Theranostics
방사성의약품 현재와 미래
(알파 핵종 중심)

2019. 6. 15.

김 정 영, Ph.D.

RI 응 용 부

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KOREA INSTITUTE OF RADIOLOGICAL & MEDICAL SCIENCES

Theranostics의 어원

Theranostic= Therapy + Diagnostic
(Thera-) (-nostic)

‘Theranostics’의 사전적 정의

- **(Search 1)** Theranostic is a new field of medicine which combines specific targeted therapy based on specific targeted diagnostic tests.
- **(Search 2)** Theranostics is a term derived from a combination of the words therapeutics and diagnostics.
- **(Search 3)** Theranostics is a combination of diagnostics and therapy.
- **(Search 4)** Theranostics is a concept that refers to the integration of imaging and therapy in a single system.

‘테라노틱스’는 동일 객체에서 어떤 질환을 표적 하여 진단한 뒤 그 질환을 표적 치료하는 개념

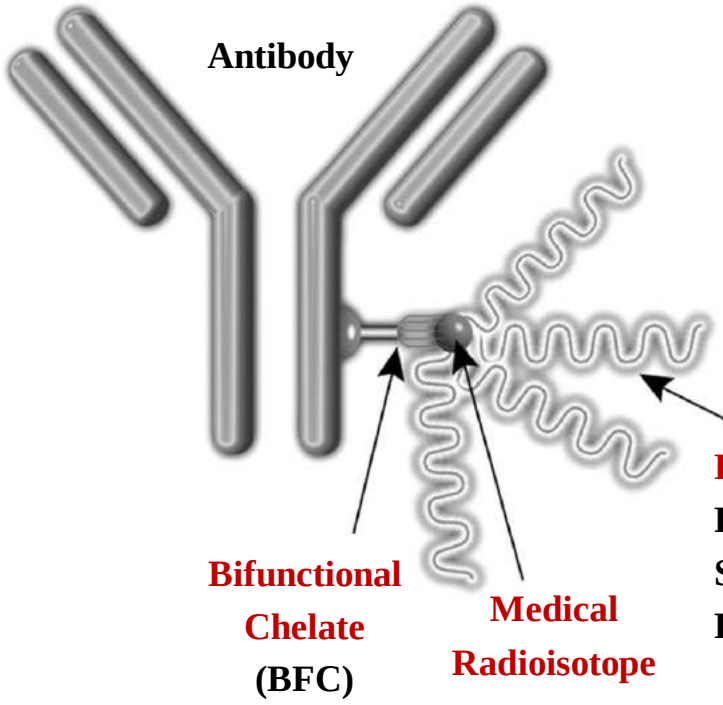
→ 정밀의학 (Personalized Medicine)

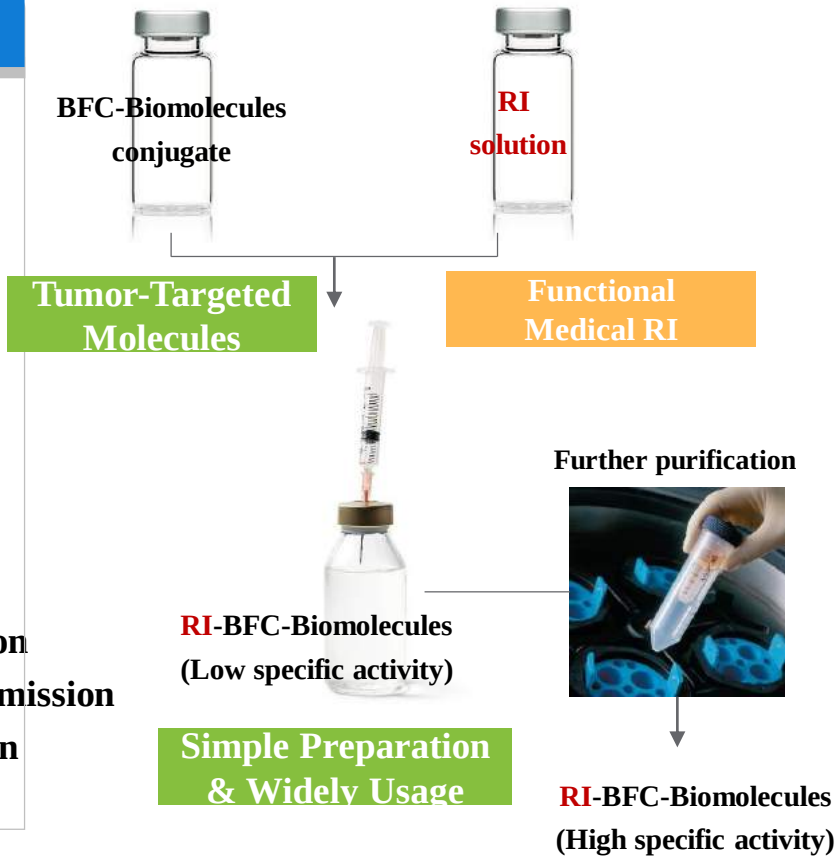
‘Theranostics’의 개념

Theranostics 방사성의약품

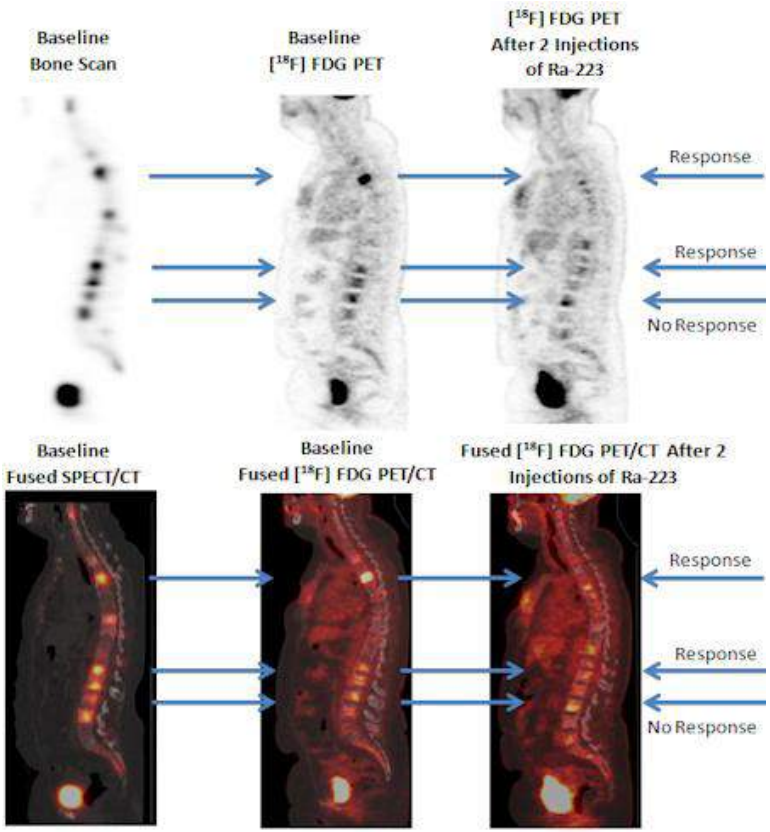
- 테라노틱스 방사성의약품은 방사성동위원소의 기능에 의해 결정

RI-BFC-Biomolecules





Ra-223 Chloride



SNMMI (Dr. Patrick Flamen and colleages, June 11, 2013)

