Actinium-225

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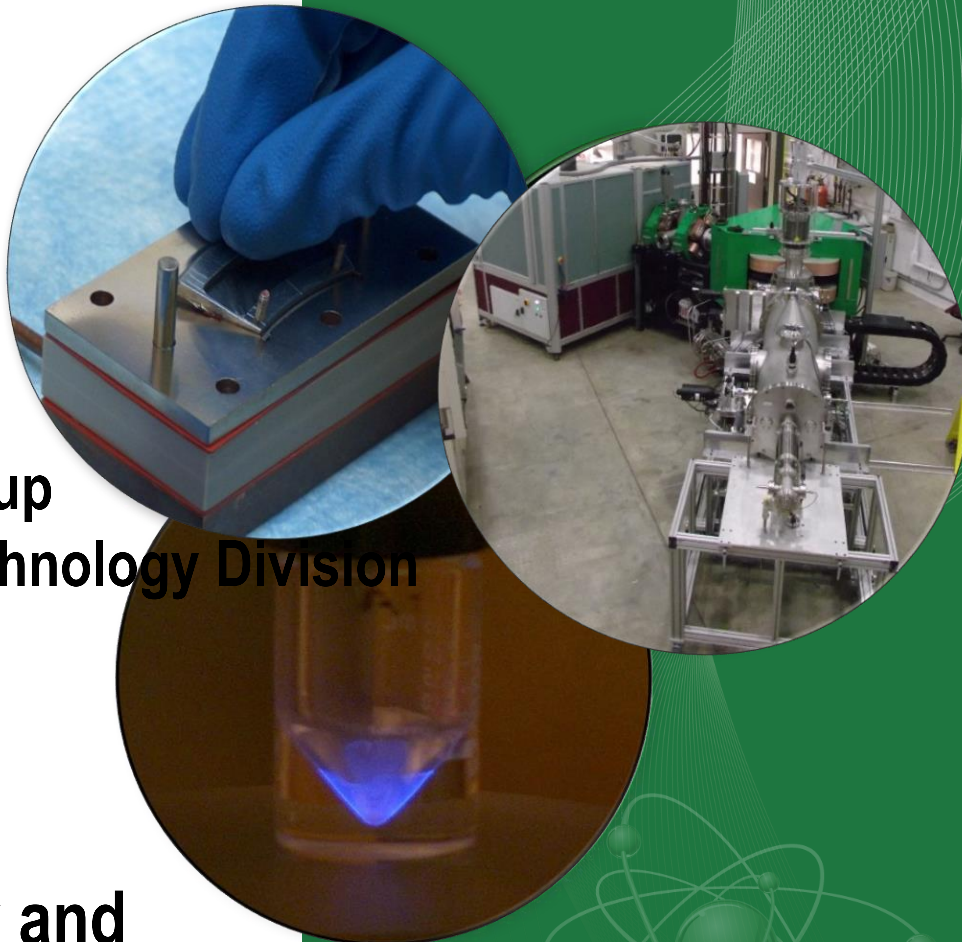
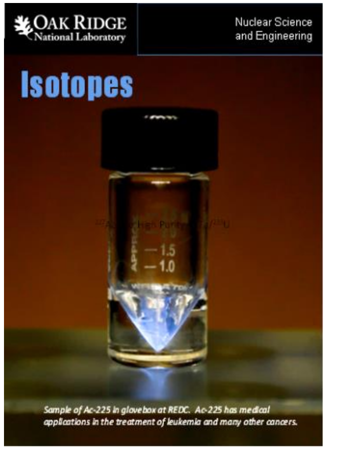


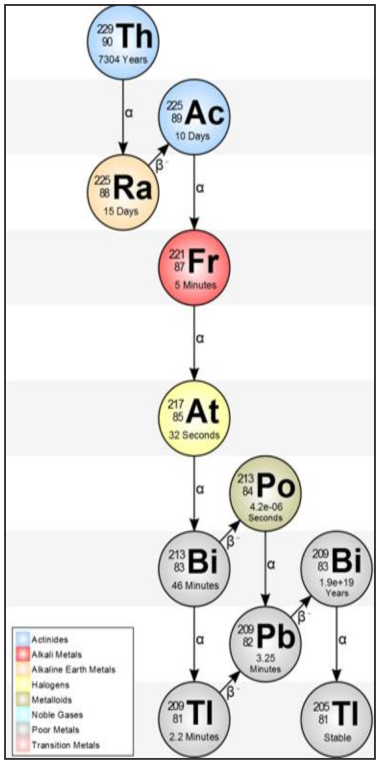
NCI Workshop on Dosimetry and Systemic Radiopharmaceutical Therapy
April 19-20, 2018

Outline



- ORNL Ac-225 History
- New initiatives to enhance production of Ac-225
- Nuclear Recoil Following α-decay, and Release of daughters from conventional ligands
- Possible mitigation via use of Nano-particles for encapsulation of α-emitting radionuclides

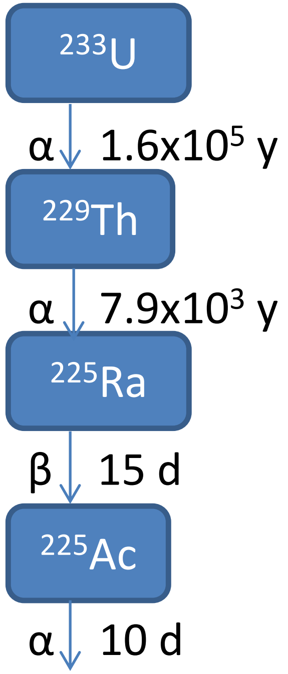
Actinium-225, A Promising Isotope for Targeted α-Therapy



