Nanoparticles in radionuclide therapy

Antonia Denkova (TU Delft, the Netherlands)
31th of January, KVI symposium

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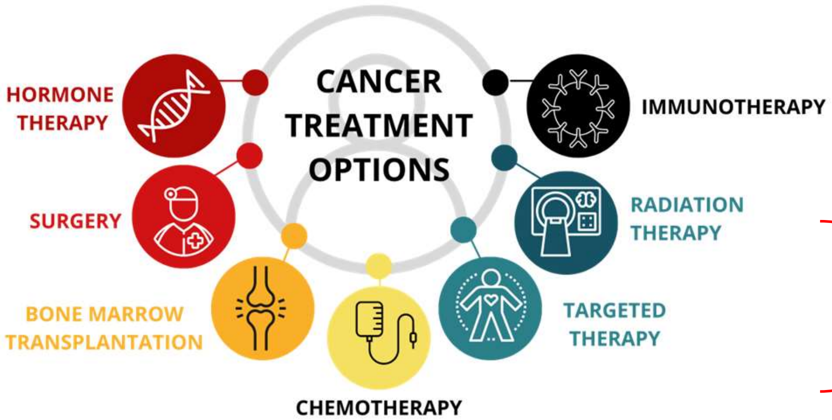
Cancer treatment

Treatment often depends on type, location and staging of the tumor



Radiotherapy includes radionuclide therapy and external radiation (beam) therapy

Targeted therapy includes also some radionuclide therapies

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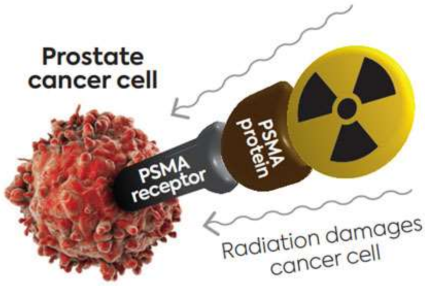
Background

Targeted Radionuclide Therapy (TRT)



- **Radionuclide:** α, β^-, Auger electron
- **Linker/Carrier:** a chelator, nanoparticles, microspheres
- **Targeting moiety:** Antibody, peptides, inhibitors

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https://www.sunwaycancercentre.com/en/targeted-radionuclide-therapy

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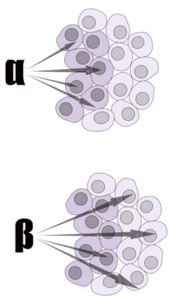
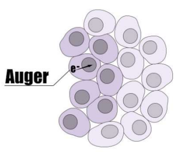
Therapeutic radionuclides: types

- Alpha emitters
- Beta emitters
- Low energy electron emitters

Decay	Energy	Range	LET (keV / µm)
α	5 – 9 MeV	40 – 100 µm	~ 80
β^-	50 – 2300 keV	0.05 – 12 mm	~ 0.2
AE/IC	eV – keV	2 – 500 nm	~ 4 – 26





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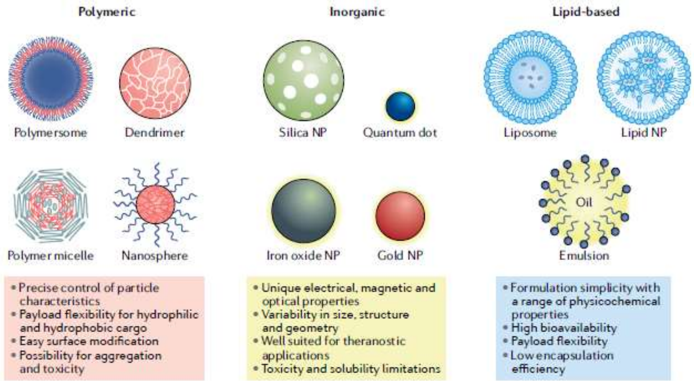
Nanoparticles for medical applications



Application of nanomedicine:
- Cancer imaging
- Cancer therapy
- Combination therapy
- Immunotherapy
- Gene therapy
- etc…

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Mitchell, M.J., Billingsley, M.M., Haley, R.M. *et al. Nat Rev Drug Discov* 20, 101–124 (2021).
Schroeder, A., Heller, D., Winslow, M. *et al. Nat Rev Cancer* 12, 39–50 (2012).

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When to use nanoparticles in targeted therapy

If particles allow for:

- Less side effects such as release of the radionuclide from its carrier
- Increase in efficiency
- Provided that there is no high uptake in sensitive tissues/organs e.g. liver

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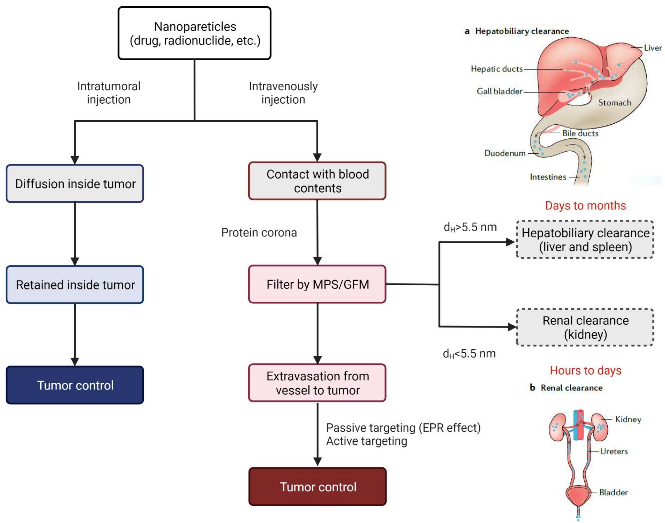
Biodistribution of nanoparticles

Journey of nanoparticles *in vivo*



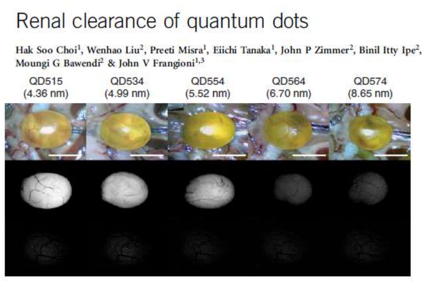
Factors influencing nanoparticle biodistribution

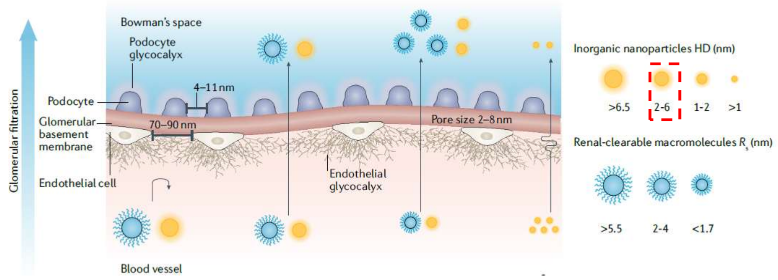
- Material
- Size (core & hydrodynamic diameter)
- Surface charge
- Capping molecules
- Hydrophobicity
- Density
- Targeting moiety
- etc.