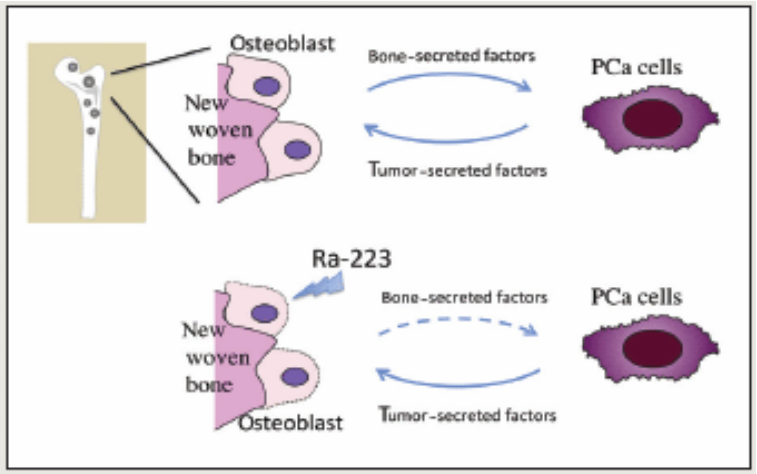
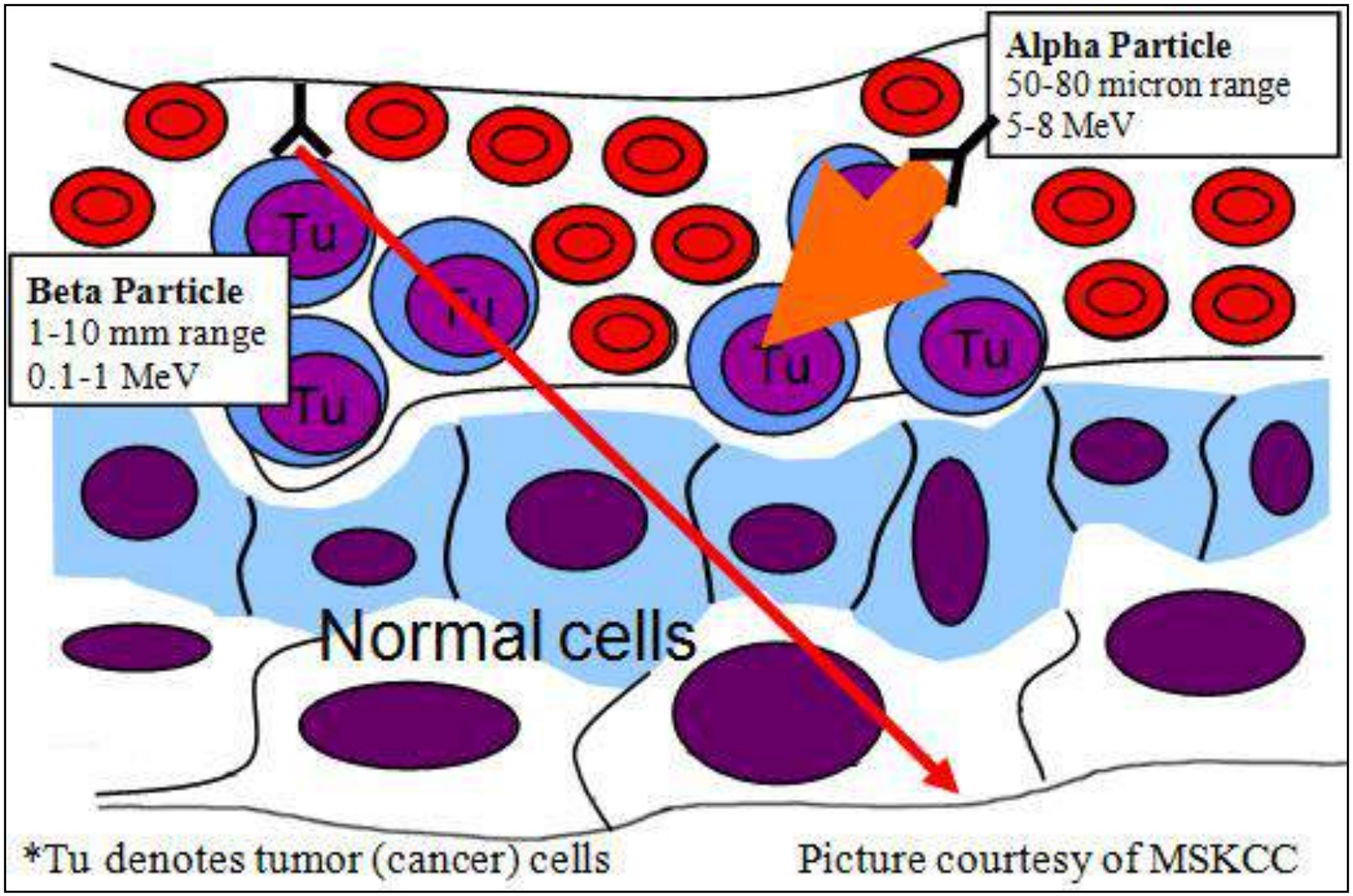


Figure: Mechanism of Ra-223 Activity in the Management of Prostate Cancer Bone Metastases—Ra-223 may disrupt a crucial paracrine loop between osteoblasts and prostate cancer (PCa) cells (top panel) by modulating the production and expression of osteoblast-derived factors (broken arrow) that support prostate cancer cell growth or survival within the bone metastases (bottom panel).

Oncology Journal, Bone Metastases, Prostate Cancer (July 15, 2015)

Radium-223 is designed to target bone metastases with high-energy alpha particles and spare healthy tissue and bone marrow.

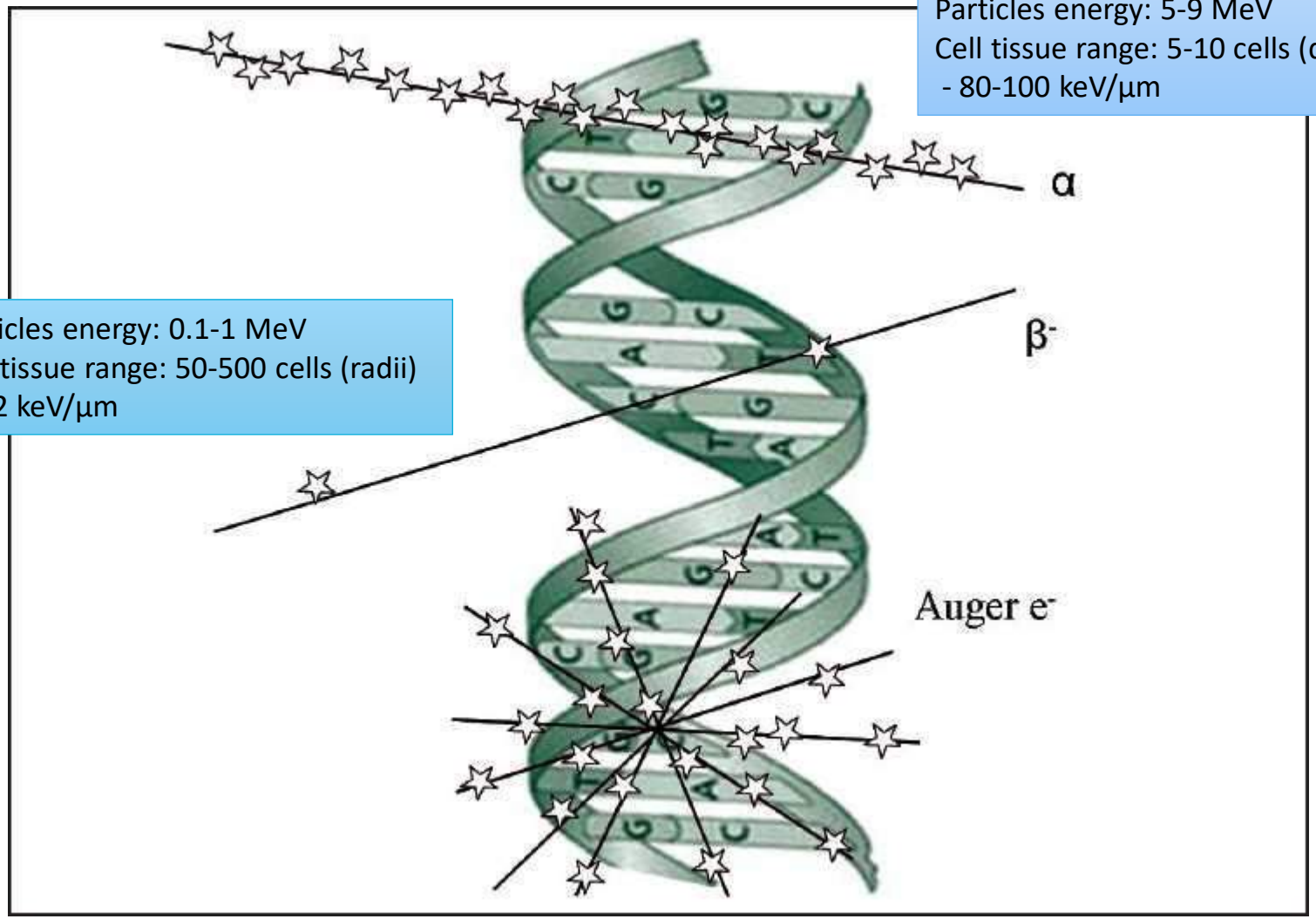
α-Particle-Emitting Radionuclides



α-Particle-Emitting Radionuclides

Particles energy: 5-9 MeV
Cell tissue range: 5-10 cells (diameter)
- 80-100 keV/μm