Cancer type	Radioconjugate	Phase	No. of patients
Leukemia	^{213}Bi-HuM195mAb	Phase I	18
Leukemia	^{213}Bi-HuM195mAb	Phase I/II	31
Leukemia	^{225}Ac-HuM195mAb	Phase I	18
Lymphoma	^{213}Bi-rituximab	Phase I	12
Melanoma	^{213}Bi-9.2.27mAb	Phase I (intralesional)	16
Melanoma	^{213}Bi-9.2.27mAb	Phase I (systemic)	38
Glioma	^{213}Bi-Substance P	- Phase I	2 6+19
Neuroendocrine tumours (GEP-NET)	^{213}Bi-DOTATOC	Phase I	25

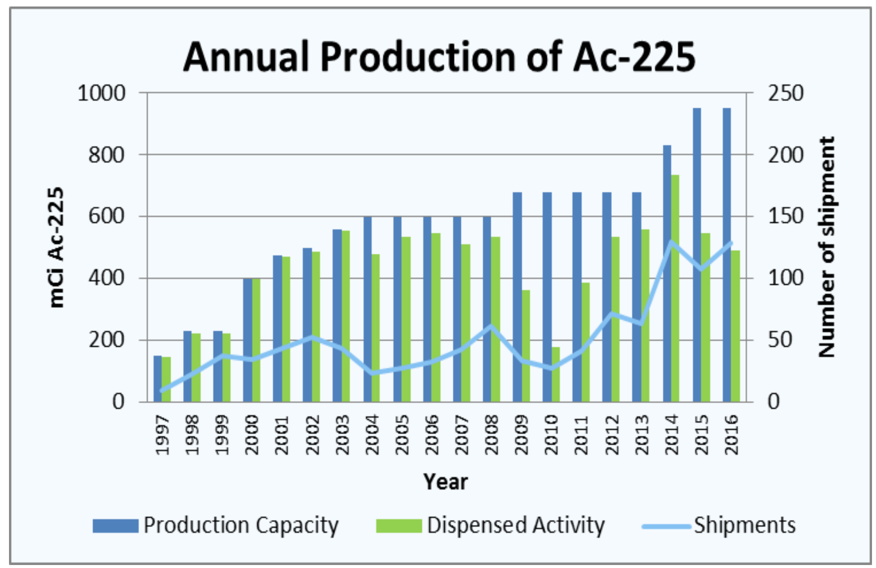
International Atomic Energy Agency. Technical Meeting Report "Alpha Emitting Radionuclides and Radiopharmaceuticals for Therapy" IAEA Headquarters Vienna, Austria. 24-28 June **2013**.

Background of actinium-225 production at ORNL



- ORNL has been the main supplier of ^{225}Ac (via decay of existing ^{229}Th stock) since 1997.
- 700-900 mCi of ^{225}Ac is harvested annually from 130–mCi ^{229}Th stock at ORNL.
- 6-12 campaigns are performed per year, and campaign **190** is currently underway

- **The present supply of ^{225}Ac is insufficient for current medical and research demands of ~6 Ci/year.**



Recognition of the Need for Enhanced Supply of ^{225}Ac

NSAC-I: Compelling Research Opportunities Using Isotopes (2009)
"Invest in new production approaches of alpha-emitters with highest priority for ^{225}Ac. Extraction of the thorium parent from ^{233}U is an interim solution that needs to be seriously considered for the short term until other production capacity can become available."

Th-229 content of ^{233}U is currently estimate at **~14 Ci**, which can supply **85 Ci** of ^{225}Ac per year – sufficient for preparation of **>100,000 patient doses**

New Initiatives to Enhance Production of Ac-225

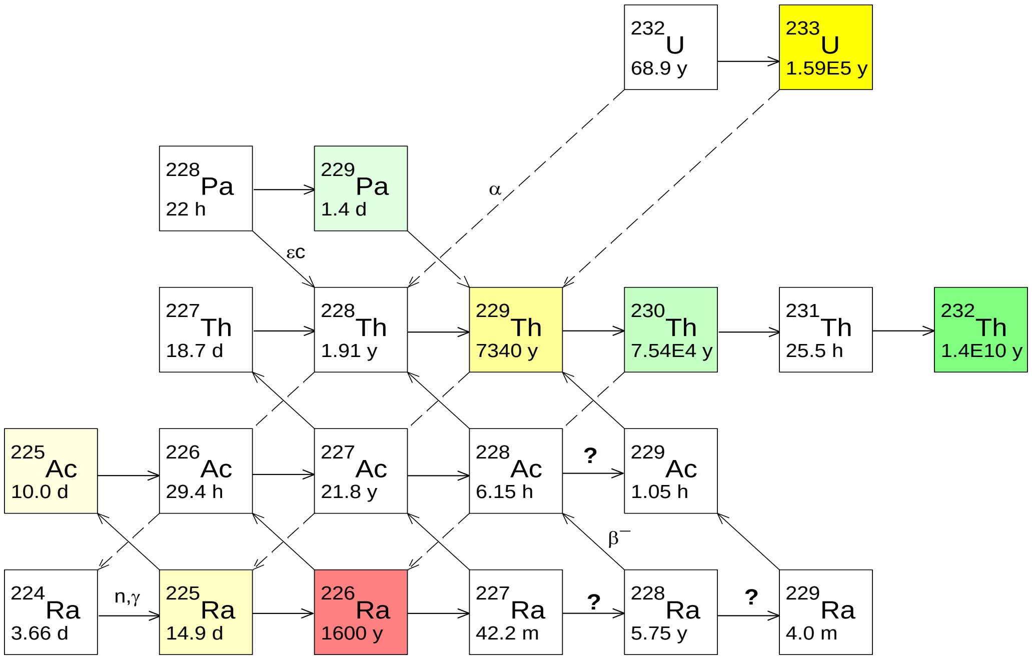
- Direct production of ^{225}Ac in a high energy proton accelerator
- Reactor Production of ^{229}Th at ORNL High Flux Isotope Reactor (Nuclear Data)
- Production of ^{229}Th via low energy protons (Nuclear Data)