Du, B., Yu, M. & Zheng, J., *Nat Rev Mater* 3, 358–374 (2018).
Cheng, P., Pu, K. *Nat Rev Mater* 6, 1095–1113 (2021).

7

nature biotechnology First paper reporting nanoparticle renal clearance (2007)





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Soo Choi, H., Liu, W., Misra, P. et al. *Nat Biotechnol* 25, 1165–1170 (2007)
Du, B., Yu, M. & Zheng, J., *Nat Rev Mater* 3, 358–374 (2018).
Cheng, P., Pu, K. *Nat Rev Mater* 6, 1095–1113 (2021).

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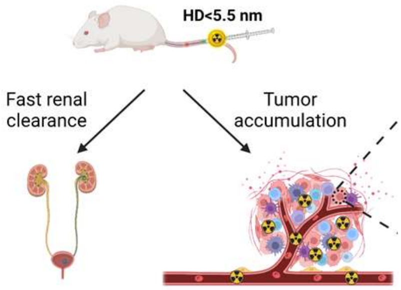
Renal Clearable NP & Radionuclide therapy



Function of nanoparticles in RNT:
- Radionuclide carrier
- Radiosensitizer

Fast clearance from body:

Pro:
Low toxicity to healthy organs

Con:
Low tumor uptake

- Fractionated doses
- Active targeting

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ACS Appl. Nano Mater. 2022, 5, 8680−8709

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Criteria of NPs selection

- d_H<5.5 nm
- No/low protein absorption
- Biocompatible
- Possibility of surface modification (targeting moiety, dye, drug, etc.)
- Imaging if possible
- Radiolabeling
- Simple synthesis and good reproducibility (for GMP)

Gold, silver and platinum

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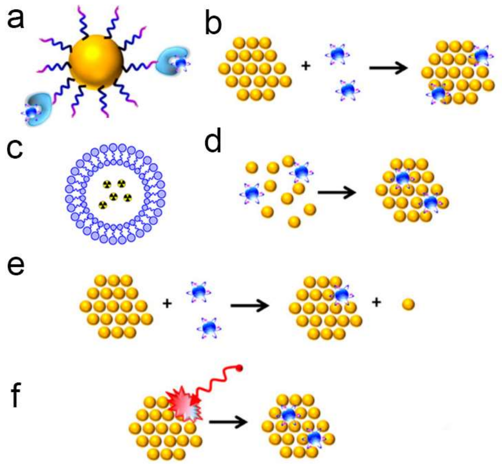
Radiolabeling of nanoparticles



- **Chelation**
- **Surface adsorption**
- Encapsulation
- **Radionuclide doping**
- Cation exchange
- Bombardment by neutrons or protons

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In vivo radionuclide generators

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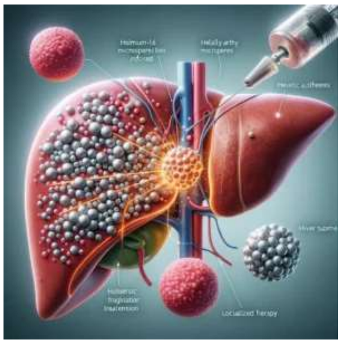
$^{166}Dy/^{166}Ho$ generator

- ^{166}Ho is used in radionuclide therapy
- A radionuclide generator of ^{166}Ho more beneficial
- ^{166}Dy ($t_{1/2}$ = 81.5 h) provides 3 times longer half-life time than ^{166}Ho
- **$^{166}Dy/^{166}Ho$ in vivo generator**



N. Klaassen et al. EJNMMI Radiopharmacy and Chemistry. 4. 10.1186/s41181-019-0066-3.

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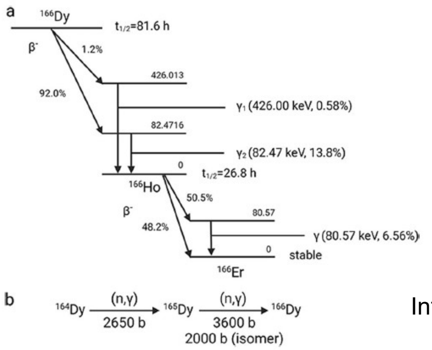
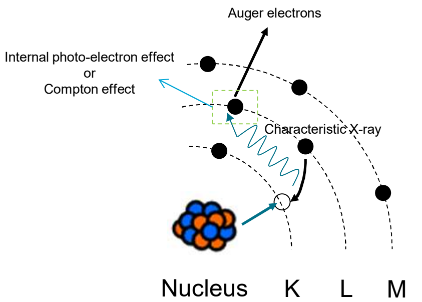
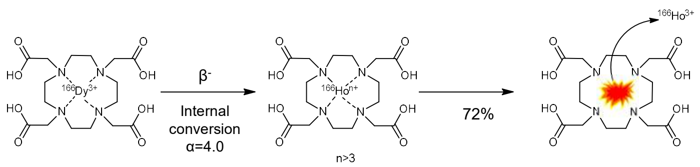
$^{166}Dy/^{166}Ho$ and internal conversion





Internal conversion ~ 72 %

Internal conversion → Auger cascade → Ion (Ho) with high positive charge



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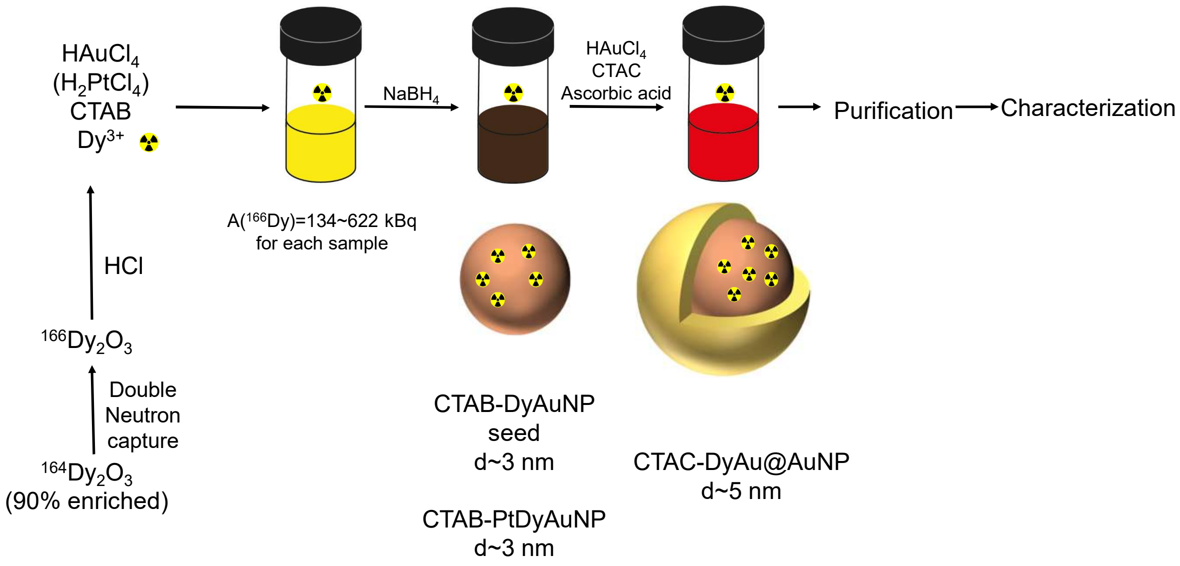
Au based nanoparticles as carriers for $^{166}Dy/^{166}Ho$