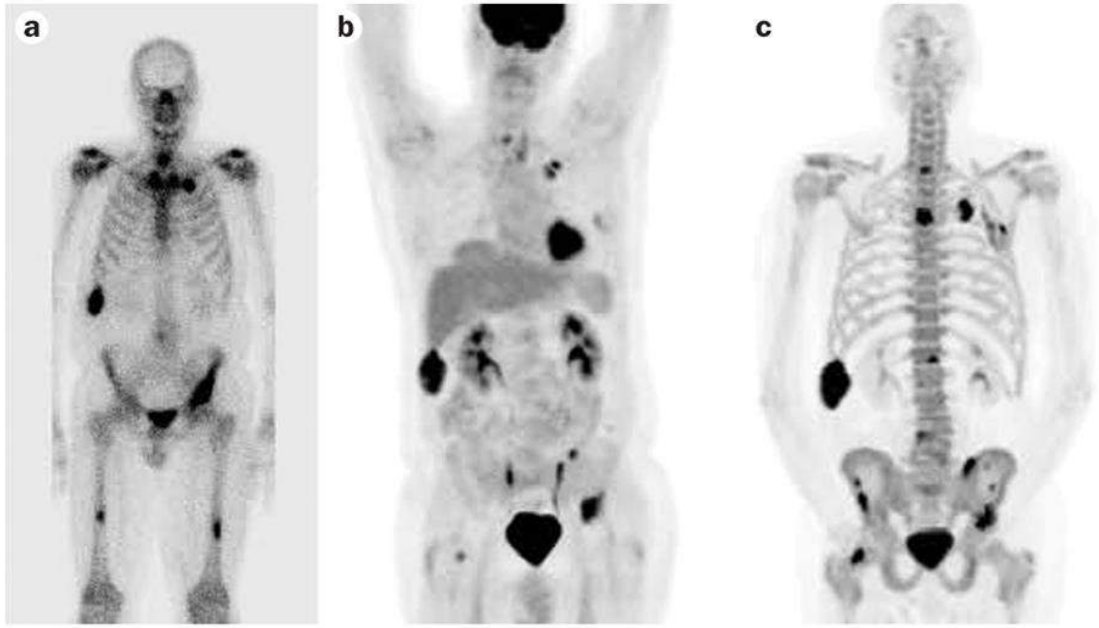
Particles energy: 0.1-1 MeV
Cell tissue range: 50-500 cells (radii)
- 0.2 keV/μm



Journal of Cancer Research and Therapeutics, Vol. 6(3) 2010, pp. 239-248

Ra-223와 Na[F-18]

Figure 2 Radionuclide imaging of a patient with castration-resistant prostate cancer.



Scher, H. I. *et al.* (2013) Validation and clinical utility of prostate cancer biomarkers *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.30

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molecular pharmaceutics

Article

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Evaluation of [^{89}Zr]-Oxalate as a PET Tracer in Inflammation, Tumor, and Rheumatoid Arthritis Models

Ji-Ae Park,[†] Yong Jin Lee,[†] Ji Woong Lee,[†] Ran Ji Yoo,[†] Un Chol Shin,[†] Kyo Chul Lee,[†] Byung il Kim,[‡] Kyeong Min Kim,[†] and Jung Young Kim*[,†]

[†]Molecular Imaging Research Center, Korea Institute of Radiological & Medical Science, Seoul 139-706, Republic of Korea

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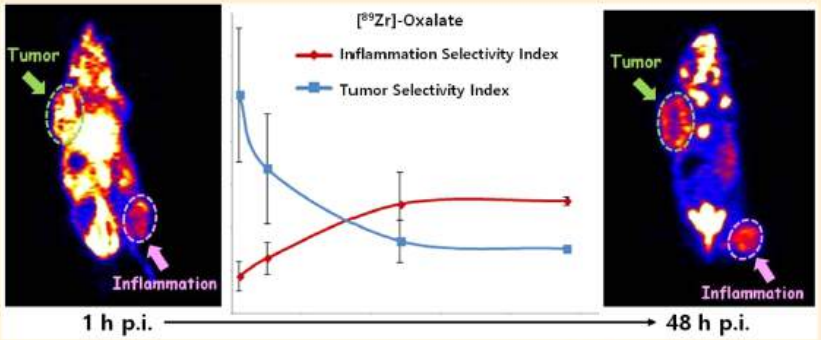
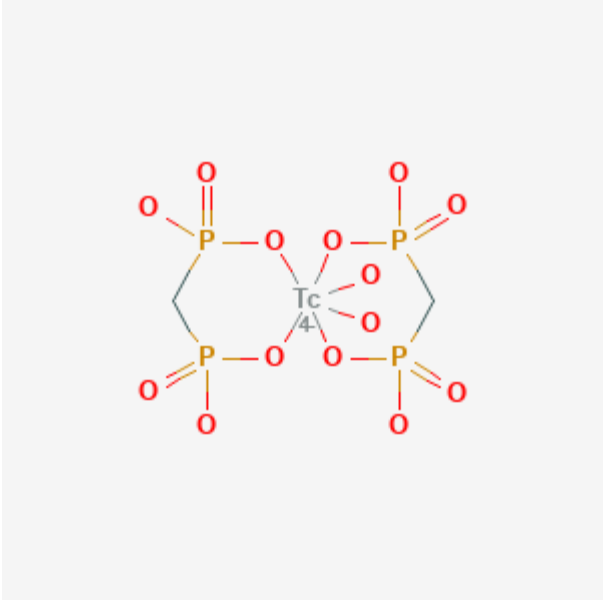


ABSTRACT: To obtain an additional pharmacological agent for the diagnosis of inflammation, we investigated the medical use of ^{89}Zr-oxalate as a positron emission tomography (PET) probe for the in vivo imaging of inflammation and compared its efficacy to that of 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) and sodium [^{18}F]fluoride. ^{89}Zr-oxalate exhibited observable higher uptake in a macrophage cell line than in tumor cells. The inflammatory lesions and tumors were clearly visualized by PET imaging and autoradiography using ^{89}Zr-oxalate. Compared to [^{18}F]FDG and sodium [^{18}F]fluoride, ^{89}Zr-oxalate demonstrated a high selectivity index to the tumor at an early time point after injection and to inflammation at a delayed time point after injection (24 h). Through histological examination, large numbers of macrophages and neutrophils were observed in the tumor lesions with the highest ^{89}Zr-oxalate uptake. In a rheumatoid arthritis (RA) mouse model, ^{89}Zr-oxalate demonstrated a high level of accumulation in inflammatory lesions. ^{89}Zr-oxalate is a new strategic tool for tumor imaging and inflammatory processes.

KEYWORDS: *^{89}Zr-oxalate, inflammation, tumor, rheumatoid arthritis, PET*

심화 Tc-99m MDP

Chemical name:	^{99m}Tc-Methyl diphosphonate
Abbreviated name:	^{99m}Tc -MDP
Synonym:	^{99m}Tc -Methylene diphosphonate, Technetium 99mTc Medronate
Agent Category:	Compound
Target:	Type 2 class of aminoacyl-tRNA synthetases
Target Category:	Enzymes
Method of detection:	Single photon emission computed tomography (SPECT); planar gamma imaging



심화 Sn-117m DTPA (1997, J.N.M.)

Tin-117m(4+)DTPA: Pharmacokinetics and Imaging Characteristics in Patients with Metastatic Bone Pain

Gerbail T. Krishnamurthy, Fayez M. Swailem, Suresh C. Srivastava, Harold L. Atkins, Laura J. Simpson, T. Kent Walsh, Frederick R. Ahmann, George E. Meinken and Jayendra H. Shah
Veterans Administration Medical Center and University of Arizona School of Medicine, Tucson, Arizona; and Brookhaven National Laboratory, Upton, New York

Biokinetics and imaging characteristics of ^{117m}Sn(4+)DTPA have been studied in patients with metastatic bone pain. **Methods:** Seventeen patients with bone pain due to metastasis were given three dose levels: 180 μCi/kg (6.66 MBq/kg), 229 μCi/kg (8.47 MBq/kg) and 285 μCi/kg (10.55 MBq/kg) body weight. Periodic blood and daily urine samples were collected for 14 days to measure percent injected activity retained in blood and that excreted in urine. Simultaneous anterior and posterior view whole-body images were obtained under identical scan settings at 1, 3.5 and 24 hr and on Days 3 and 7 and between 4–6 and 8–10 wk postinjection. The total body retention was calculated using the geometric mean counts. **Results:** After intravenous injection, the total body clearance of ^{117m}Sn(4+)DTPA shows two components: a soft-tissue component and a bone component. The soft-tissue component accounts for 22.4% of the dose and consists of four subcomponents with an average biologic clearance half-time of 1.45 days (range 0.1–3.2 days). The bone component accounting for the remaining 77.6% of the dose shows no biologic clearance. A mean 22.4% of the dose is excreted in urine in 14 days; 11.4% within 24 hr. The uptake pattern appears similar to that of ^{99m}Tc-MDP. Peak uptake is observed in normal bone by 24 hr and metastatic lesions by 3–7 days. Pain palliation was observed with all three doses levels. **Conclusion:** Among the four potential bone pain palliation radionuclides, ^{117m}Sn(4+)DTPA demonstrates the highest bone uptake and retention. Some biokinetic and radionuclidic features of ^{117m}Sn(4+)DTPA are similar to other agents, but many features are different and unique and may make it an ideal bone pain palliation agent. Double-blind comparative studies are needed to determine its exact role in bone pain palliation.

