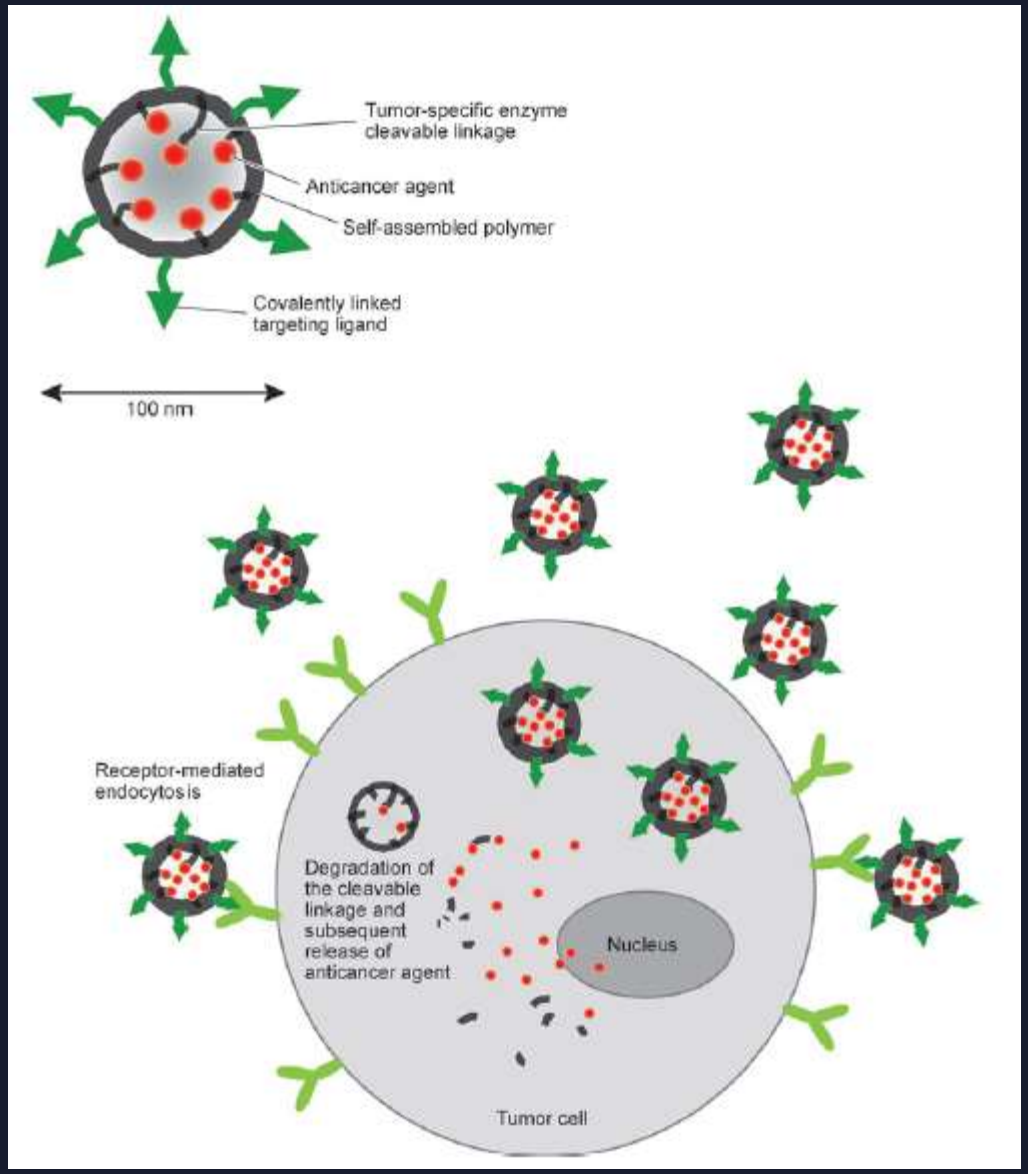
Nanoparticle passive targeting



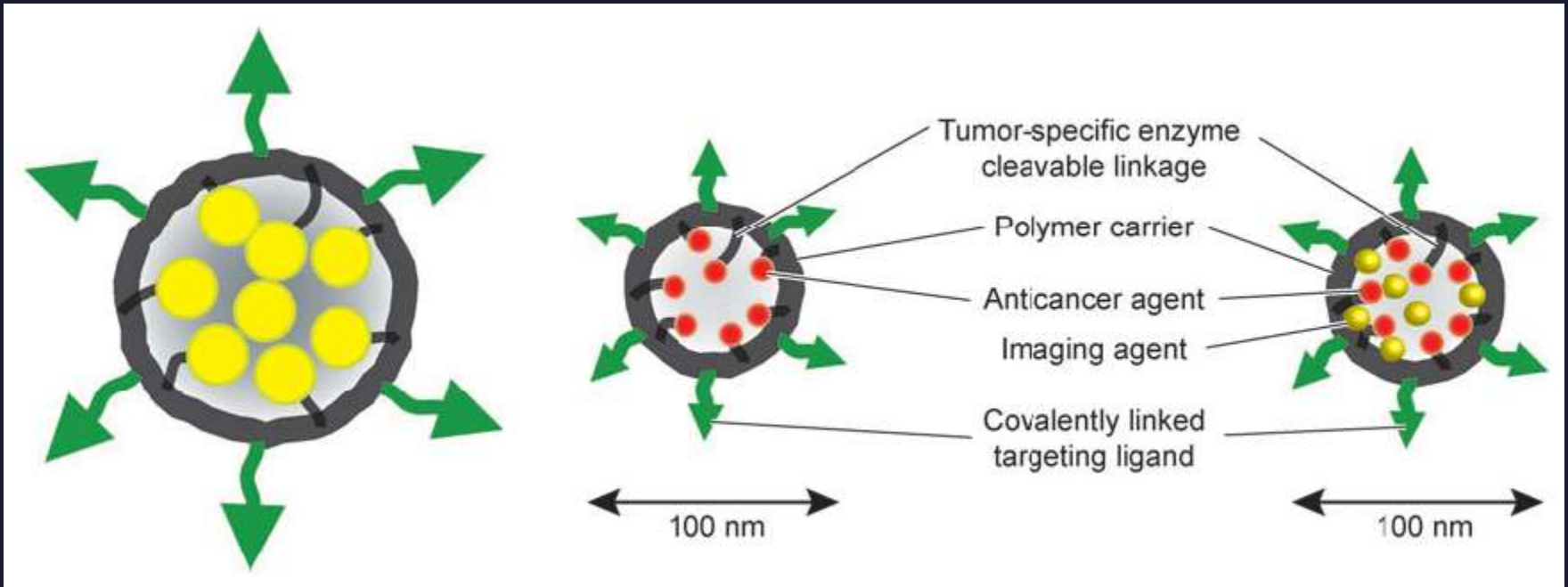
Nanoparticle active targeting



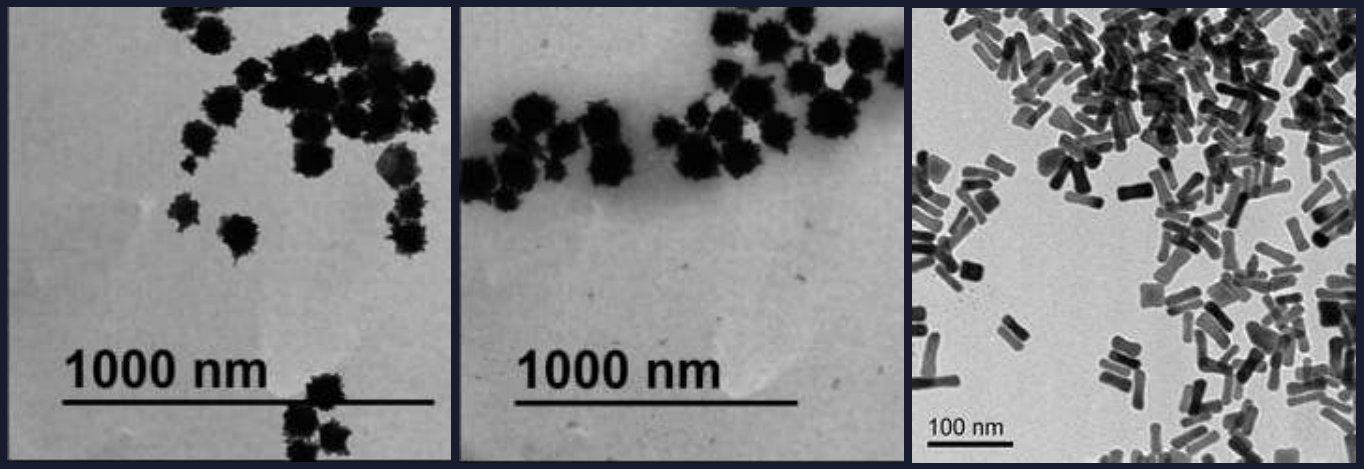
Targeting and controlled release