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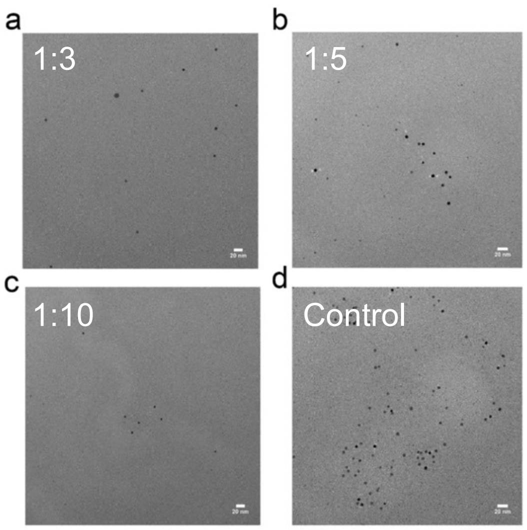
Results: Physical properties of DyAu@AuNPs



d~4.9 nm
Scale bar=20 nm

Incorporation of Dy content had little influence on the size of AuNPs

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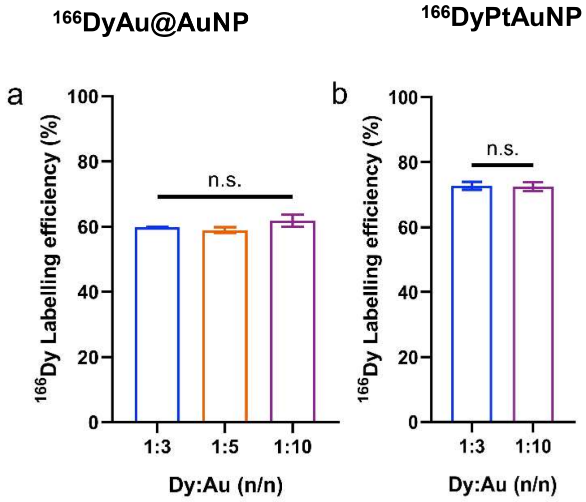
Results: ^{166}Dy radiolabelling efficiency



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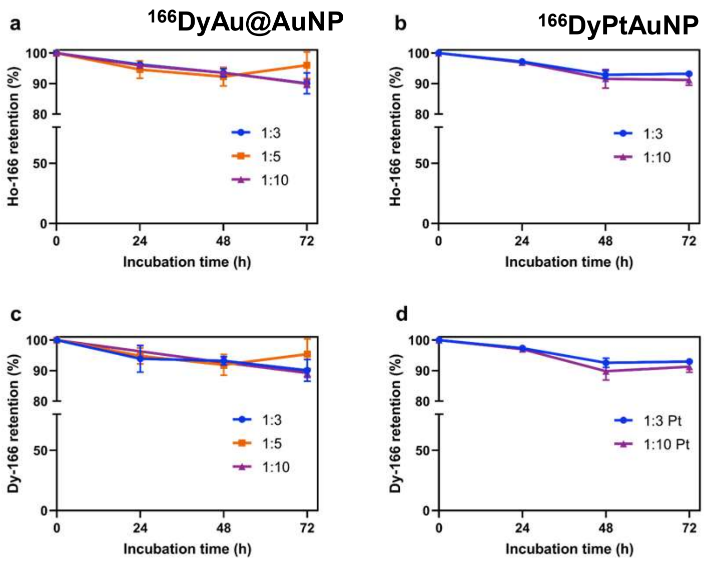
Results: ^{166}Dy and ^{166}Ho retention

^{166}Ho

^{166}Dy



2.5 mM DTPA
37 ℃
72 h

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Why is ^{166}Ho retained?

- Retention of ^{166}Dy:

Incorporation into the lattice structure of AuNP

- Retention of ^{166}Ho:

1) Incorporation into the lattice structure of AuNP
2) High amounts of free electrons in AuNP
3) High affinity of Au to electrons from environment

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Same concept can be applied to other in vivo generators – ^{212}Pb/^{212}Bi generator

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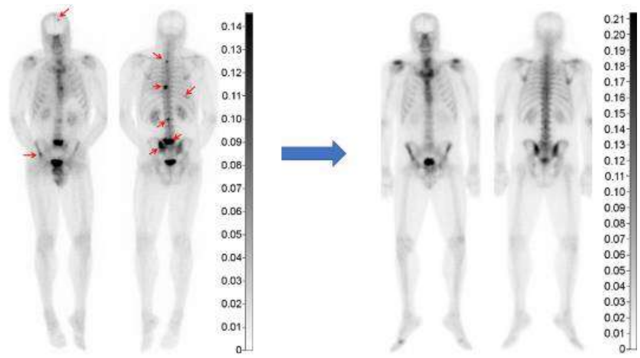
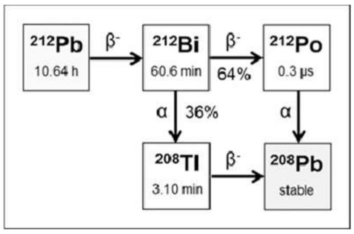
. ^{212}Pb/^{212}Bi in vivo generator

Targeted α-Emitter Therapy with ^{212}Pb-DOTAMTATE for the Treatment of Metastatic SSTR-Expressing Neuroendocrine Tumors





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Delpassand ES et.a;. J Nucl Med. 2022 Sep;63(9):1326-1333.