Key Words: bone pain palliation; pharmacokinetics; tin-117m(4+)DTPA
J Nucl Med 1997; 38:230–237

Received Mar. 1, 1996; revision accepted May 8, 1996.
For correspondence or reprints contact: G.T. Krishnamurthy, MD, FACP, Nuclear Medicine Service (115), VA Medical Center, Tucson, AZ 85723.

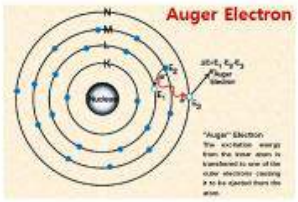
Of the estimated 1.35 million people in the U.S. who would be diagnosed of some form of cancer in 1996, slightly more than half will develop metastasis (*1*). In patients whose primary

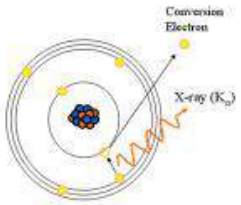
Decay & Energy of ^{117m}Sn

Half-life : *13.6 ± 0.04 d*

Major Radiations	Energy (keV)	Intensity (%)
Auger-L	3	91.0
Auger-K	21	10.8
CE-K1	126.8	64.8
CE-K2	129.4	11.7
CE-L1	151.6	26.1
CE-L2	154.1	1.5
CE-M1	155.1	5.6
Gamma	158.6	86.4

Suresh C Srivastava, et al. Dosimetry implant for treating restenosis and hyperplasia (WO2009014806 A2, 2009)





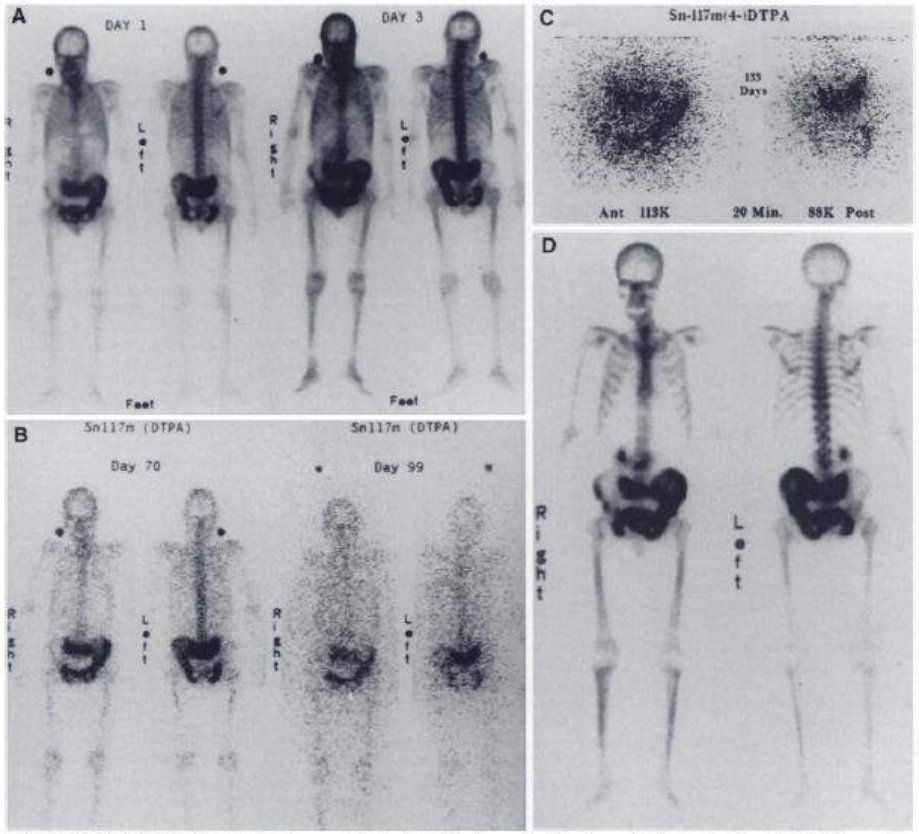
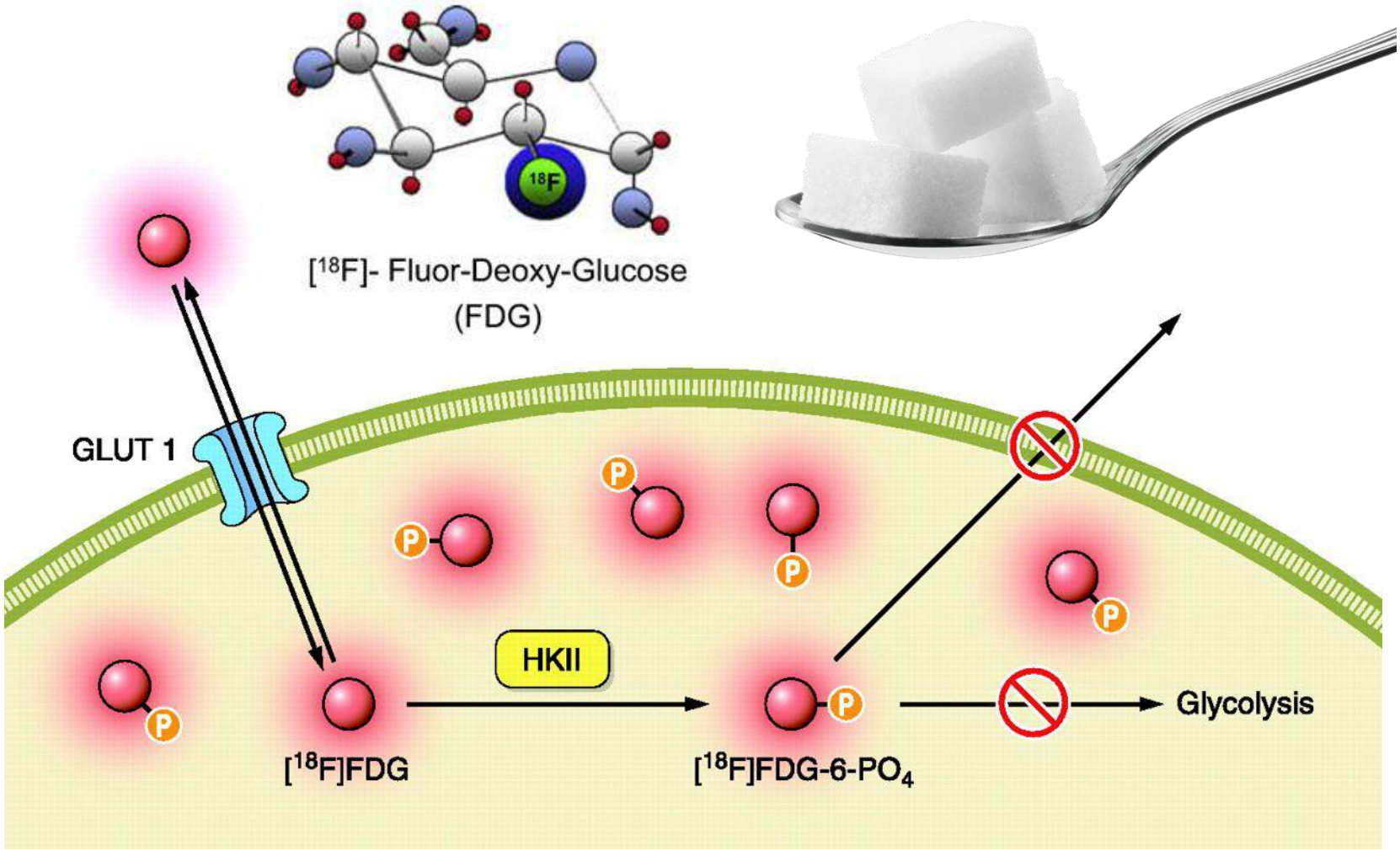