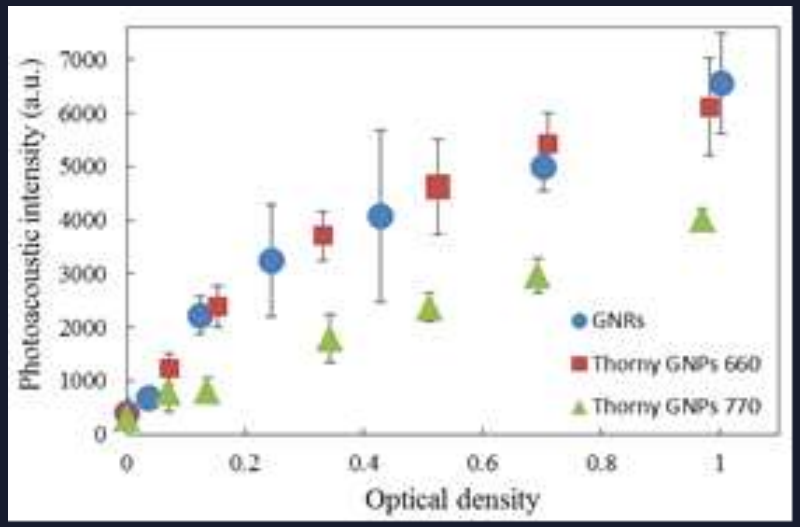


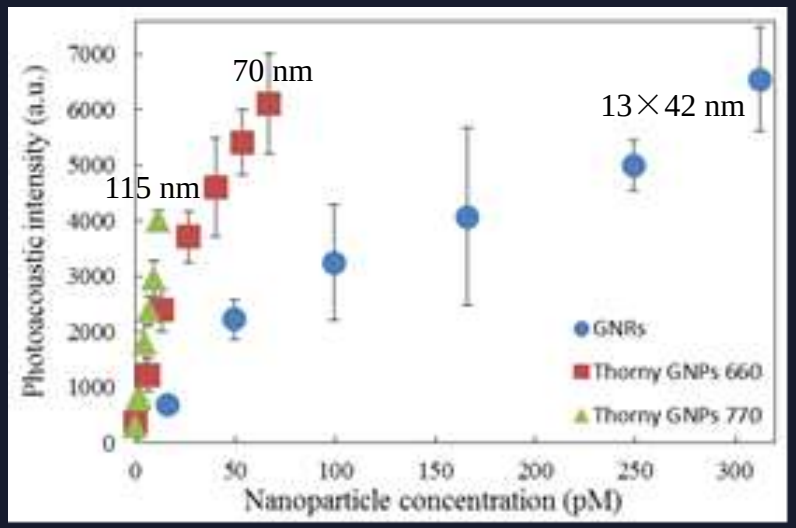
Multifunctional nanoparticles



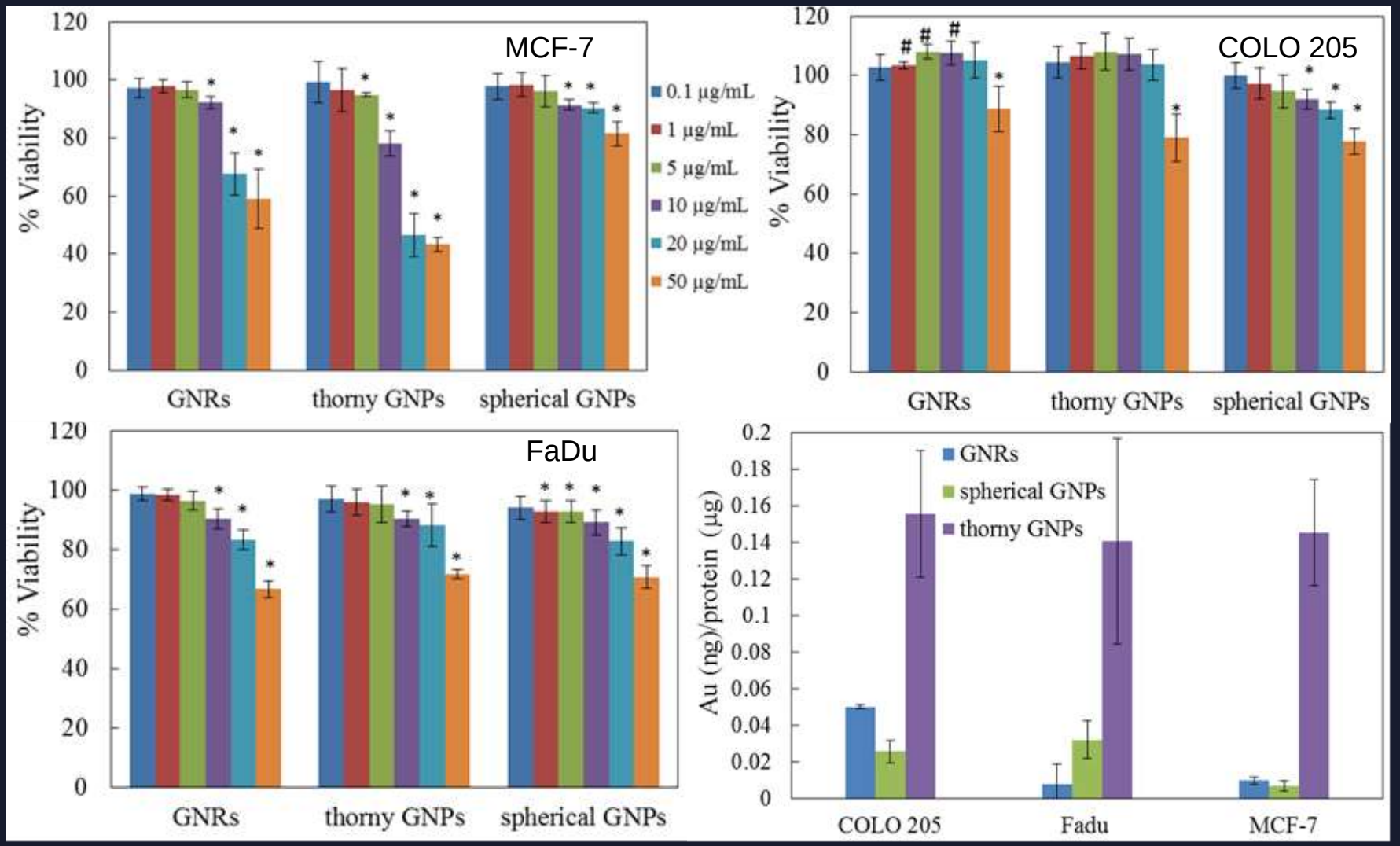
Photoacoustic Signal Intensity is Dependent on Morphology of Au-NP (thorny sphere vs rod)