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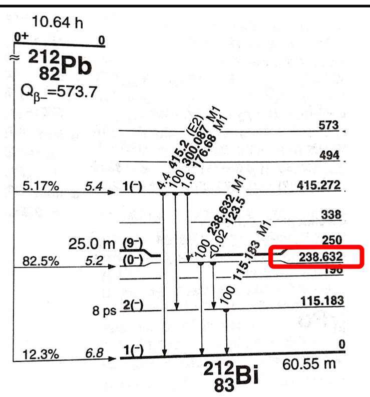
Radiochimica Acta 60, 1 – 10 (1993)

The Chemical Fate of ^{212}Bi-DOTA Formed by β^- Decay of ^{212}Pb(DOTA)$^{2-}$ *,**

By Saed Mirzadeh[1,2], Krishan Kumar[3] and Otto A. Gansow[1]
Chemistry Section, Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892

(Received August 30, 1991; revised March 2, 1992)



α=0.84

Internal conversion%=α/(1+α)=0.84/(1+0.84)=45.6%
Branching ratio=82.5%
In total: 45.6%*82.5%=37.6%

^{212}Pb-Pretargeted Theranostics for Pancreatic Cancer

David Bauer, Lukas M. Carter, Mohamed I. Atmane, Roberto De Gregorio, Alexa Michel, Spencer Kaminsky, Sebastien Monette, Mengshi Li, Michael K. Schultz and Jason S. Lewis

Journal of Nuclear Medicine November 2023, jnumed.123.266388; DOI: https://doi.org/10.2967/jnumed.123.266388

- 40% released from chelators
- 15 % in vivo
- Uptake of Bi in cells reduces loss

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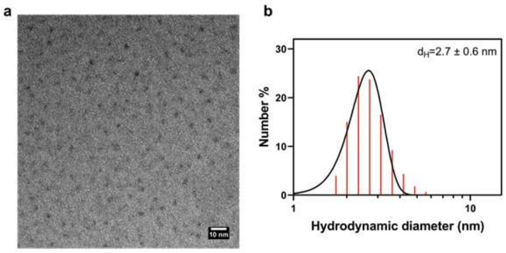
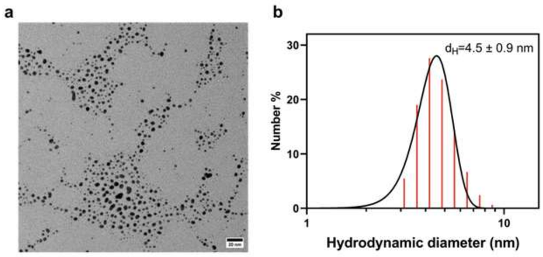
Silver and gold nanoparticles as carriers for ^{212}Pb

Pb-GSH-Ag_2TeNP (2.1 ± 0.3)



Pb-PEG350-AuTeNP (3 ± 0.9 nm)



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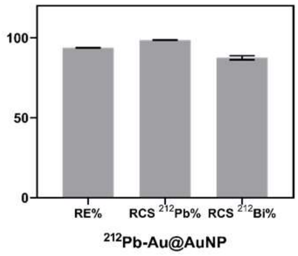
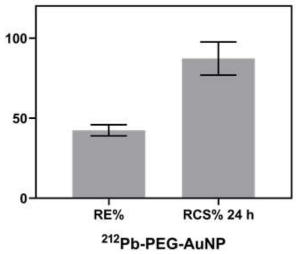
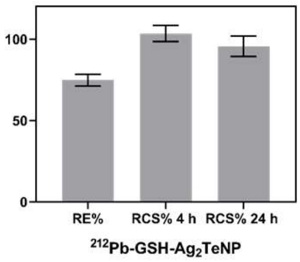
Radiolabeling efficiency and retention of ^{212}Bi







Excellent retention of ^{212}Bi on all particles

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R. Wang, H. Wolterbeek, A. Denkova, Journal of Labelled Compounds and Radiopharmaceuticals, 2024

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Possible mechanism

- Solidify
- Introduce to electron rich environment (high Z)

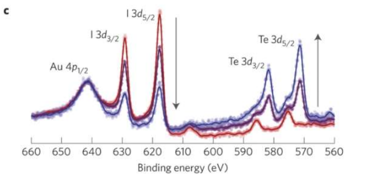
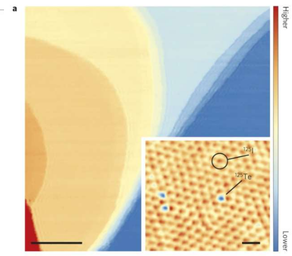


Figure 2: Atomic-scale characterization of radioactive ^{125}I monolayer and nuclear transmutation.



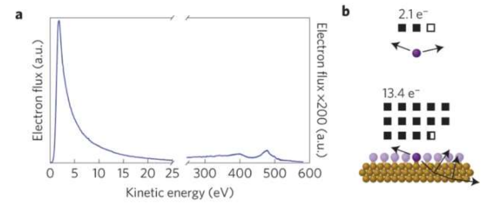
^{80m}Br: internal conversion coefficient=300

TABLE I

Complex	Concn. of complex, M	% retention	
$Co(NH_3)_5Br^{+2}$	0.01	0	
$[Co(NH_3)_5Br](NO_3)_2$	(solid)	14	
$PtBr_6^{-2}$	0.00166	52	52
	0.0005	70[a]	53
	0.0005 with 0.003 M NaBr	54	
$(NH_4)_2PtBr_6$	(solid)	100	

[a] Possibly some photocatalyzed exchange.

Figure 3: Electron emission from radioactive ^{125}I monolayer.



a, Representative electron emission spectrum shows that, in addition to the expected electron capture decay process Auger peaks at 480 eV (intensity ×200), a multitude of low-energy (0–20 eV) electrons are emitted from the ^{125}I/Au film. b, Schematic of electron backscattering from the metal film (bottom) that leads to sixfold enhancement of low-energy electron emission compared with atomic ^{125}I (top). Each square represents the average emission of 1 electron per decay with kinetic energy <10 eV (ref. 3).

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Adamson AW, Grunland JM. J Am Chem Soc. 1951;73(11):5508.
A. Pronschinske, P. Pedevilla, et al., Nat Mater 2015, 14, 904-907.