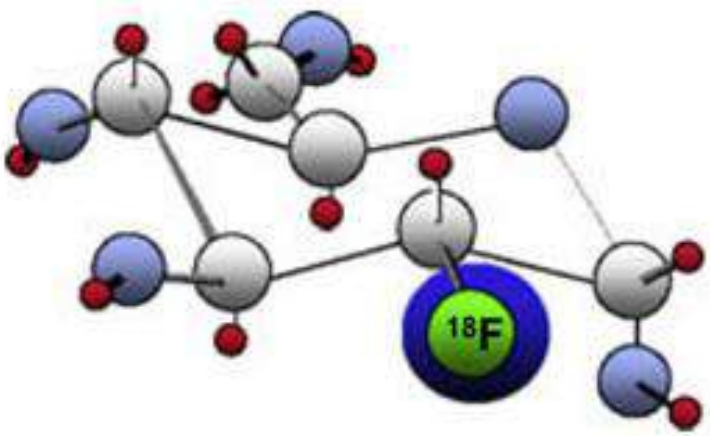
FIGURE 1. Serial ^{117m}Sn(4+)DTPA whole-body images obtained under identical parameters. There is excellent localization in bone by 24 hr (A) in a prostate cancer patient with local metastasis in the left hemipelvis extending to the right ischial tuberosity. Uptake in front of L4–L5 vertebra is due to low-lying horseshoe kidney. By Day 3, almost all of the radioactivity localizes in the bone. Images on Days 70 and 99 (B) show radioactivity mostly in the left hemipelvic bone and right ischial bone. The decrease in intensity in the later images is the effect of physical decay. Round activity on the right side of the neck is the external standard kept for calculation of regional uptake. At 133 days, the image shows persistent uptake in the left hemipelvis (C). Pre-therapy ^{99m}Tc-MDP scan (D) shows a pattern of distribution similar to ^{117m}Sn(4+)DTPA (A). Horse-shoe kidney is prominent in front of L4–L5 vertebra.

FDG의 크기

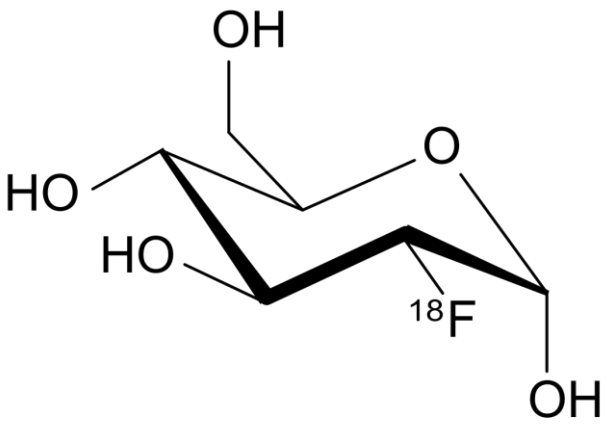


Michelle L. James, and Sanjiv S. Gambhir Physiol Rev 2012;92:897-965
European Journal of Pharmaceutics and Biopharmaceutics 74 (2010) 50–54

FDG의 크기



[18F]- Fluor-Deoxy-Glucose
(FDG)

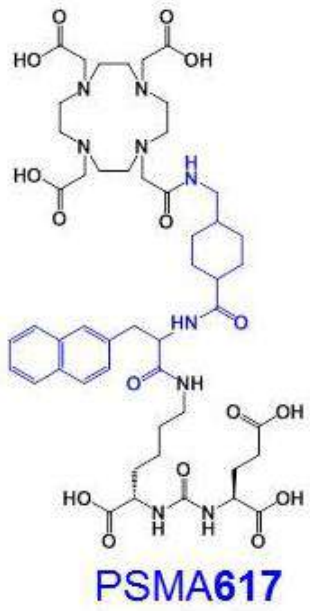


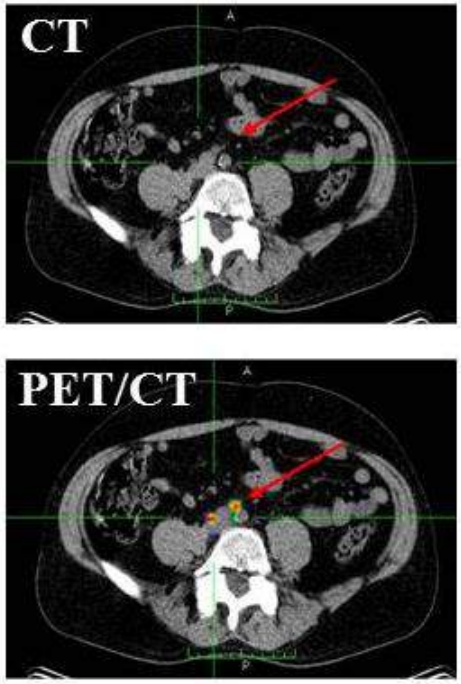
Bond	Ave. Length
C-C	154 pm
C=C	133 pm
C≡C	120 pm
H-O	96 pm
H-C	109 pm
H-F	91.7 pm
H-H	74 pm

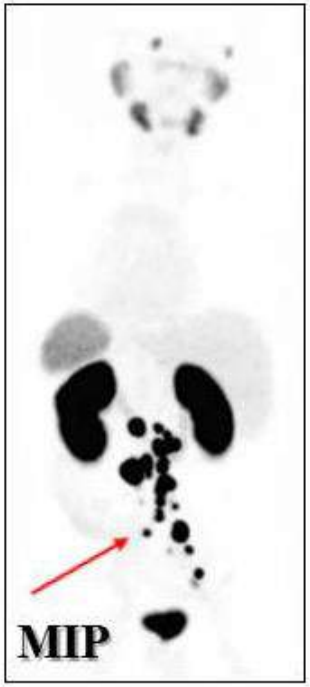
Ga-68 PSMA-617

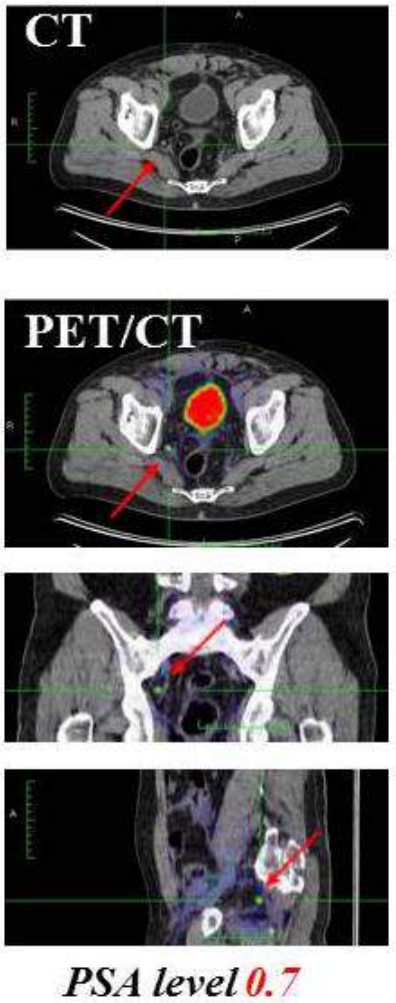
First human **PET/CT imaging** ^{68}**Ga-labeled PSMA617**

1 h post injection









PSA level 0.7

Afshar-Oromieh, Kratochwil et al., Department of Nuclear Medicine, University Hospital Heidelberg