Direct production of ^{225}Ac in a proton accelerator

The new collaboration between ORNL, BNL and LANL aims at developing a plan for full-scale production and stable supply of ^{225}Ac by irradiating ^{232}Th targets in the BNL BLIP and LANL IPF, and target processing at ORNL

ORNL Contributions:

- Develop the processing chemistry
- Evaluate yields and impurities
- Construct and evaluate ^{225}Ac/^{213}Bi Generator
- Provide Ac and generator to selected customers for in vivo evaluation



1st publication of tri-lab efforts: Griswold et al, Large Scale Accelerator Production of ^{225}Ac: Effective Cross Sections for 78-192 MeV Protons Incident on ^{232}Th Targets, 2016

Challenges Associated with Accelerator-Based Production of ^{225}Ac -- Complex Chemistry

Thorium Target Mass :
1-10 g – initial mass, 50-100 g – anticipated for Ci-level targets

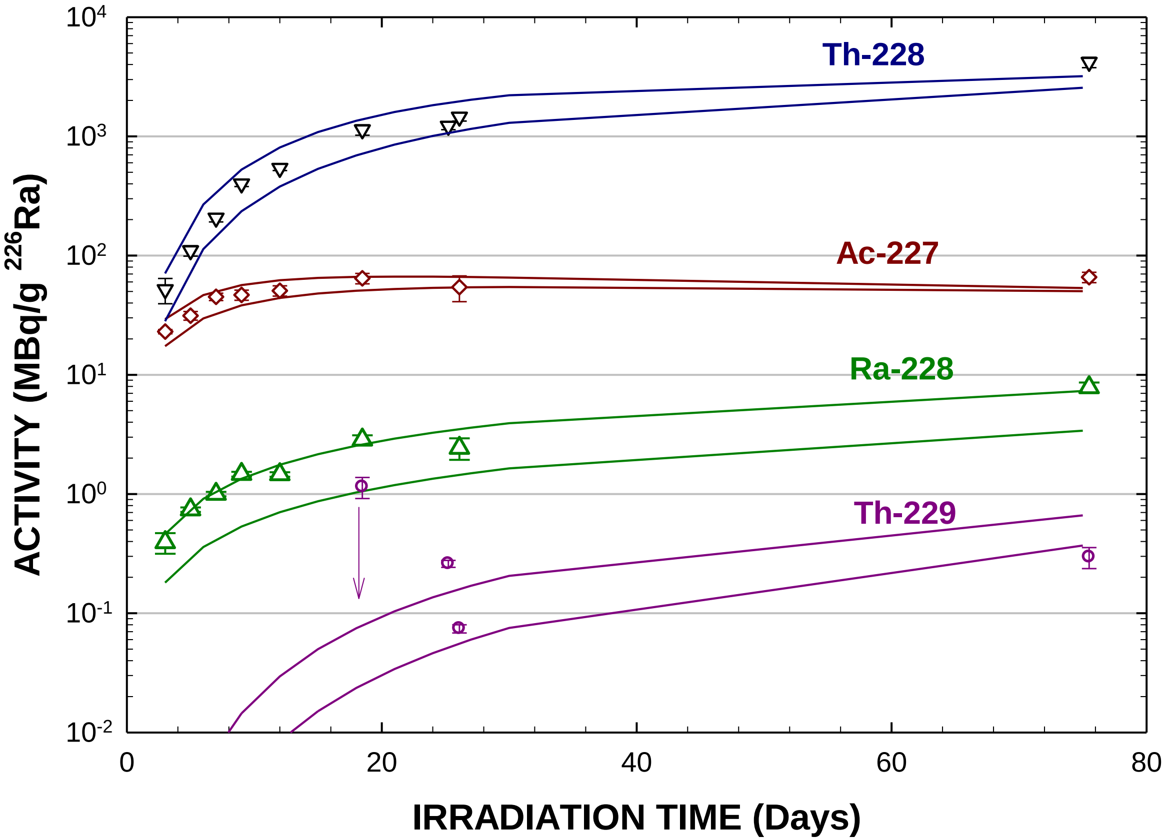
Production of Radiolanthanides:
Significant challenge to separate trivalent Ln-isotopes from ^{225}Ac (specifically ^{140}La and ^{141}Ce)

Production of large quantities of fission products:
In the 100-200 MeV proton energy range, for every mCi of ^{225}Ac, 12.5 mCi of fission products are produced

Timing: The ^{227}Ac/^{225}Ac ratio (~0.2% at EOB) gets worse with time

Toxicity: Biological toxicity of minute amount of 0.2% ^{227}Ac in ^{225}Ac is not evaluated