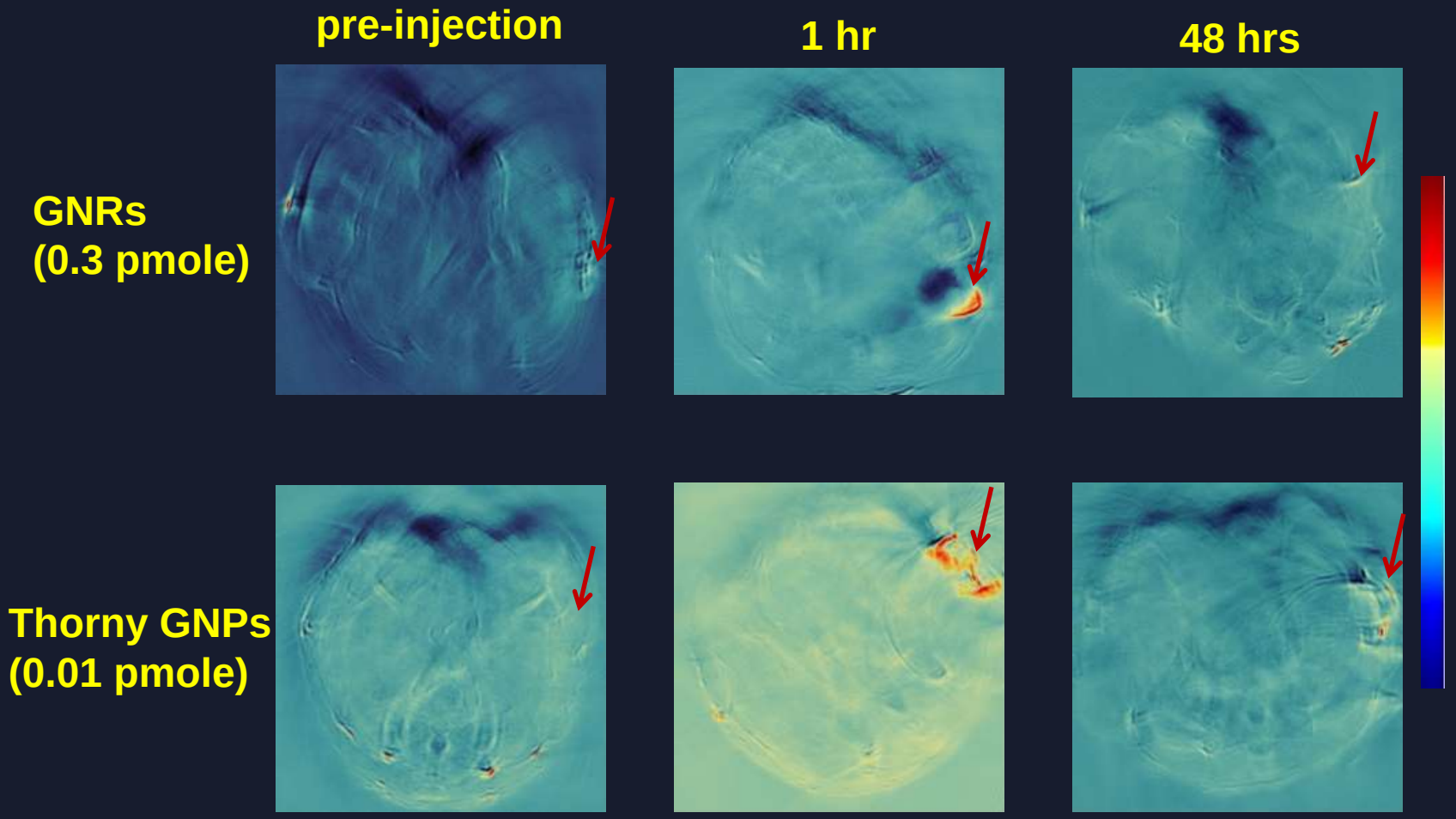




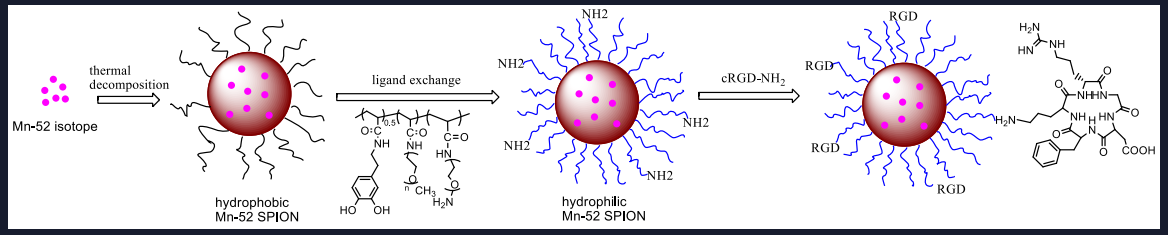
Cell uptake of Au-NPs is dependent on NP morphology

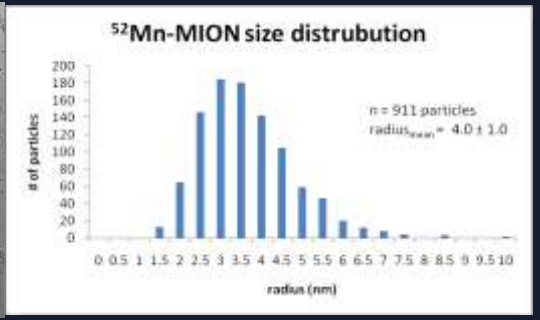


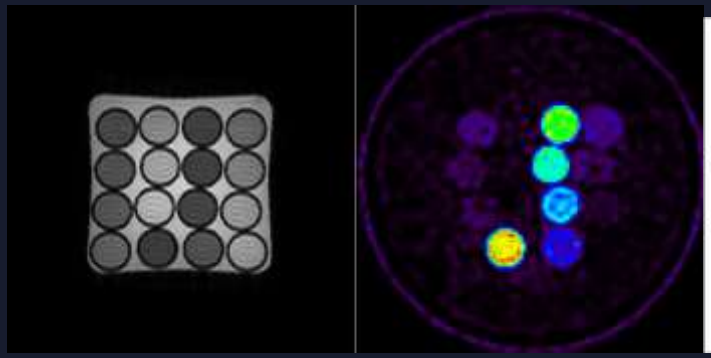
In vivo photoacoustic imaging of thorny and rod Au-NPs

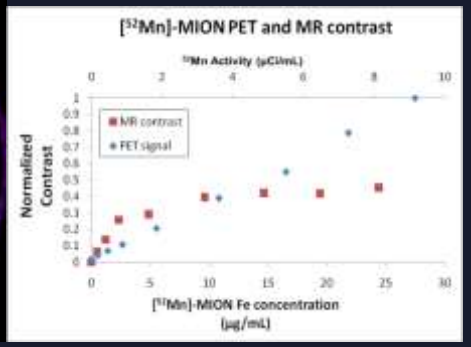


[^{52}Mn]-MIONs synthetic scheme, size distribution characterization and PET/MRI phantom imaging correlation