Radionuclides for Targeted Radiotherapy

β-particle emitters
0.1-1 keV/μm LET

^{131}I, ^{177}Lu, ^{90}Y

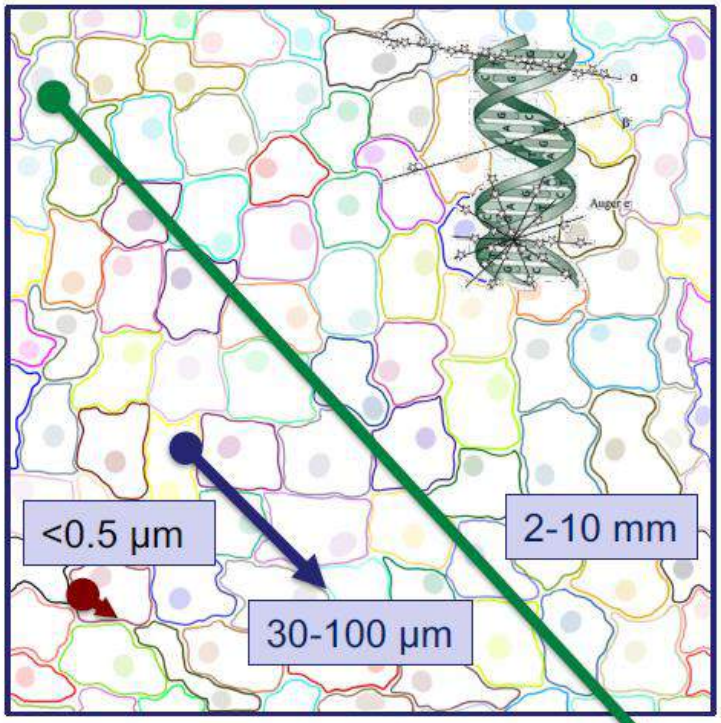
^{211}At, ^{223}Ra, ^{213}Bi

α-particle emitters
60-110 keV/μm LET

Auger electron
4-26 keV/μm LET

^{123}I, ^{67}Ga, ^{111}In

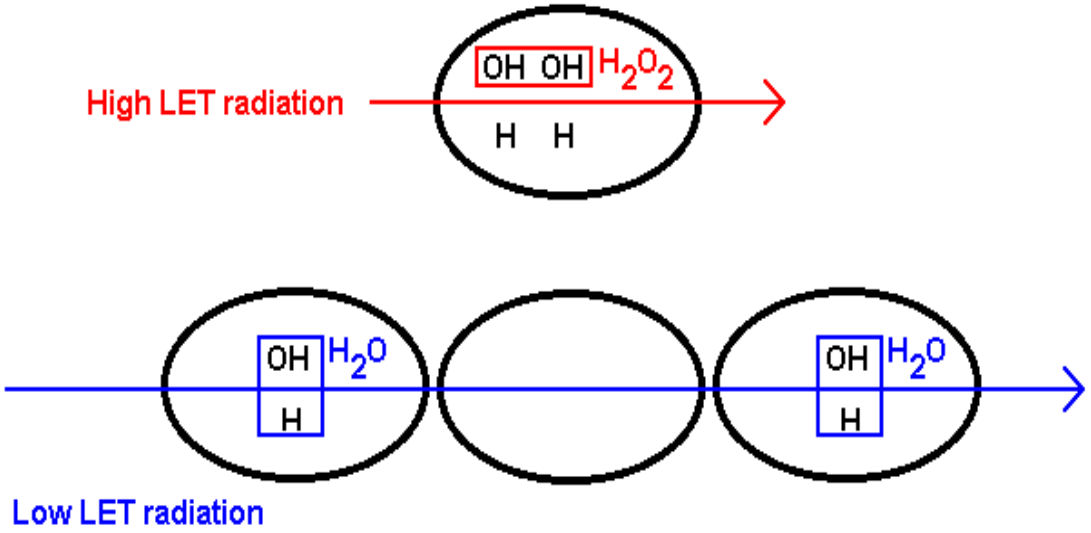
Targeting requirements:



α-particle

By courtesy of Dr. Zalutsky

LET (Linear Energy Transfer)



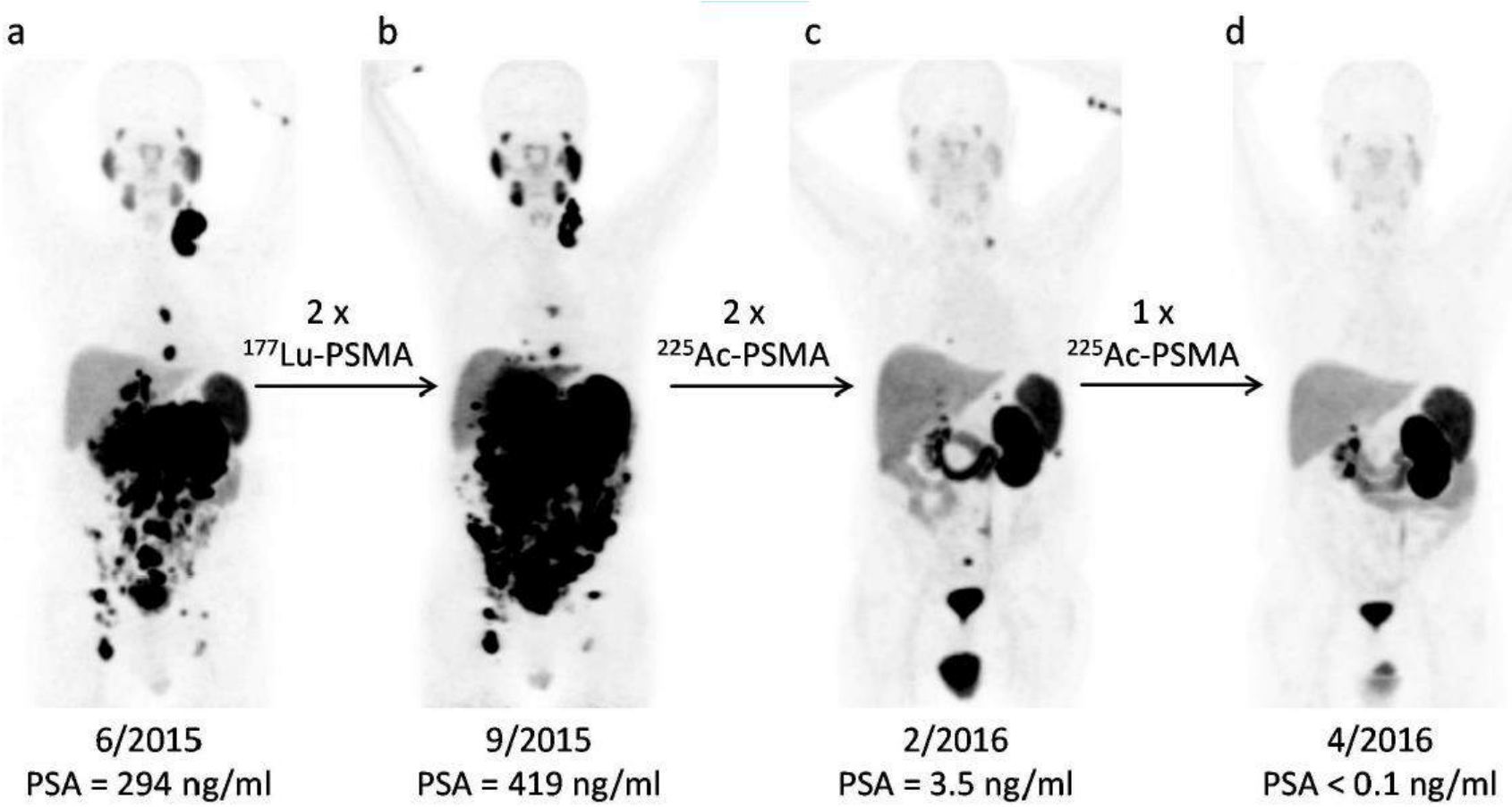
LET (linear energy transfer) is **the amount of energy** released by a radioactive particle or wave over the length of its decay track.

High LET radiation (like **alpha** & **beta particles**) ionizes water into **H** and **OH** radicals over a very short track. In the example, two events occur in a single cell so as to form a pair of adjacent **OH** radicals that recombine to form **peroxide**, H_2O_2, which can produce oxidative damage in the cell.

Low LET radiation (like **X-** or **gamma rays**) also ionizes water molecules, but over a much longer track. In the example, two events occur in separate cells, such that adjacent radicals are of the opposite type: the **H** and **OH** radicals reunite and reform H_2O.

by Steven M. Carr

PSMA 방사성의약품, 전립선암 치료 결과



전신 전이된 전립선암 환자를 ^{225}Ac-PSMA-617로 치료한 결과
(출처: Kratochwil C, Bruchertseifer F & Giesel FL et al., 2016: 1941-1944)

α-Emitting Radionuclides

한국원자력의학원 KOREA INSTITUTE OF RADIOLOGICAL & MEDICAL SCIENCES

TABLE 1. CHARACTERISTICS OF α-EMITTING RADIONUCLIDES OF POTENTIAL INTEREST FOR THE THERAPY OF CANCERS

Nuclide	*Half-life*	*Decays*	*Energy α (MeV)*	*Production*	*Clinical trial status*
^{225}Ac	10 days	4 α, 2 β^-	5.1–8.4	^{233}U decay/cyclotron	First phase I ongoing
^{211}At	7.2 hours	1 α, 1 EC	5.9 or 7.4	Cyclotron	Two phase I published
^{212}Bi	61 minutes	1 α, 1 β^-	6.1/7.8	^{228}Th decay/^{224}Ra generator	Preclinical
^{213}Bi	46 minutes	1 α, 2 β^-	6.0/8.4	^{225}Ac generator	Phase I/II
^{223}Ra	11.4 days	4 α, 2 β^-	5.7–7.5	^{227}Ac generator	Phase I/II/III
^{149}Tb	4.1 hours	1 α, EC	4.0	Accelerator	Preclinical
^{227}Th	18.7 days	5 α, 2 β^-	5.7–7.5	^{227}Ac generator	Preclinical
^{212}Pb/^{212}Bi[a]	10.6 hours	1 α, 2 β^-	6.1/7.8	^{224}Ra generator	First phase I ongoing

[a]Although ^{212}Pb is not an α-particle emitter, it is included in this table for its considerations in several studies as an *in vivo* generator of the α-particle emitter ^{212}Bi. See Yong and Brechbiel[2] for a definition of the concept.