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Nanoparticles as carriers of Auger emitters

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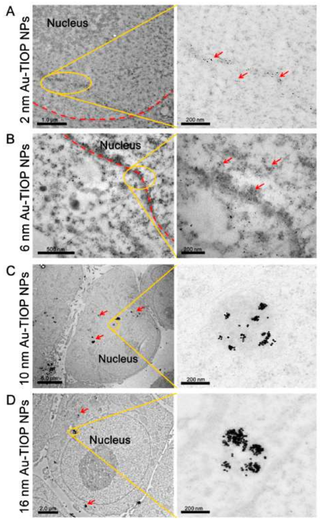
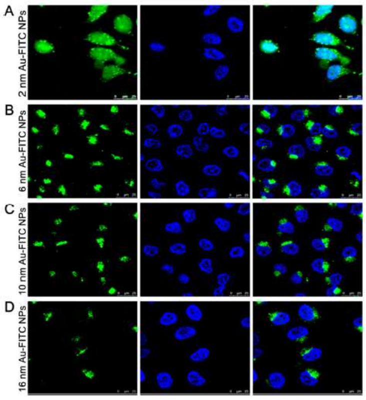
Penetration of nanoparticles inside cell nucleus





ACS Nano 2014, 8, 6, 5852–5862

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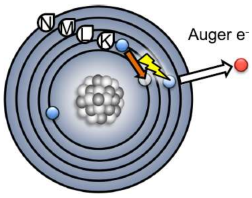
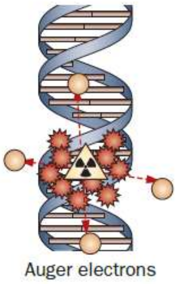
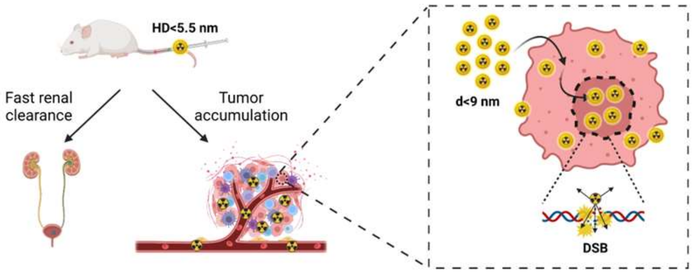
^{111}In - properties

^{111}In is used nowadays as a SPECT radionuclide for diagnostics

14.7 AE per decay







LET: 4–26 keV/µm

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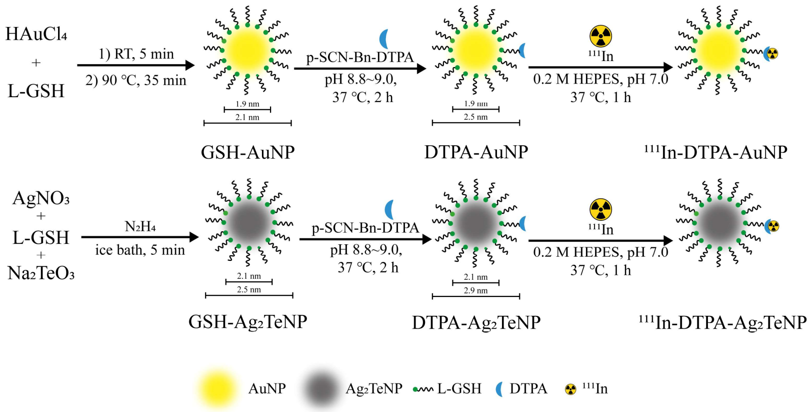
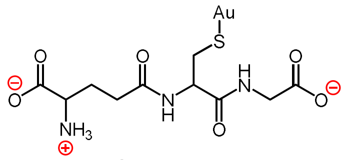
^{111}In-GSH-AuNP & ^{111}In-GSH-Ag_2TeNP





Glutathione

R. Wang, H. Wolterbeek, A. Denkova, manuscript in preparation

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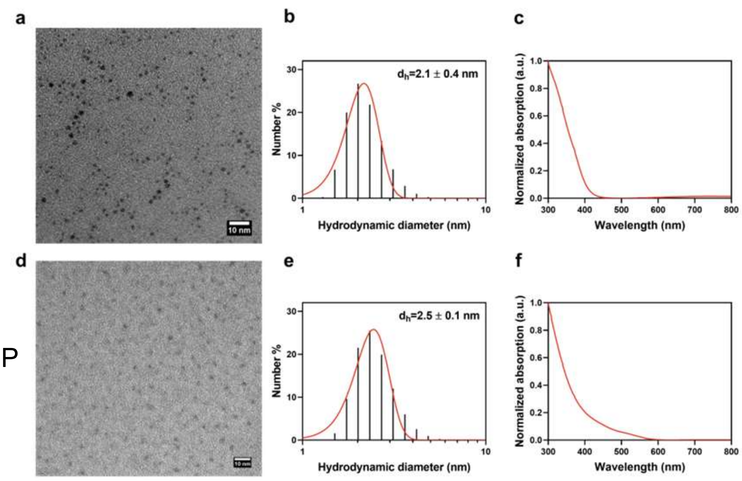
GSH-AuNP & GSH-Ag_2TeNP physical properties

GSH-AuNP
d=1.9 nm
d_H=2.1 nm

GSH-Ag_2TeNP
d=2.1 nm
d_H=2.5 nm



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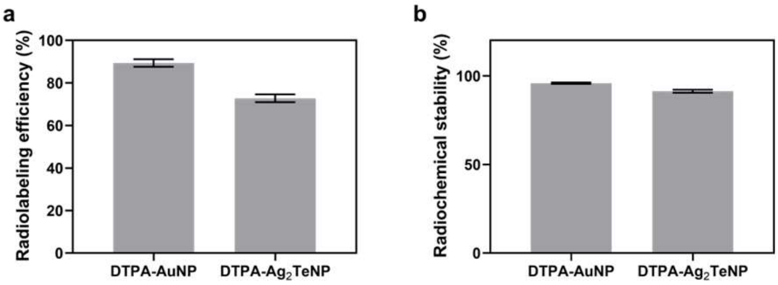
GSH-AuNP & GSH-Ag_2TeNP radiolabeling

RCY

24 h RCS



RCS>95%

DTPA:NP=~1
NP:^{111}In=100:1
0.2 M HEPES pH 7.0, 37 ℃, 1 h

PD-10 column, PBS as eluent

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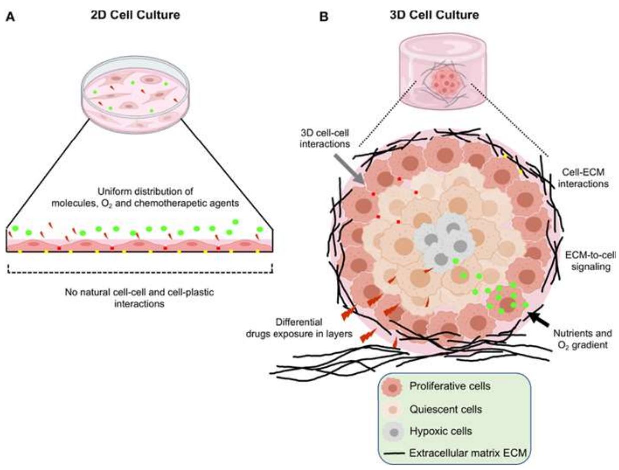
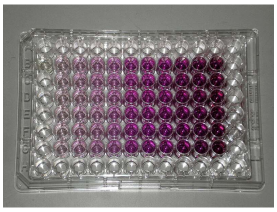
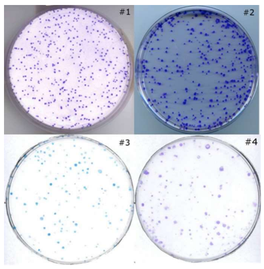
Cell experiments