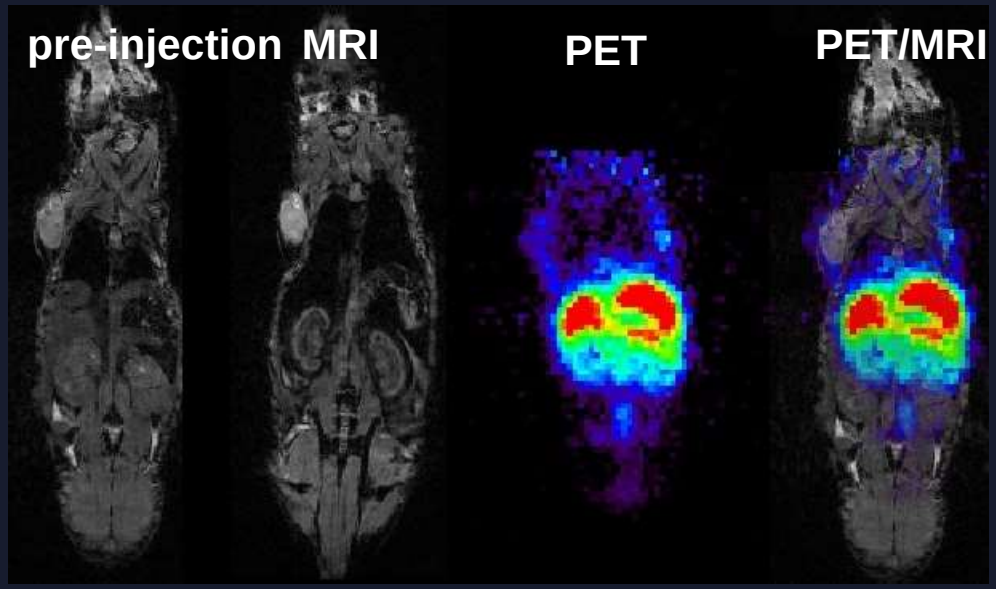




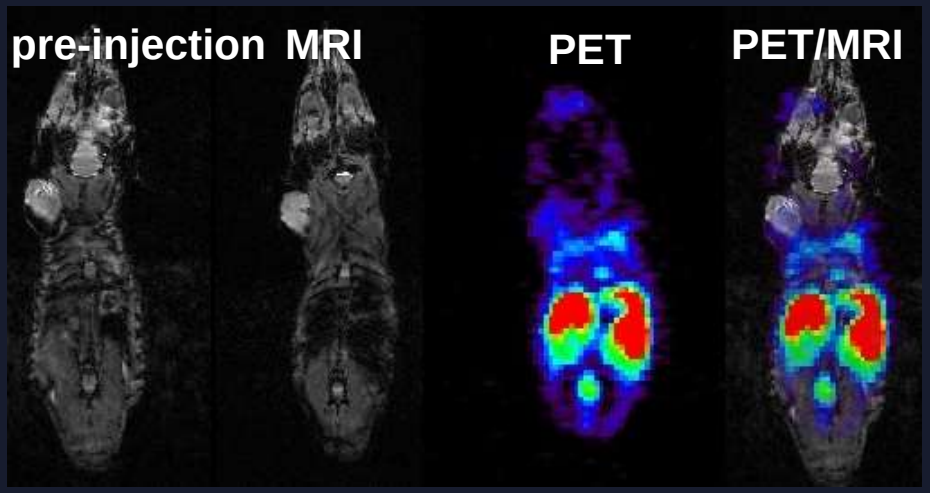


Coronal images of [^{52}Mn]-MIONs and [^{52}Mn]- cRGD-MIONs 24 hrs post-injection.

[^{52}Mn]-MIONs
(Passive targeting)



[^{52}Mn]-cRGD-MIONs
(Active targeting)



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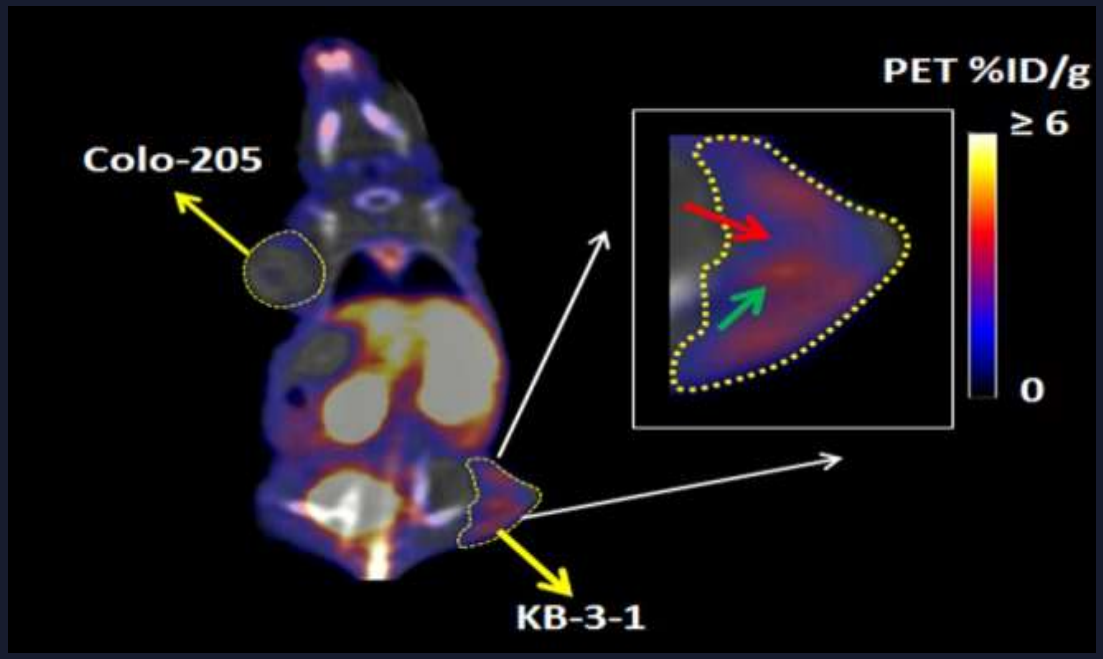
[^{18}F]-Fluorocarboplatin



PET Imaging of [^{18}F]-FCP in Dual Tumor Bearing Mouse: As expected, the uptake in the Colo-205 tumor (1 %ID/g) was much lower than that in the KB-3-1 tumor (2.6 %ID/g). Furthermore, the heterogeneity of the uptake is clearly evident in the KB-3-1 tumor (inset), showing regions of high (cyan arrow) and low (red arrow) uptake. Relating intra-tumoral uptake to protein profile of the different tumor regions accumulating different amounts of the drug might reveal the association of the drug uptake with alterations in the protein profile.