Reactor Production of Thorium-229

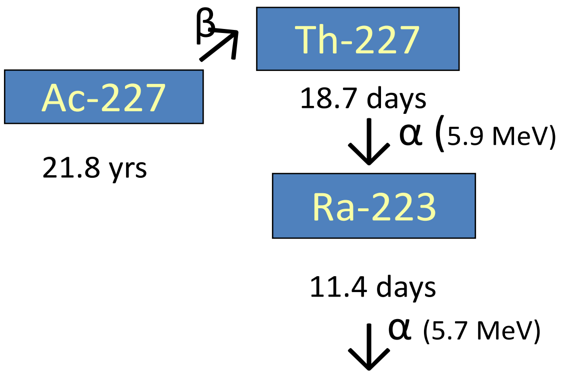


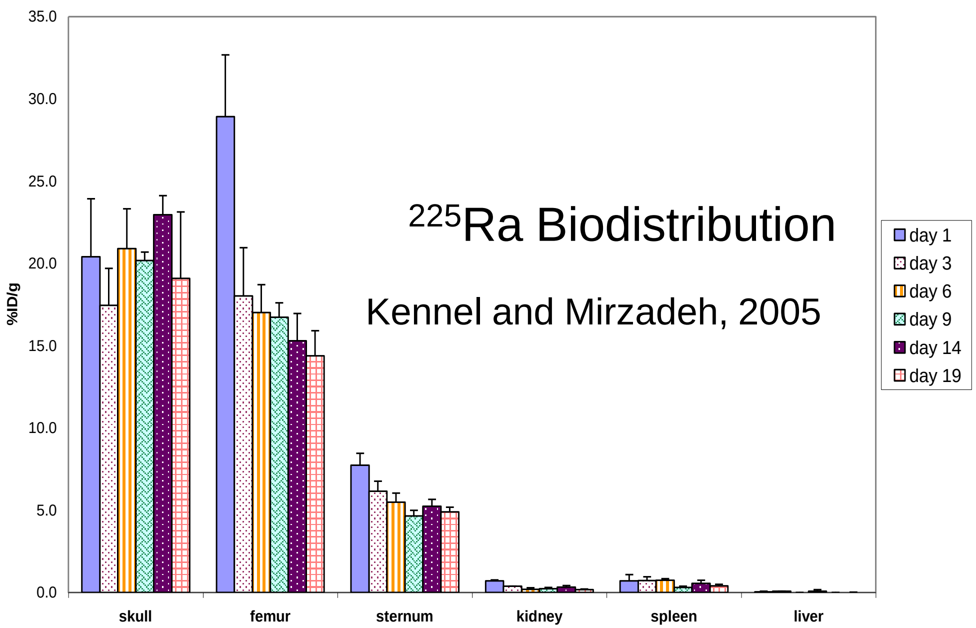
- Projected ^{229}Th yield for 6 cycle irradiations: 18-23 mCi per g of ^{226}Ra, with ^{228}Th and ^{227}Ac contaminations of 3000 and 50 times larger.

- 20 mCi of ^{229}Th will generate ~140 mCi of ^{225}Ac per year

Reactor Production of Thorium-229, Hogle, et al., ARI, 114, 19-27 (2016)

Xofigo, 1st approved "targeted" alpha therapy for treatment of advanced prostate cancer





Lanthanum phosphate NPs system for sequestering radionuclides and daughter products

- Monazite is **resistant to radiation damage**, even under heavy metal ion bombardment
- Low aqueous solubility (**K_{sp}~ 10^{-37}**) and numerous metal-oxygen covalent bonds
- Can be loaded with more than one radionuclide
- Physical and chemical properties for additional functionalities
- **Rigidity of ceramic-based NPs will allow for dispersion of recoil energy -- mitigate global radiotoxicity**

Monazite:
Monoclinic crystalline structure

Major obstacles:

- NPs aggregation
- Recognition of NPs by phagocytic cells

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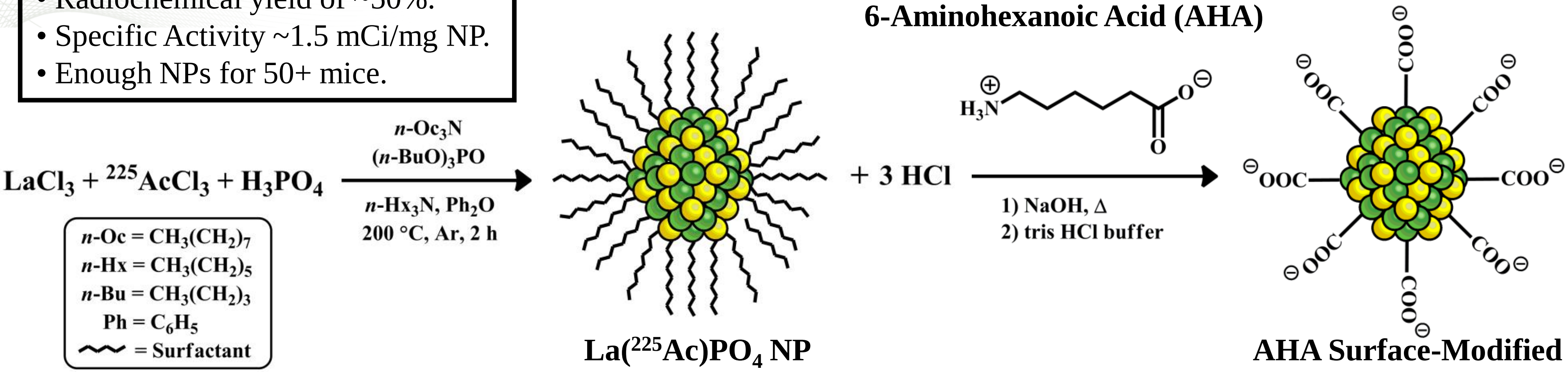
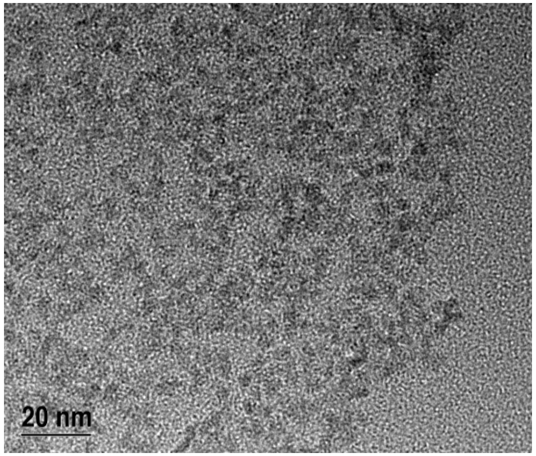
Synthesis and Surface Modification of La(^{225}Ac)PO_4 Nanoparticles

- Reaction yields ~5 mg NPs.
- Radiochemical yield of ~50%.
- Specific Activity ~1.5 mCi/mg NP.
- Enough NPs for 50+ mice.