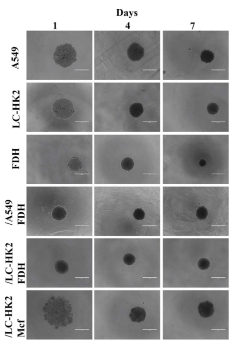




Viability assay



Colonies assay – cell survival



Size (volume) assays

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Salinas Vera. Frontiers in Oncololgy 2022

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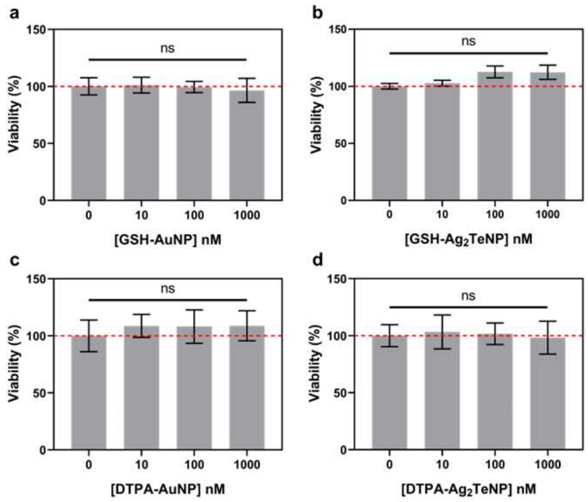
^{111}In-GSH-AuNP & ^{111}In-GSH-Ag_2TeNP cell experiments



NPs are biocompatible w/o DTPA

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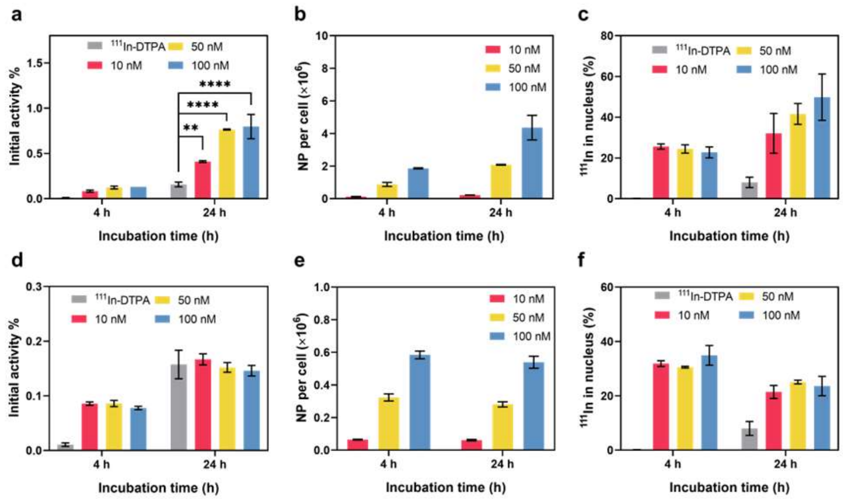
^{111}In-GSH-AuNP & ^{111}In-GSH-Ag_2TeNP *in vitro* exp. 2D uptake

AuNP

2D: 0.8%
Nucleus: 49.8%

Ag_2TeNP

2D: 0.15%
Nucleus: 23.6%



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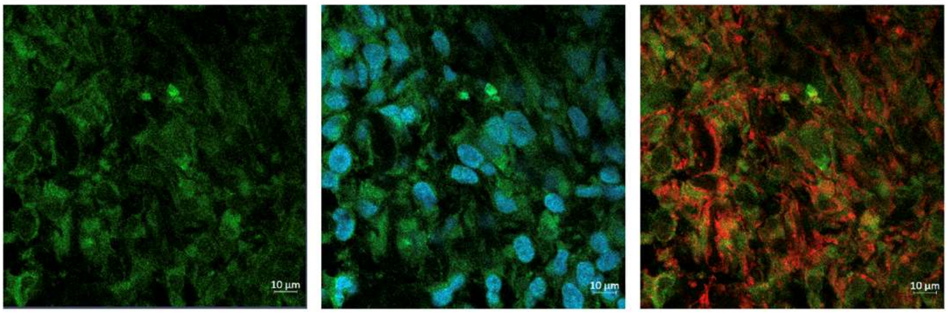
FITC-Ag_2TeNP confocal microscopy

NP | Nucleus+ NP | Nucleus+ NP + Cytoplasam



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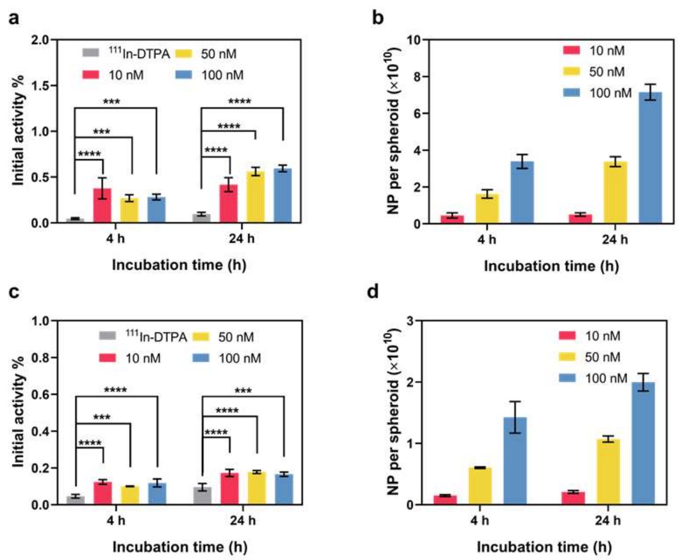
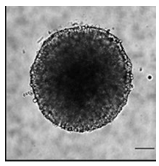
^{111}In-GSH-AuNP & ^{111}In-GSH-Ag_2TeNP *in vitro* exp. 3D uptake