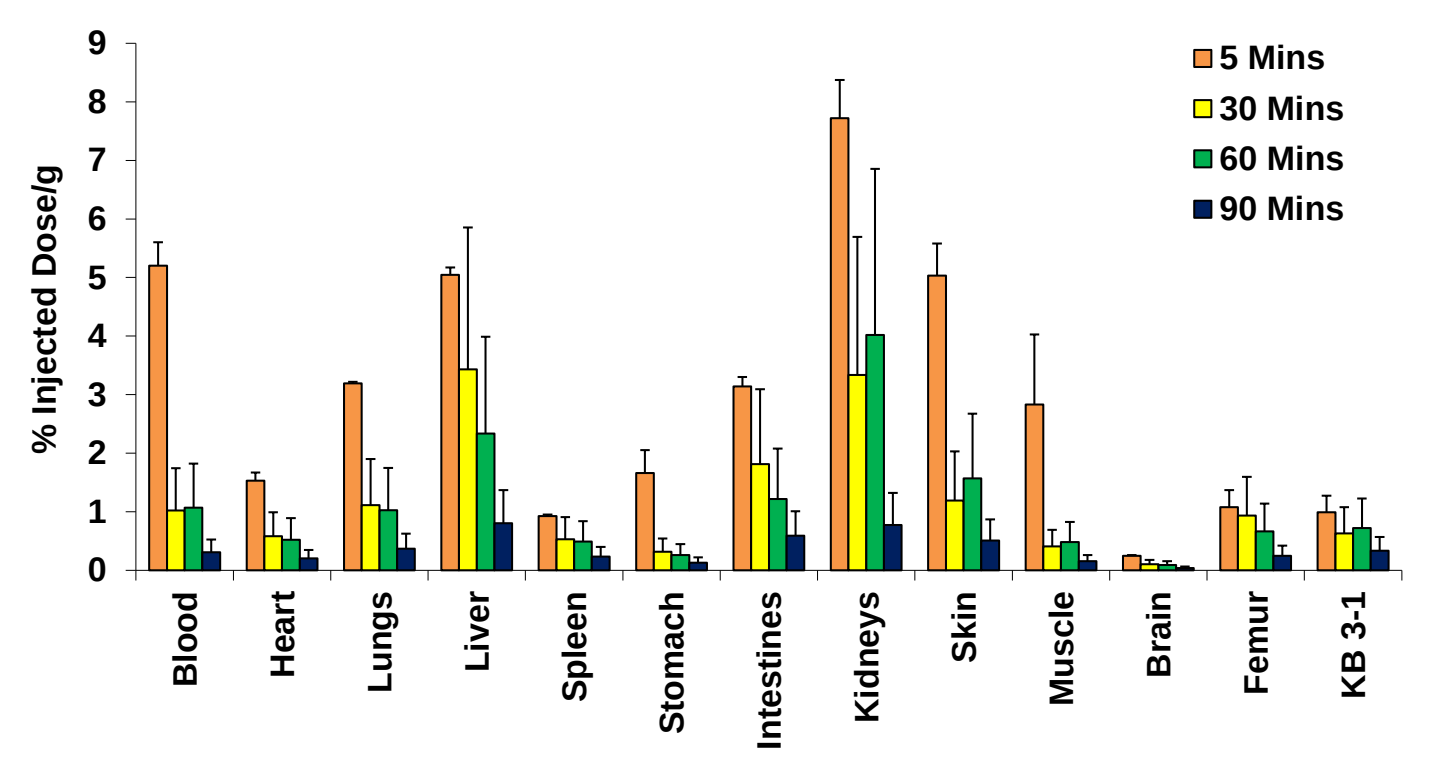
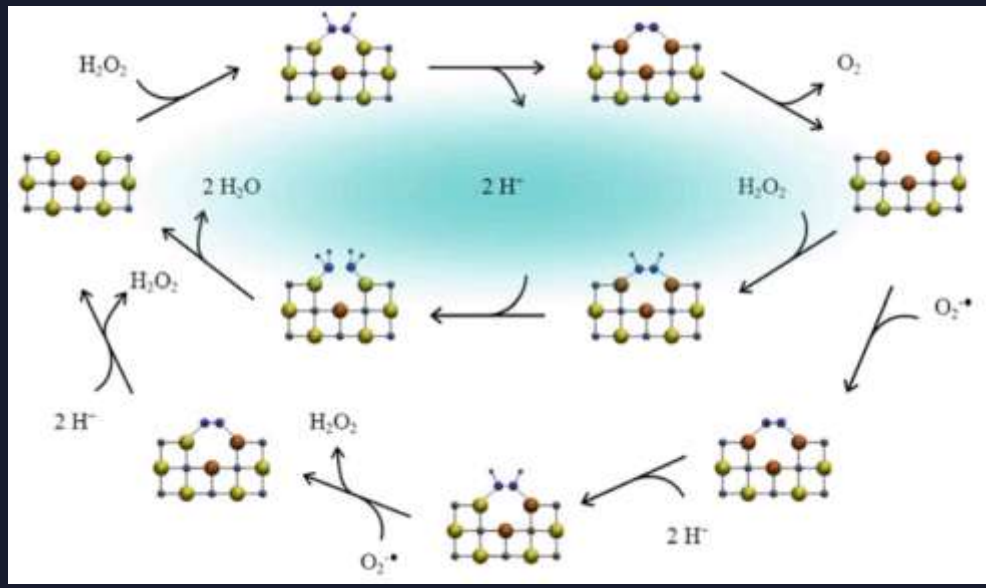


Figure 1: Biodistribution of [^{18}F]-FCP in adult tumor-bearing nude mice (n=3/time point) at 5, 30, 90 minutes after intravenous injection. Radio tracer uptake in percent injected dose per gram of tissue (% ID/g) was determined by gamma counting. KB-3-1 = Cervical Tumor Xenograft.

Cerium Oxide Nanoparticles (CONPs)

- Unique Properties
  - Surface Cerium
    - Ce^{+3} or Ce^{+4}
  - Antioxidant Radical Scavenging
    - $Ce^{+3} \leftrightarrow Ce^{+4}$
      - SOD or catalase mimetic
    - Redox cycling
- Applications in industry and health



Perullini, M., Bilmes, S.A.A., and Jobbágy, M. (2013). Cerium Oxide Nanoparticles: Structure, Applications, Reactivity, and Eco-Toxicology. In Nanomaterials: A Danger or a Promise?, R. Brayner, F. Fiévet, and T. Coradin, eds. (Springer London), pp. 307–333.

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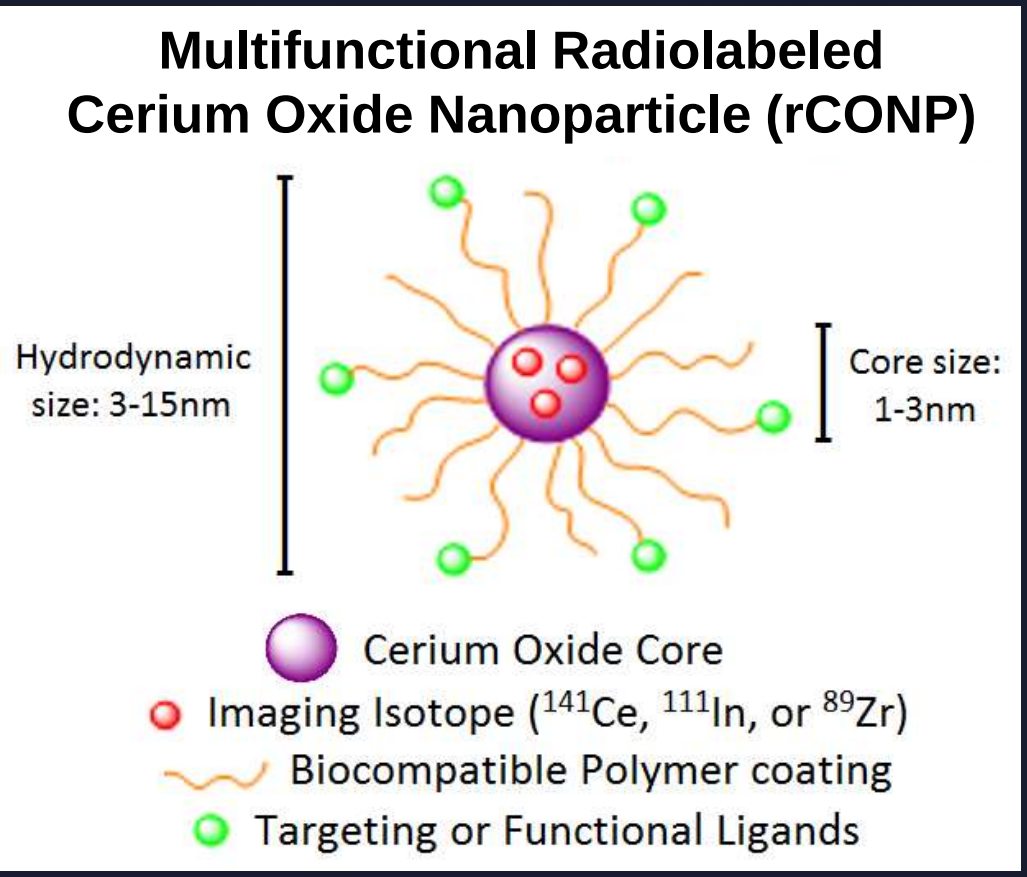
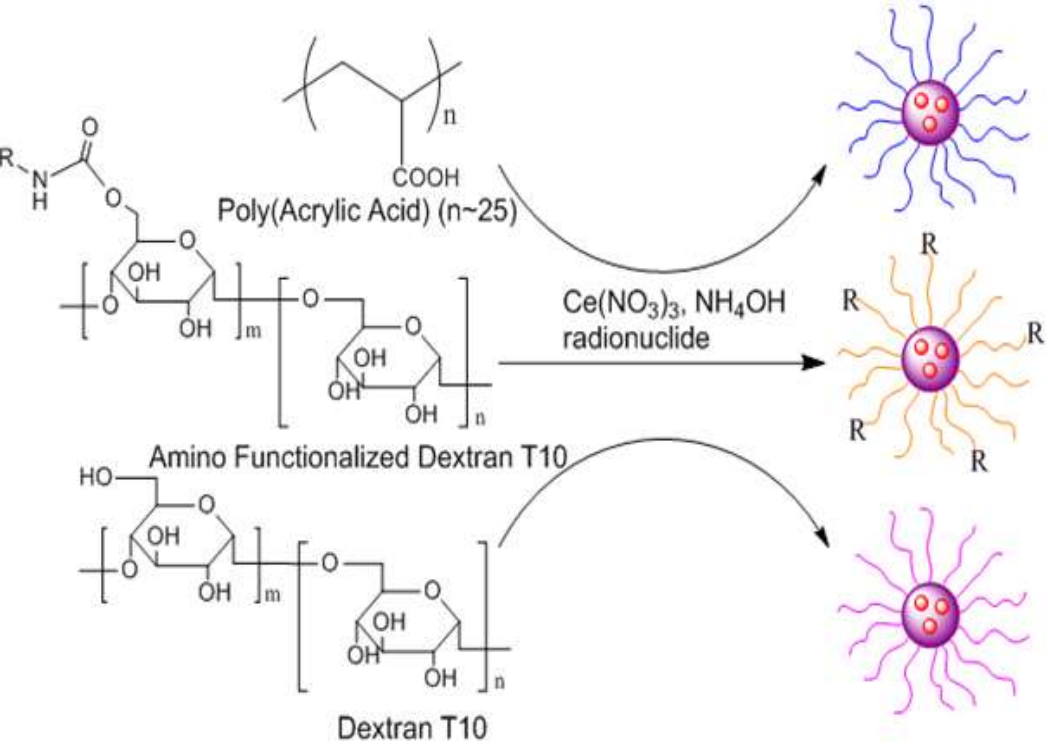
Multifunctional Radiolabeled Cerium Oxide Nanoparticles (rCONPs)