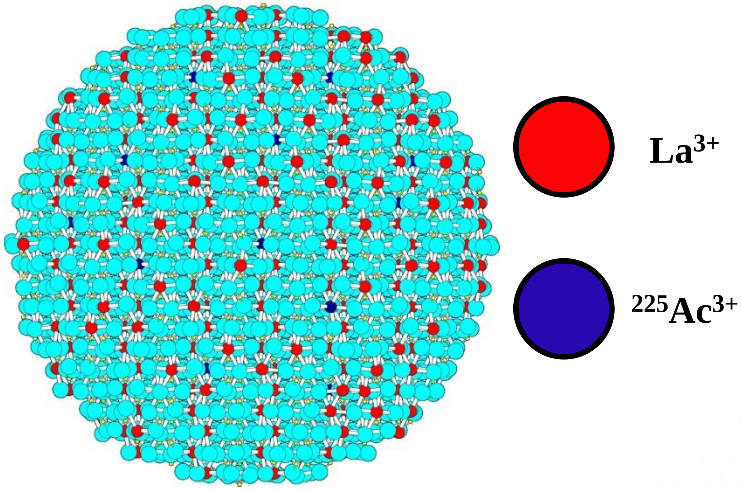


La(^{225}Ac)PO_4 NP

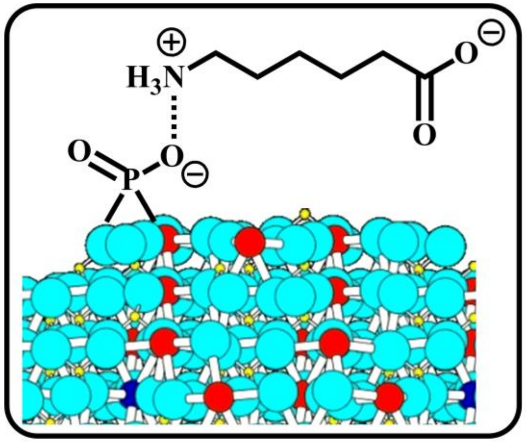
AHA Surface-Modified La(^{225}Ac)PO_4 NP



TEM image of cold $LaPO_4$ NPs



$^{225}Ac^{3+}$ can be incorporated into $LaPO_4$ NPs



Strong ionic bond between AHA and surface phosphate moieties

Lehmann, O.; *et al.*, *J. Phys. Chem. B*, **2003**, *107*, 7449-7453.
Meiser, F.; *et al.*, *Angew. Chem.-Int. Edit.*, **2004**, *43*, 5954-5957.

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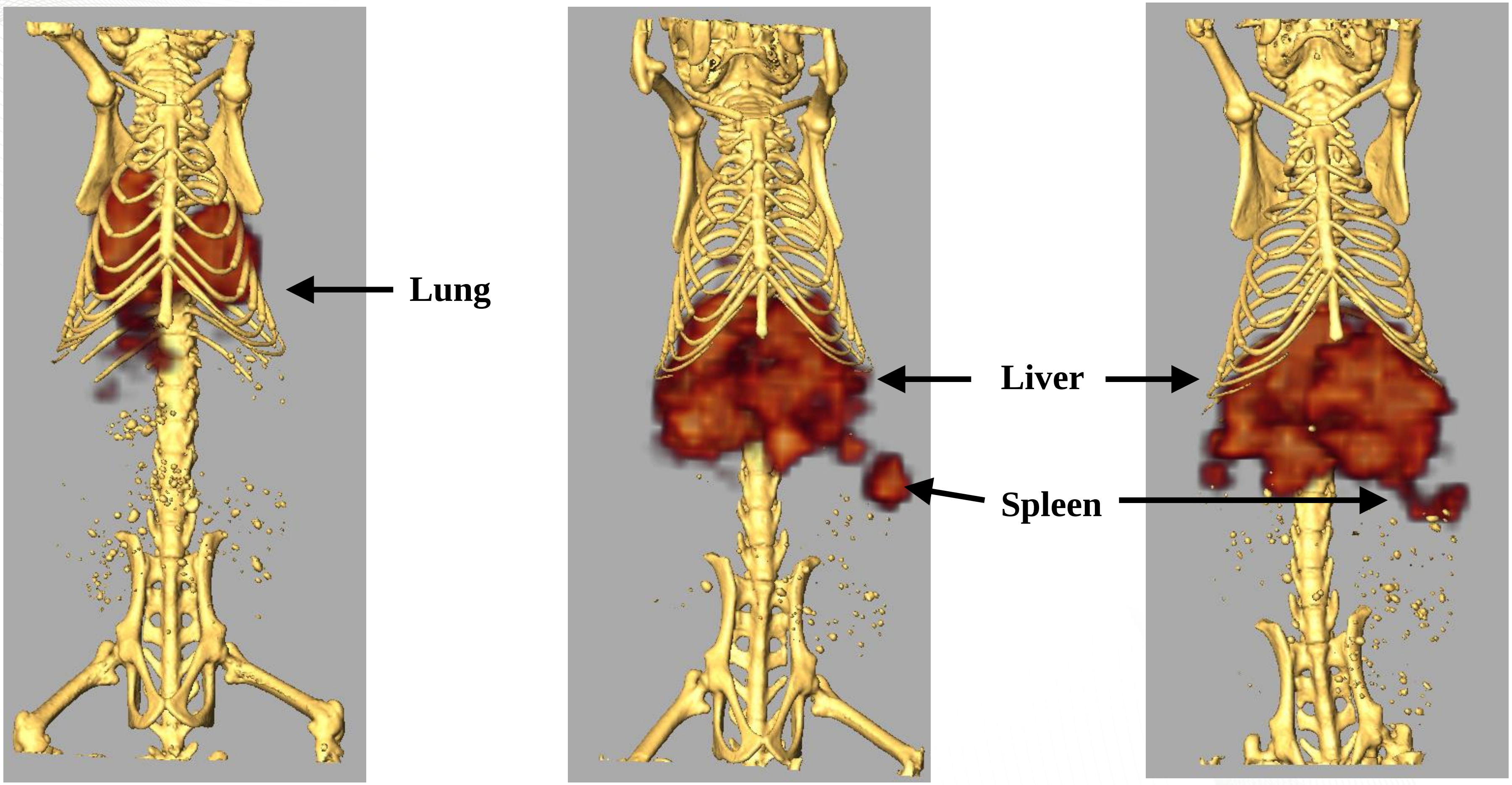
SPECT/CT Images of Biodistribution of $La(^{225}Ac)PO_4$-mAb Conjugates