AuNP
3D: 0.6%

Ag_2TeNP
3D: 0.17%





Tumour spheroid

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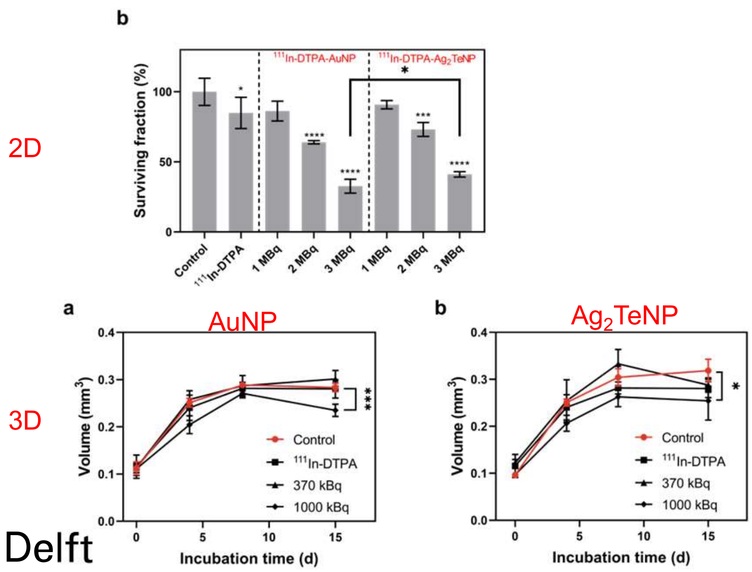
^{111}In-GSH-AuNP & ^{111}In-GSH-Ag_2TeNP *in vitro* exp. toxicity



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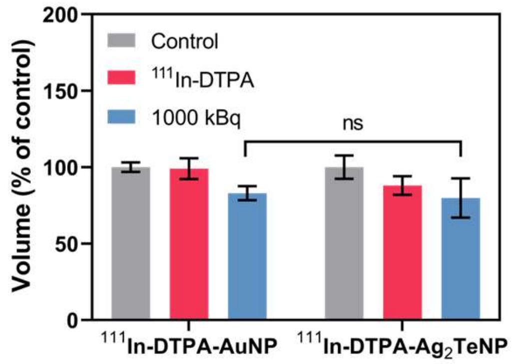
^{111}In-GSH-AuNP & ^{111}In-GSH-Ag_2TeNP *in vitro* exp. toxicity



Why there is no any difference between Au and Ag despite the much lower uptake of Ag?

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Take home message

- Nanoparticles can be used to retain radionuclides from being released, allowing in vivo generators to be created
- The combination of ultra-small nanoparticles and Auger electron emitters provides a new path on the design of radiopharmaceuticals
- With further modification of targeting groups while maintaining the small size, the radiolabeled ultra-small nanoparticles hold great potential for theranostic applications.

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Acknowledgements

Runze Wang

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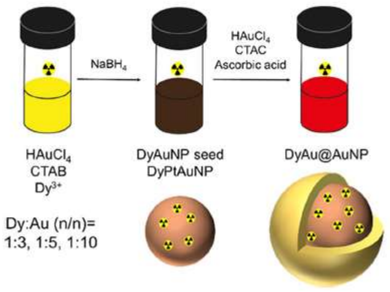
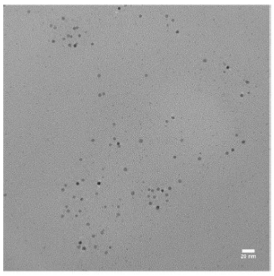
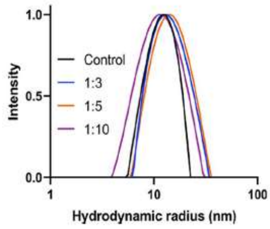
CTAB-AuNP + ^{166}Dy/^{166}Ho

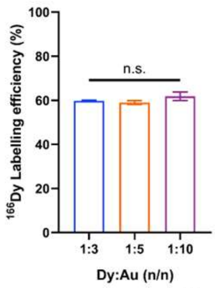


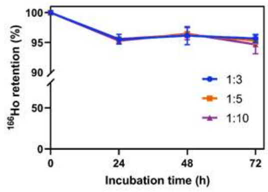


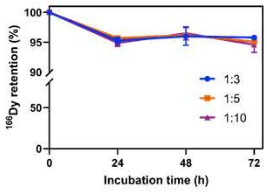
d~5 nm



HD~20 nm







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Wang, R., Wolterbeek, H., Denkova, A. et al. *EJNMMI radiopharm. chem.* 7, 16 (2022).

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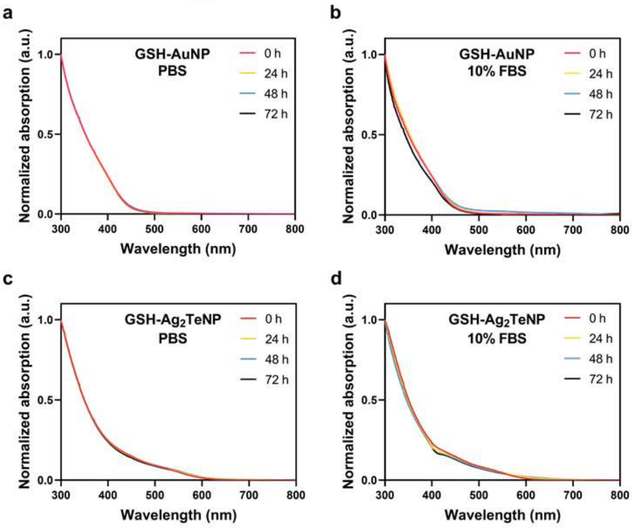
GSH-AuNP & GSH-Ag_2TeNP physical properties



High colloidal stability in PBS and 10% FBS

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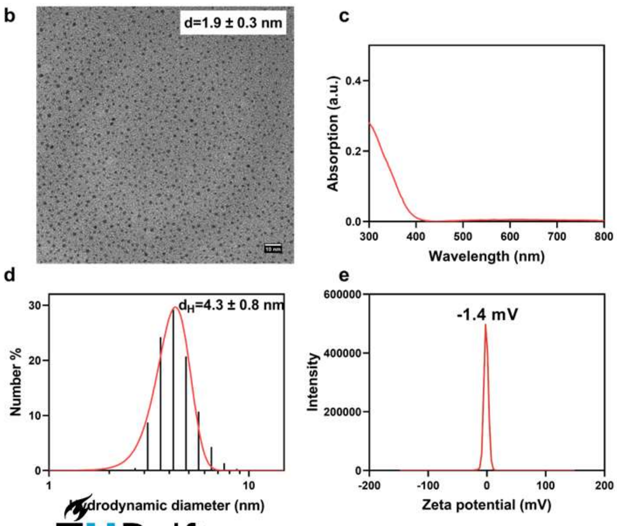
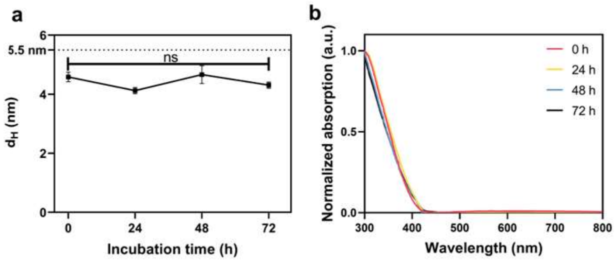
PEG-AuNP physical properties