Guerard et al., Cancer Biother Radiopharm 2013;28:1-20

Astatine-211

- α-particle-emitting radiohalogen
- Half life: 7.2 h
- Linear Energy Transfer (LET): 60-110 keV/μm
- Mean tissue range: 0.04-0.1 mm
  - Highly focal and cytotoxic radiation on cancer cell
- Production of ^{211}At

국가	기관	생산량	비고
미국	**Duke University**	6.6 GBq (1.68 GBq/h)	Dry distillation 정제
미국	**University of Washington**	4.44 GBq (1.1 GBq/h)	
미국	University of Pennsylvania	396 MBq (104 MBq/h)	Dry distillation 정제
유럽	Copenhagen University Hospital, Denmark	3.6 GBq	Dry distillation 정제
일본	QST, NIRS	450 MBq (15 μA, 2 h)	Dry distillation 정제
일본	**Fukushima Medical University**	0.9 GBq/h	Dry distillation 정제

Zalutsky et al., ***J. Nucl. Med*** 2001;42:1508-1515

Astatine-211 Production

Astatine-211 is prepared by cyclotron irradiation of a **bismuth-209 target** with **alpha particles**.

The **energy of the alpha particles** must be fine tuned (**maximum around 28 MeV** on target) to prevent production of astatine-210, which decays in the long half-life alpha emitter polonium-210.

A **1:10,000** ratio of **astatine-210/astatine-211** is proposed as **safe** for **clinical applications**.

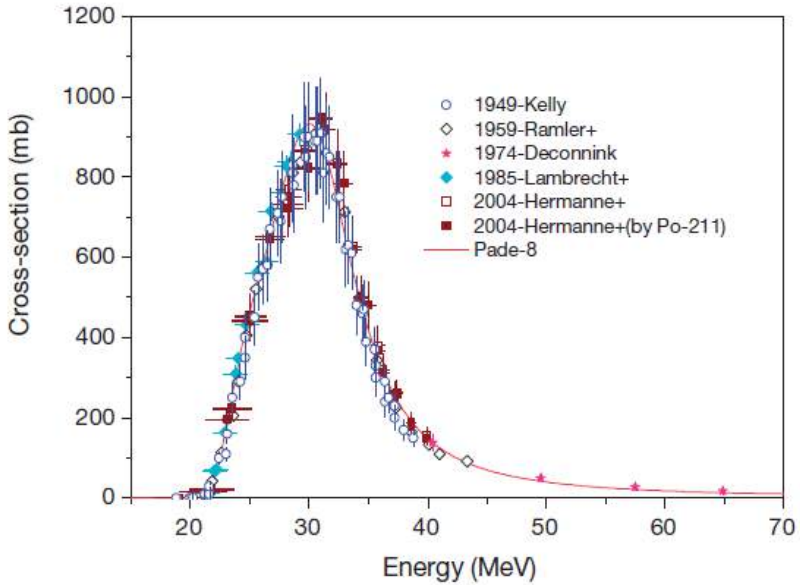


FIG. 2.4.2. Excitation function for the $^{209}Bi(\alpha, 2n)^{211}At$ reaction.

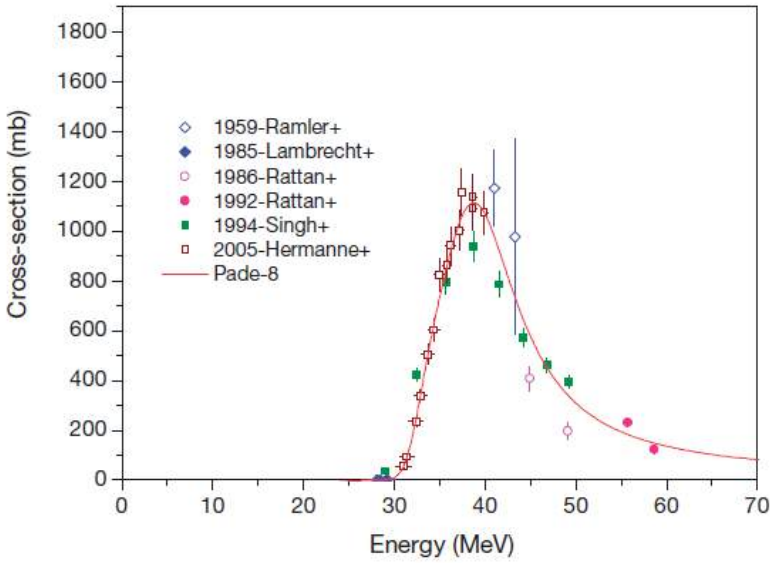
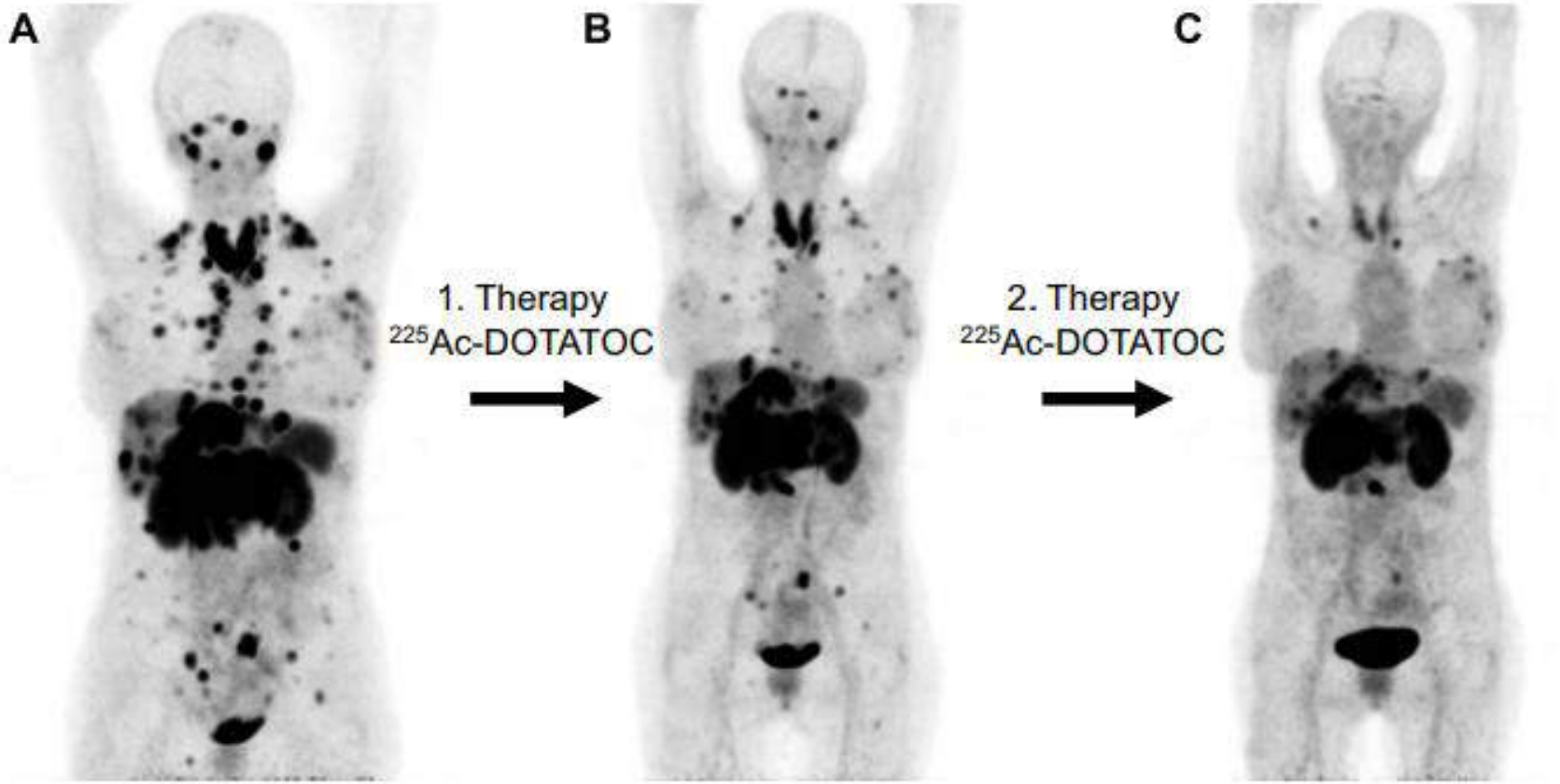


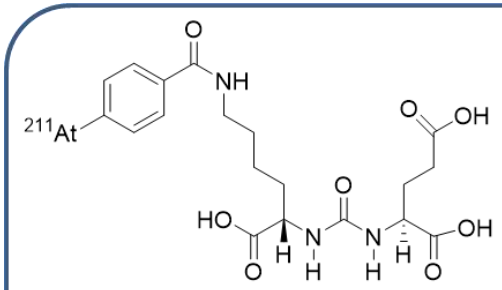
FIG. 2.4.3. Excitation function for the $^{209}Bi(\alpha, 3n)^{210}At$ reaction.