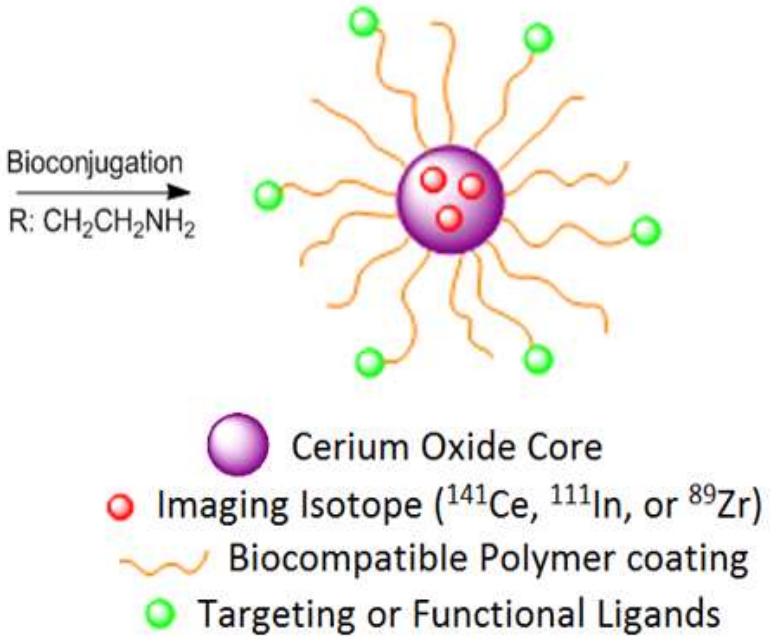


- Core of cerium oxide (CeO_2)
- Polymer surface coating
  - PAA
  - DT10
  - DT10-NH_2
    - Sulfobetaine
    - PEG
    - Other targeting/functional ligands
- Radioisotope in core for uptake detection and SPECT/PET imaging
  - ^{65}Zn ($T_{1/2}$: 244d)
  - ^{141}Ce ($T_{1/2}$: 32.5d)
  - ^{111}In ($T_{1/2}$: 2.8d)
  - ^{89}Zr ($T_{1/2}$: 3.3d)
- Core Size range ~ 1 - 3 nm
- Hydrodynamic size ~ 3 - 15nm

rCONP Synthesis



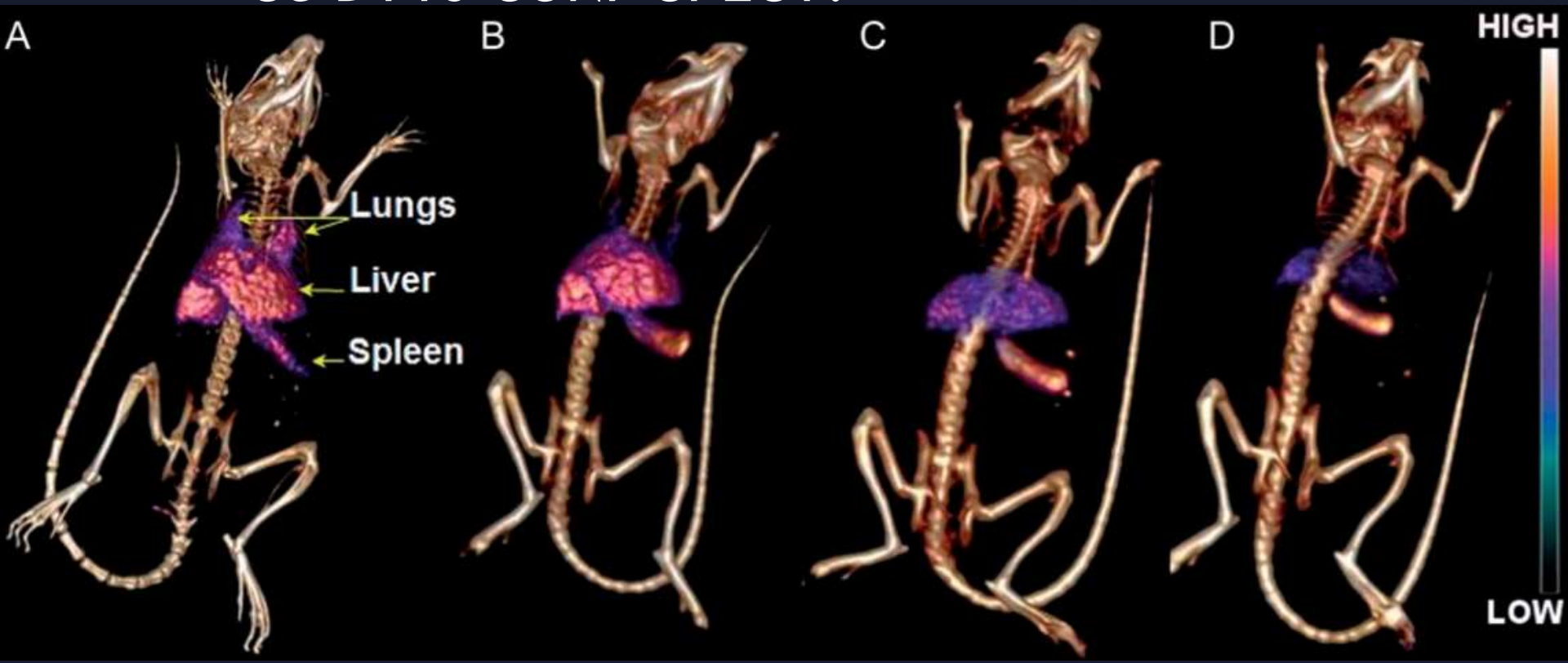
Multifunctional Radiolabeled Cerium Oxide Nanoparticle (rCONP)



Yang, L., Sundaresan, G., Sun, M., Jose, P., Hoffman, D., McDonagh, P.R., Lamichhane, N., Cutler, C.S., Perez, J.M., and Zweit, J. (2013). Intrinsically radiolabeled multifunctional cerium oxide nanoparticles for in vivo studies. J. Mater. Chem. B *1*, 1421–1431.