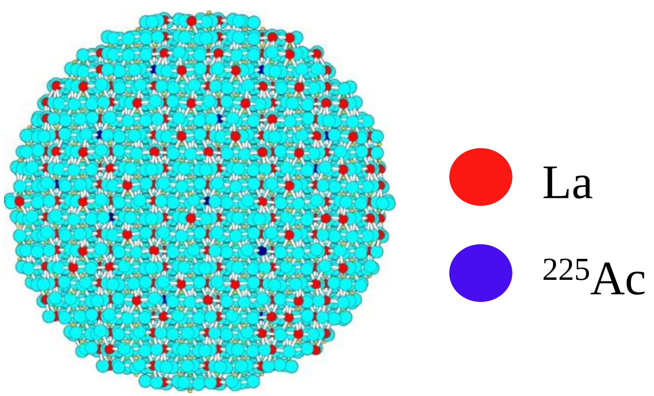
NP-mAb 201B

NP-mAb 201B + unconjugated mAb 201B

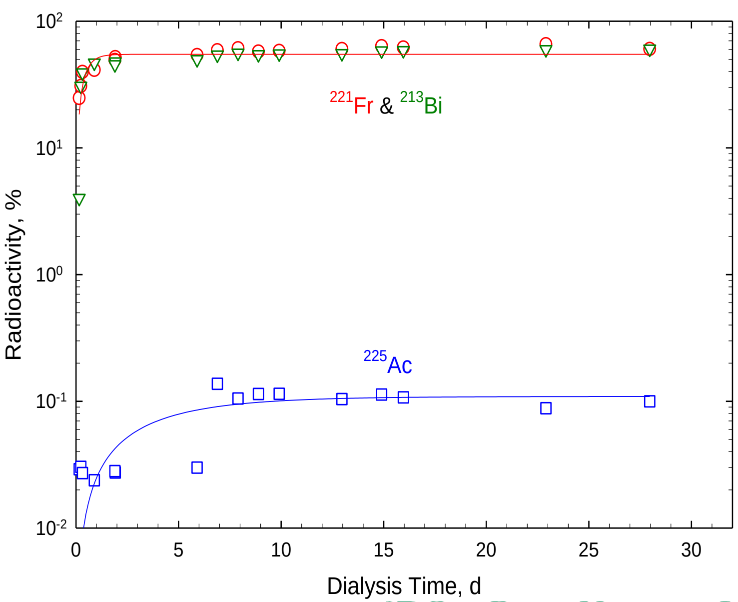
NP-mAb 33

$LaPO_4$ Nanoparticles Platform for in-vivo Delivery of Actinium-225

Isotope	Half-life	α-Energy (MeV)	α-Recoil Energy (keV)	Recoil Range (nm)
^{225}Ac	10 d	5.829	107	20
^{221}Fr	4.9 m	6.341	116	22
^{217}At	32.3 ms	7.067	130	24
^{213}Bi	46 m	8.376	154	29



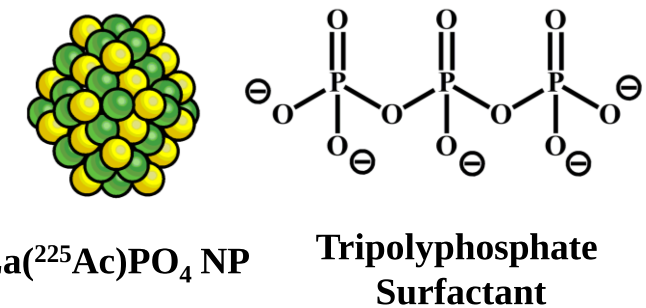
In-vitro Release of ^{225}Ac, ^{221}Fr and ^{213}Bi from $La(^{225}Ac)PO_4$ NPs



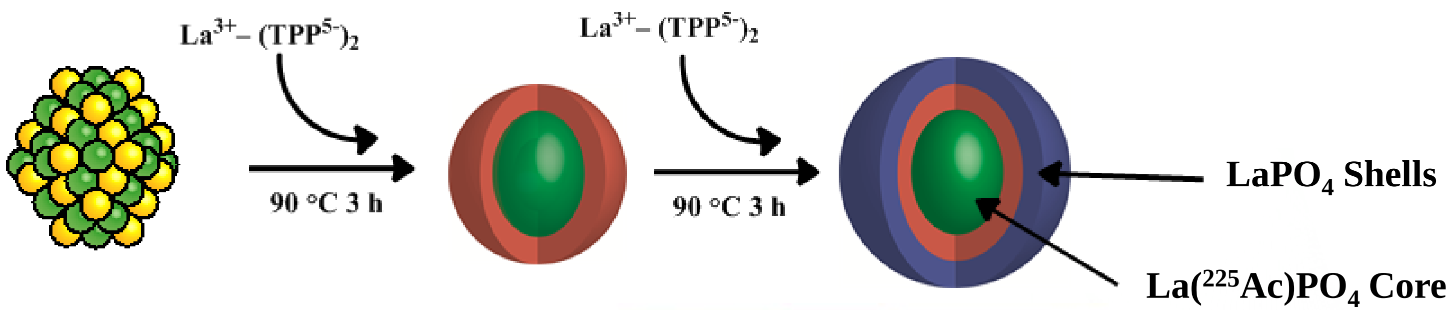
2^{nd} Generation of NPs, using aqueous synthesis and core-shell approach