d=1.9 nm
d_H=4.3 nm
Neutral surface
No SPR peak
Highly stable in PBS and 10% FBS

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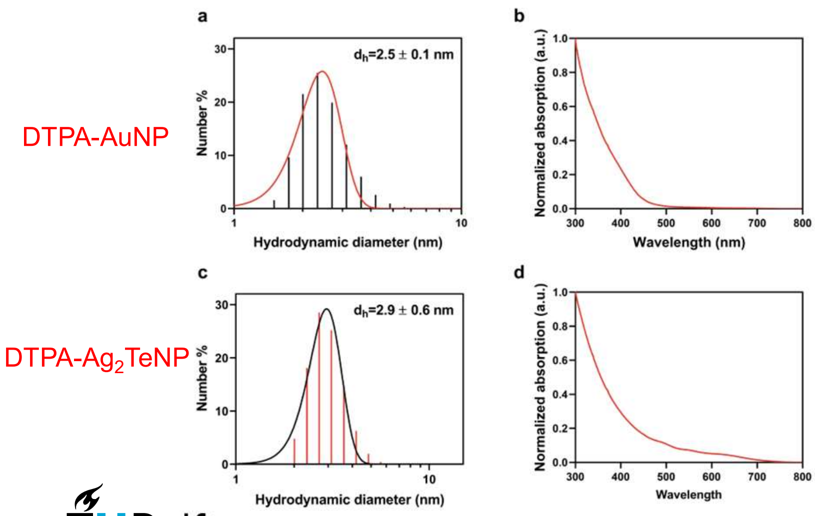
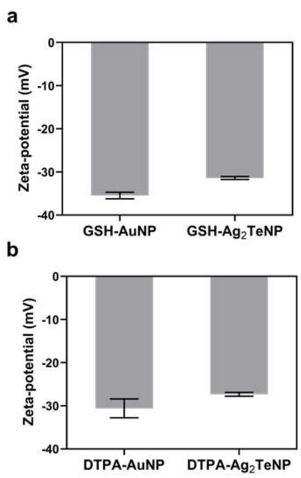
DTPA-AuNP & DTPA-Ag_2TeNP physical properties





d_H of both NP increased 0.4 nm after DTPA conjugation

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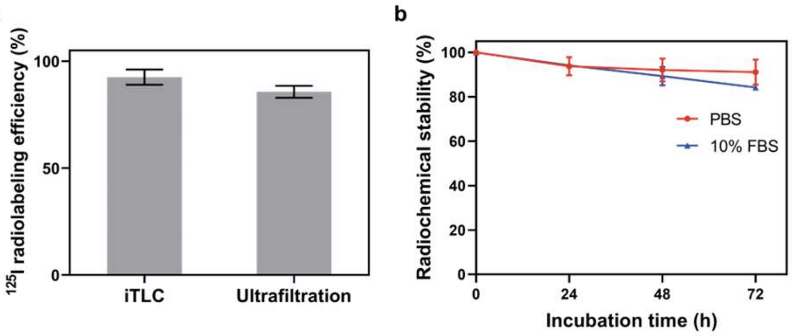
^{125}I radiolabeling



RCY>95%
RCS>90% over 72 h

NP:^{125}I=100:1 (n/n)

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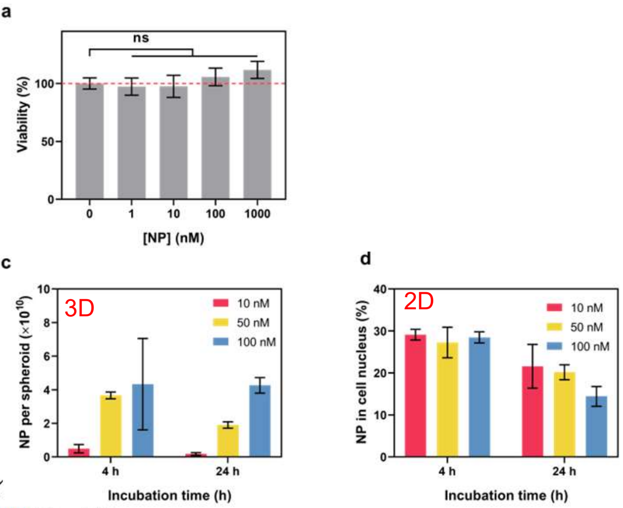
^{125}I-PEG-AuNP *in vitro* studies



- Biocompatible
- 2D uptake: time and concentration dependent
- 3D uptake: concentration dependent
- 15%~20% internalized NP found in nucleus

- ~0.06% uptake in 2D
- ~0.4% uptake in 3D

^{111}In-F3-DTPA:
0.5% uptake in 2D
30% in nucleus

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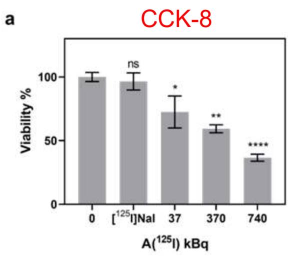
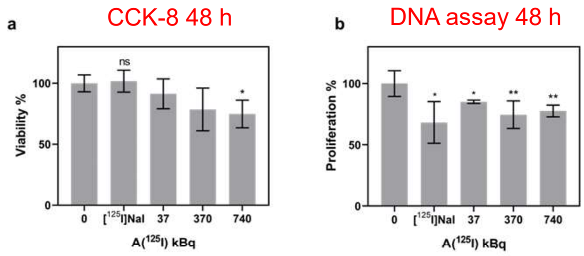
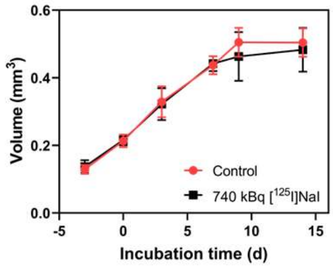
^{125}I-PEG-AuNP *in vitro* studies







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*CCK-8 and DNA assay performed 24 h after the removal of activity

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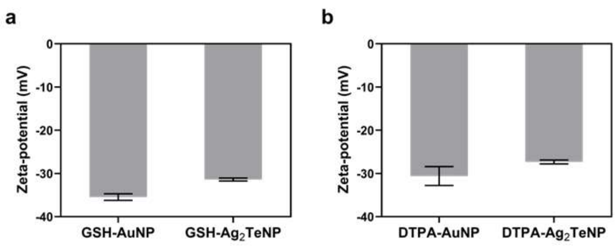

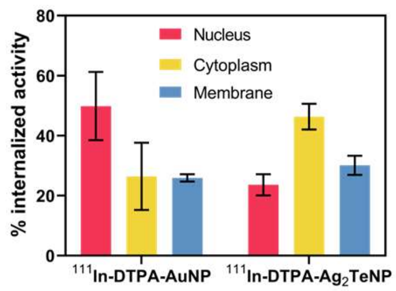

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