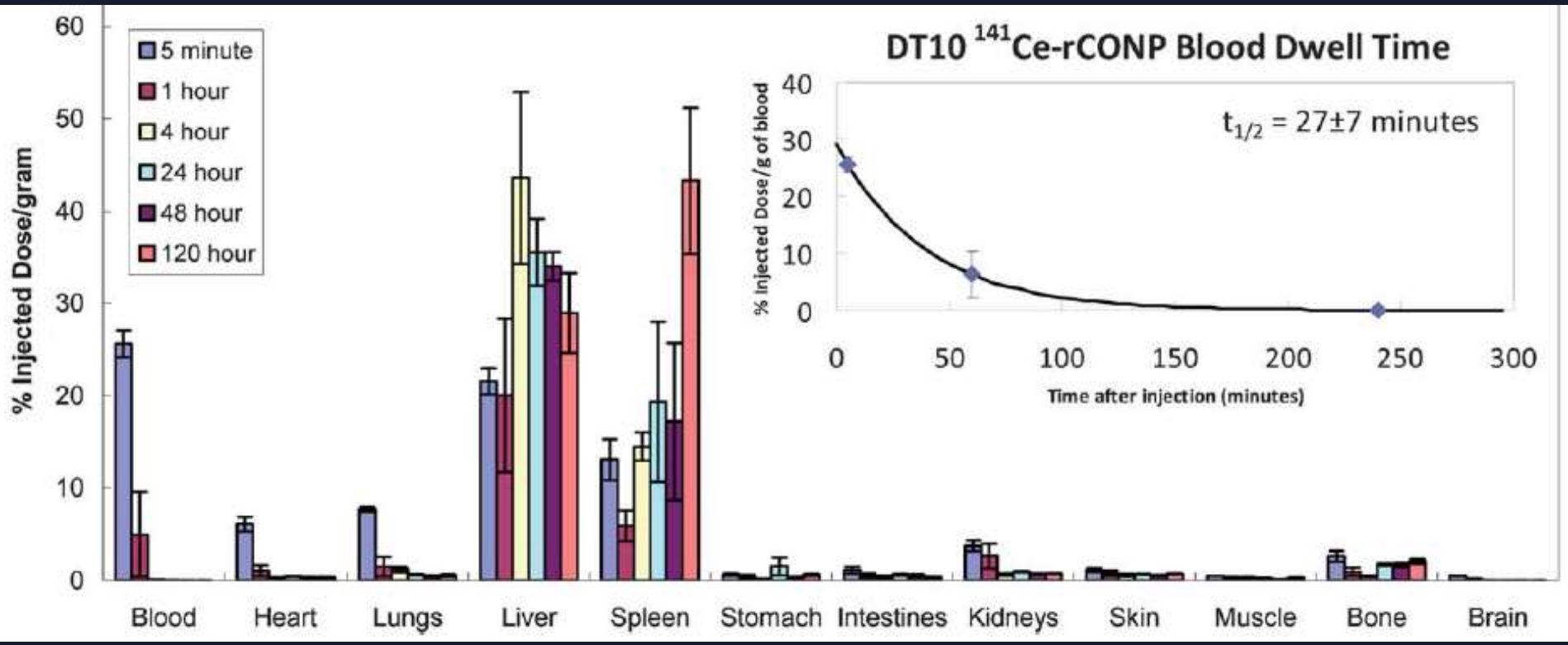
rCONP Imaging

- rCONPs as radiotracers (SPECT or PET)
- ^{141}Ce DT10 CONP SPECT:



Yang, L., Sundaresan, G., Sun, M., Jose, P., Hoffman, D., McDonagh, P.R., Lamichhane, N., Cutler, C.S., Perez, J.M., and Zweit, J. (2013). Intrinsically radiolabeled multifunctional cerium oxide nanoparticles for in vivo studies. J. Mater. Chem. B *1*, 1421–1431.

Biodistribution/Pharmocokinetics



Yang, L., Sundaresan, G., Sun, M., Jose, P., Hoffman, D., McDonagh, P.R., Lamichhane, N., Cutler, C.S., Perez, J.M., and Zweit, J. (2013). Intrinsically radiolabeled multifunctional cerium oxide nanoparticles for in vivo studies. J. Mater. Chem. B *1*, 1421–1431.