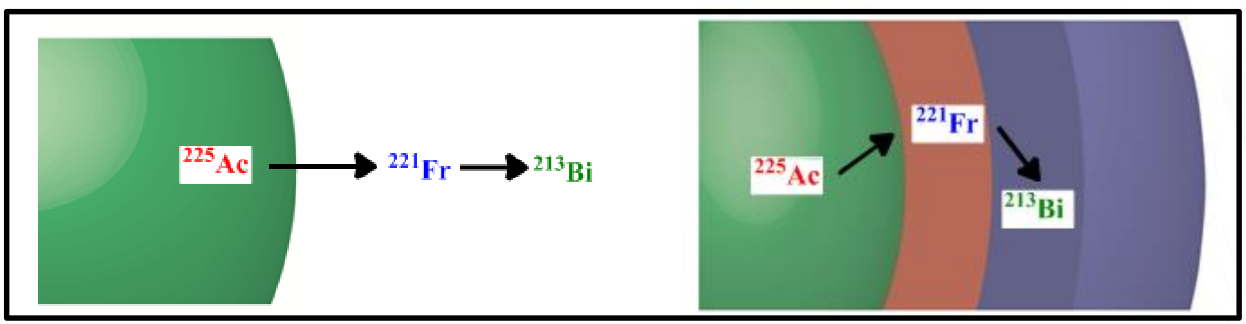
- Aqueous method: more facile, scalable, and reproducible than sol-gel process

$$La(NO_3)_3 + {}^{225}Ac(NO_3)_3 + Na_5P_3O_{10} \xrightarrow{90\ °C\ 3\ h}$$

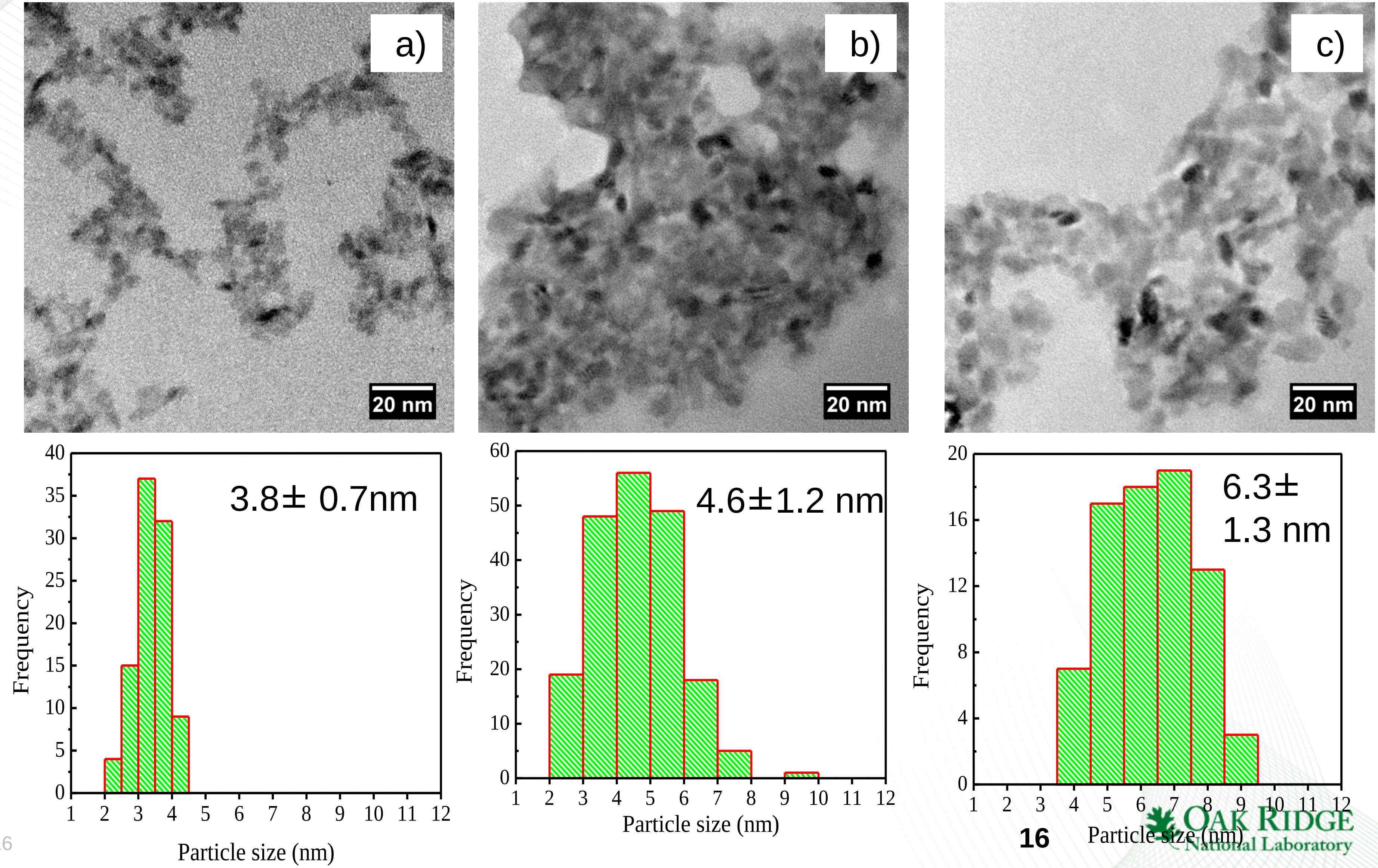


- Core-shell approach to reduce release of daughters

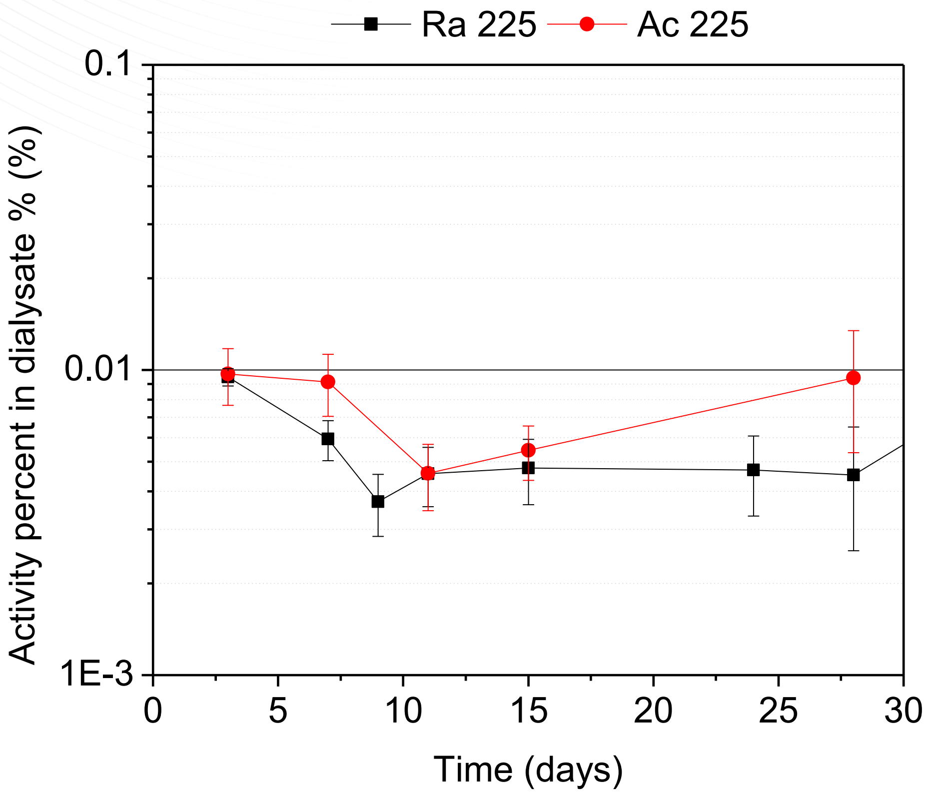




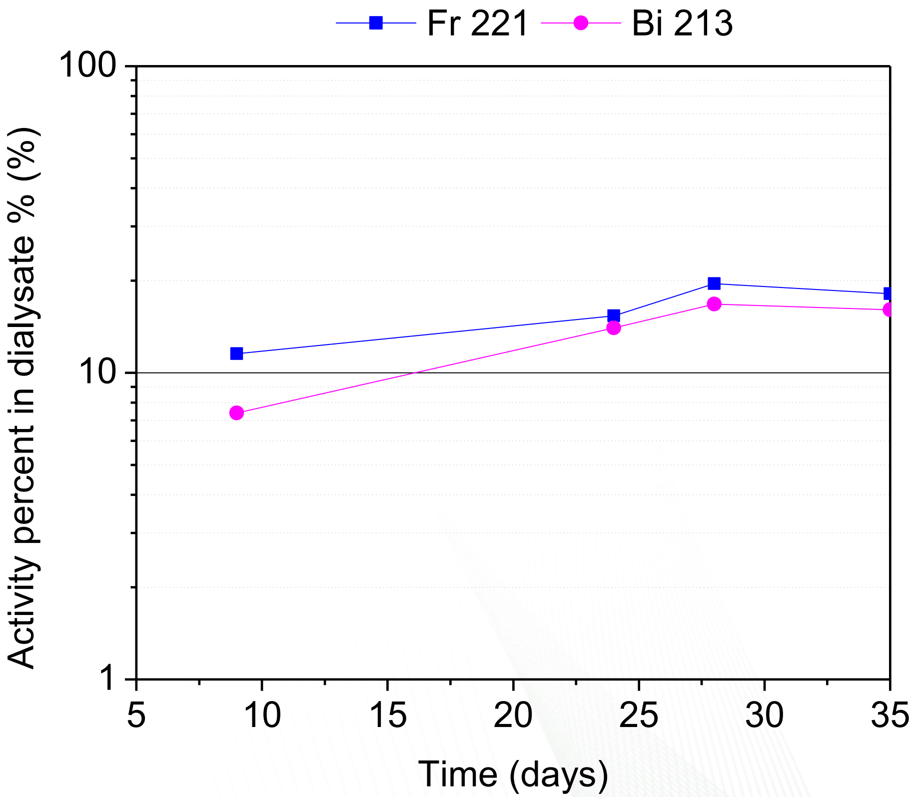
TEM images of $LaPO_4$ nanoparticles a) core b) core -1 shell and b) core -2 shells



In-vitro Release of $^{225}Ra/^{225}Ac$ from Core + 2 shells



Release of ^{225}Ra, ^{225}Ac



Release of ^{221}Fr and ^{213}Bi

Summary

- Retentions of ^{225}Ra and ^{225}Ac in the core-2 shells $LaPO_4$ NPs was >99.9% over a period of 3 weeks. >80% of decay daughters were retained after 3 weeks.

- Similar platform, core + 2 shell $LaPO_4$ NPs retained >99.9% of ^{227}Th and ^{223}Ra. Retention of ^{223}Ra daughter, ^{211}Pb, was >99% over 3 weeks

Future work to demonstrate the usefulness of $LaPO_4$ NPs as carriers for radiation therapy:

- **A complete study of NPs surface chemistry**
- **Evaluation of the *in vivo* radiotoxicity**