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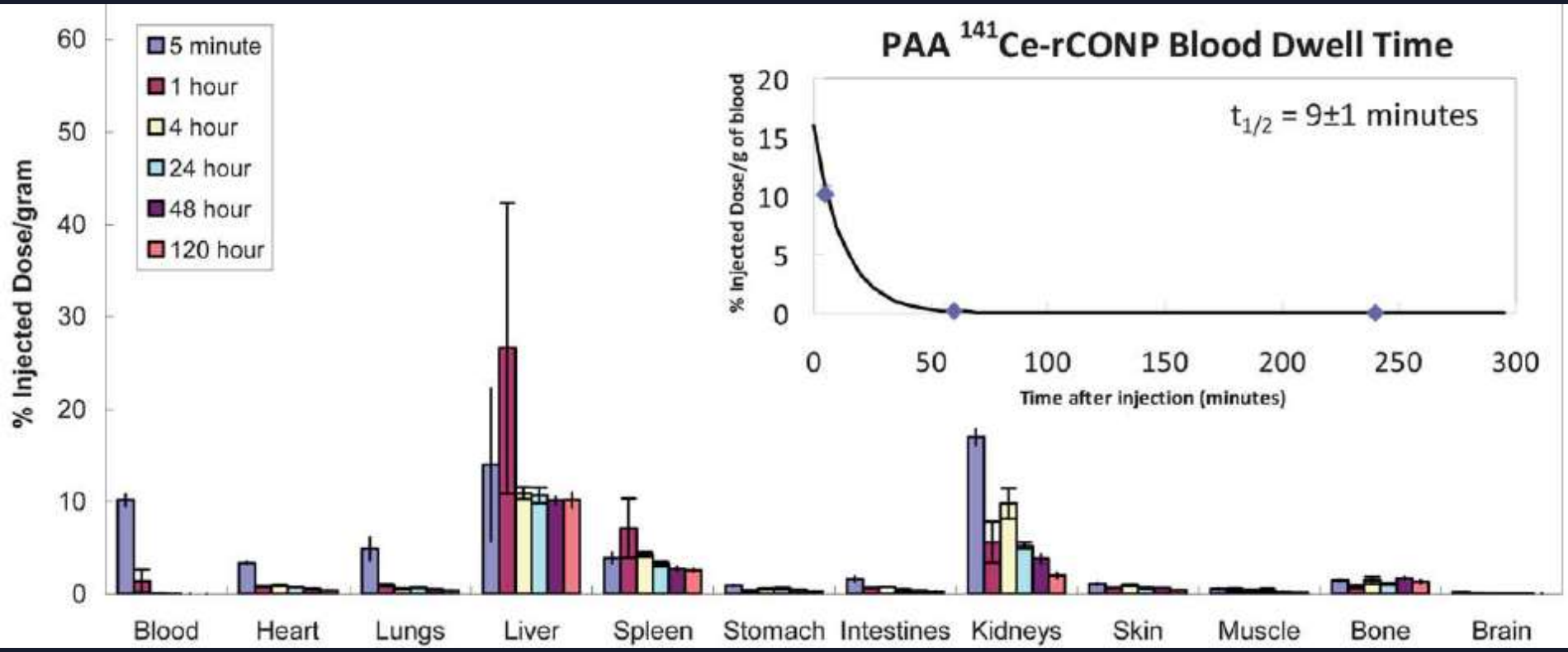
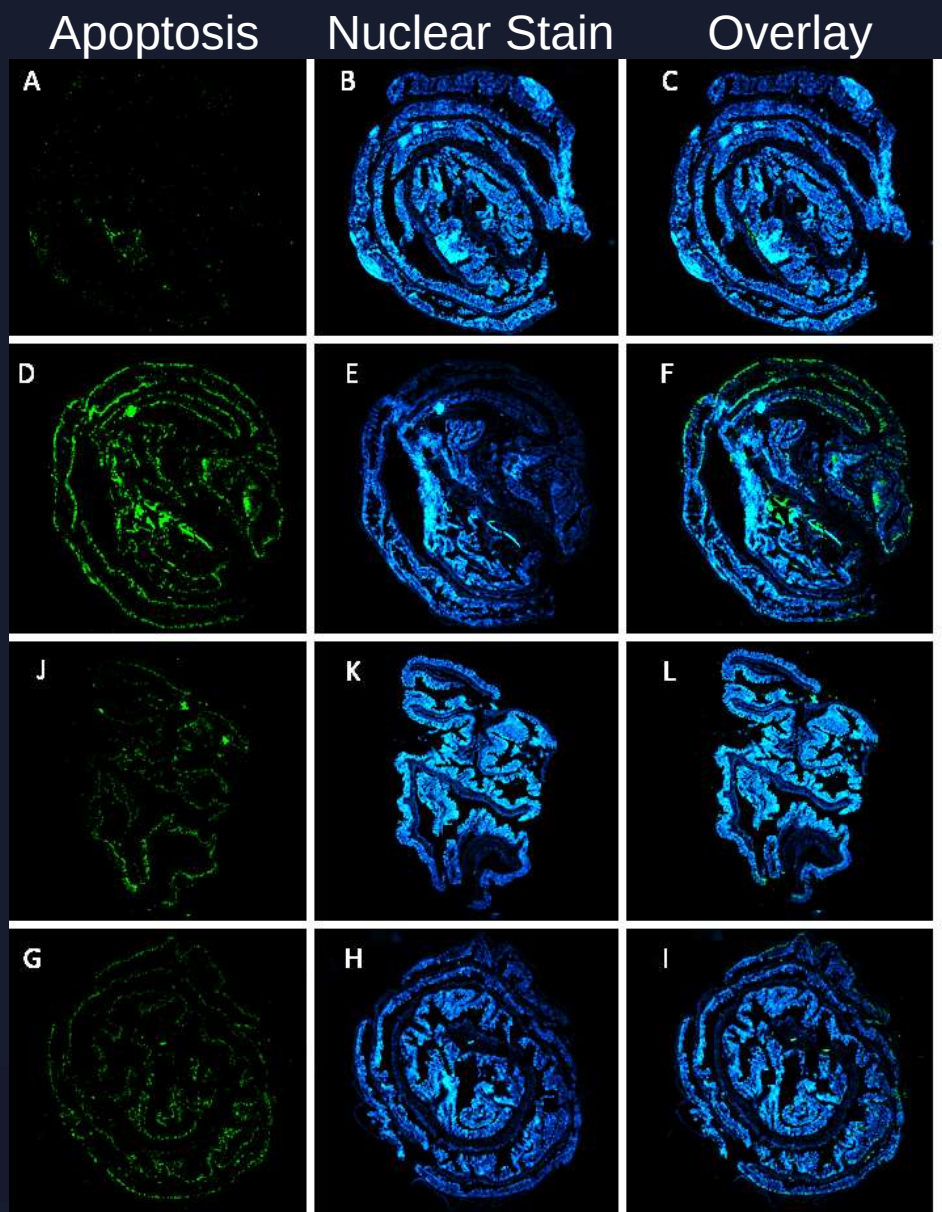
Biodistribution/Pharmocokinetics

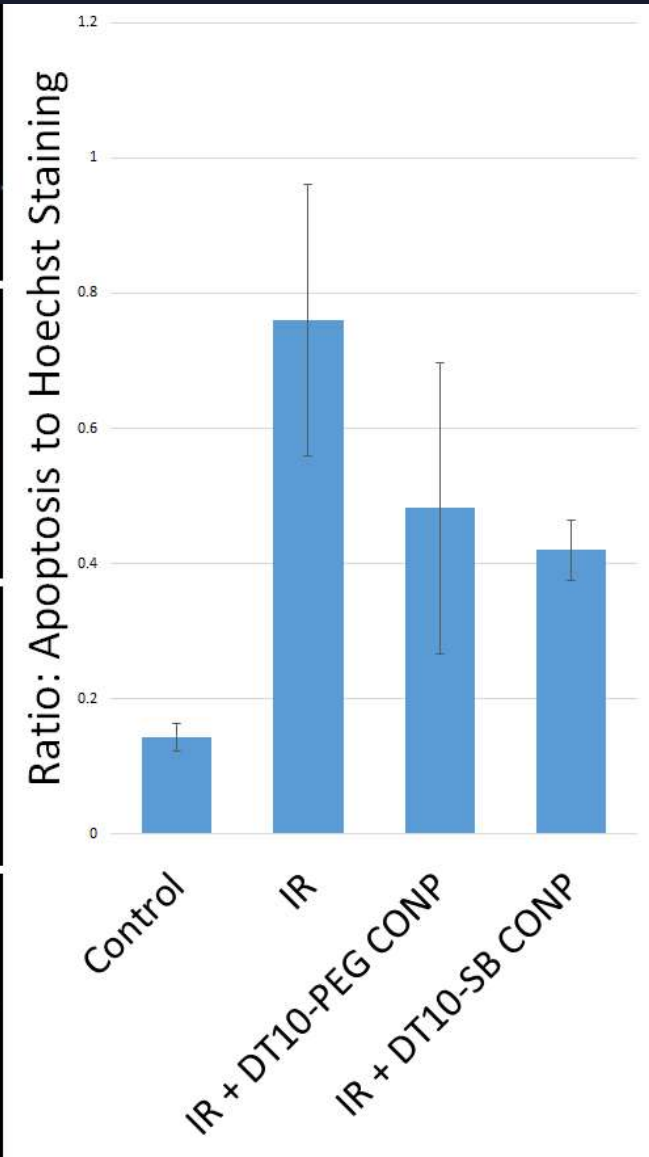


Yang, L., Sundaresan, G., Sun, M., Jose, P., Hoffman, D., McDonagh, P.R., Lamichhane, N., Cutler, C.S., Perez, J.M., and Zweit, J. (2013). Intrinsically radiolabeled multifunctional cerium oxide nanoparticles for in vivo studies. J. Mater. Chem. B *1*, 1421–1431.

Pre-Treatment with CONPs Decreases Colon Crypt Cell Radiation-Induced Apoptosis

- Control
- IR Only
- IR + DT10-PEG CONP 10 µg IV
- IR + DT10-SB CONP 10 µg IV





Summary of Potential Research

- Marrying Cancer molecular imaging and nanotechnology enables:
  - Simultaneous imaging and therapy of tumors,
  - Integrated multi-modality and multifunctional probes,
  - Multiple biologies within the same *in vivo* environment,
  - Opportunity to study tumor and TME, to link the role of the immune system in tumor biology and therapy,
  - Impact a more comprehensive biological picture of cancer tumorgenesis and workings of therapy/s.

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Developing Molecular Imaging and Nano-Technologies to Study Real Time *in vivo* Biology