TECHNICAL REPORTS SERIES No. 468

At-211 DOTA-TOC & Steve Jobs Disease

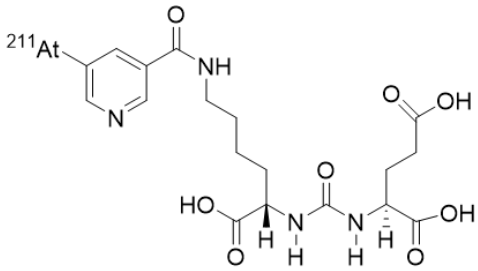


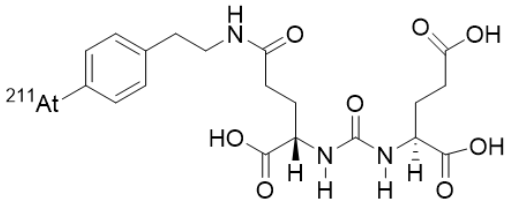
At-211 PSMA



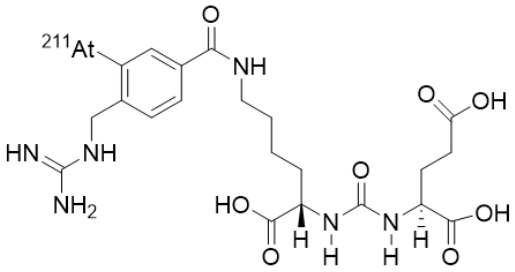
YC-I-27

Kiess et al., ***J Nucl Med*** 2016;57:1569-75

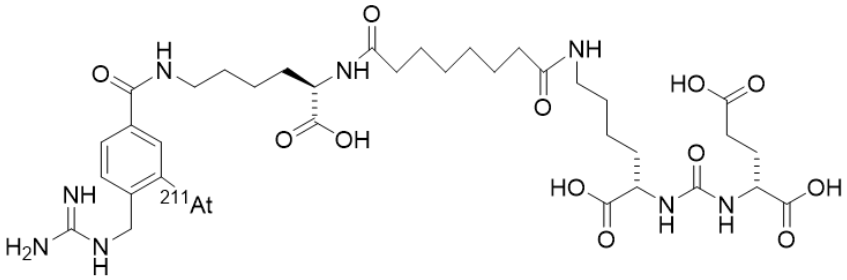




Presentation in SNM 2016



Presentation in SNM 2016

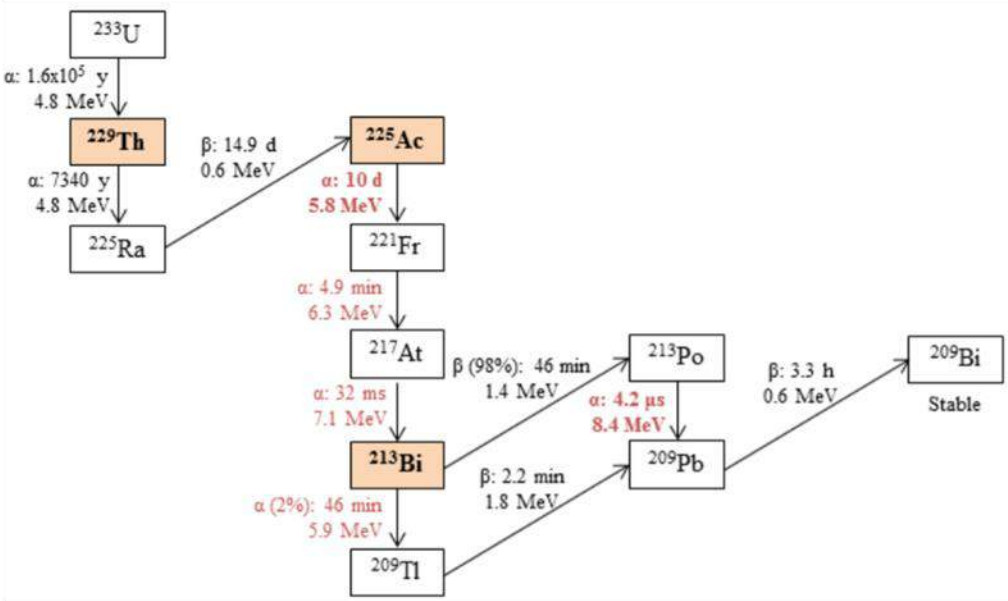


Higher tumor uptake (43.2±9.8 %ID/g), High kidney uptake was cleared from 46.7±8.2 %ID/g at 1 h to 2.6±0.8 %ID/g at 21 h.
However, it has significant stomach accumulation at 21 (~10 %ID/g) - Deastatination

Actinium-225 (Ac-225) Production

❖ Production

➢ Generator: $^{229}Th/^{225}Ac$



➢ Cyclotron: $^{226}Ra(p,2n)^{225}Ac$

*Decay product of ^{225}Ra is ^{222}Rn!!! Target handling is big issue.

Actinium-225, Chemical Properties

Isotope	$^{90}Y^{+3}$	$^{177}Lu^{+3}$	$^{225}Ac^{+3}$
Atomic number	39	71	89
Electron configuration	$[Kr]4d^{0}5s^{0}$	$[Xe]6s^{2}4f^{12}5d^{0}$	$[Rn]6d^{1}7s^{2}$
Atomic radius	180 pm	174 pm	135 pm
Atomic radius by electric effect	≒ 197 pm	≒ 185 pm	-
Electronegativity	1.22	1.27	-
Coordination number	6	3-12 (6)	4-6 (?)
Oxidation state	+1, +2, +3 (104 pm/Y^{+3})	+3 (100 pm/Lu^{+3})	+3, +2

Actinium 동위원소의 종류

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Isotope	Production	Decay	Half-life
^{221}Ac	$^{232}Th(d,9n)\rightarrow{}^{225}Pa(\alpha)\rightarrow{}^{221}Ac$	α	52 ms
^{222}Ac	$^{232}Th(d,8n)\rightarrow{}^{226}Pa(\alpha)\rightarrow{}^{222}Ac$	α	5.0 s
^{223}Ac	$^{232}Th(d,7n)\rightarrow{}^{227}Pa(\alpha)\rightarrow{}^{223}Ac$	α	2.1 min
^{224}Ac	$^{232}Th(d,6n)\rightarrow{}^{228}Pa(\alpha)\rightarrow{}^{224}Ac$	α	2.78 hours
^{225}Ac	$^{232}Th(n,\gamma)\rightarrow{}^{233}Th(\beta^-)\rightarrow{}^{233}Pa(\beta^-)\rightarrow{}^{233}U(\alpha)\rightarrow{}^{229}Th(\alpha)\rightarrow{}^{225}Ra(\beta^-)\rightarrow{}^{225}Ac$	α	10 days
^{226}Ac	$^{226}Ra(d,2n)\rightarrow{}^{226}Ac$	α, β^- electron capture	29.37 hours
^{227}Ac	$^{235}U(\alpha)\rightarrow{}^{231}Th(\beta^-)\rightarrow{}^{231}Pa(\alpha)\rightarrow{}^{227}Ac$	α, β^-	21.77 years
^{228}Ac	$^{232}Th(\alpha)\rightarrow{}^{228}Ra(\beta^-)\rightarrow{}^{228}Ac$	β^-	6.15 hours
^{229}Ac	$^{228}Ra(n,\gamma)\rightarrow{}^{229}Ra(\beta^-)\rightarrow{}^{229}Ac$	β^-	62.7 min
^{230}Ac	$^{232}Th(d,\alpha)\rightarrow{}^{230}Ac$	β^-	122 s
^{231}Ac	$^{232}Th(\gamma,p)\rightarrow{}^{231}Ac$	β^-	7.5 min
^{232}Ac	$^{232}Th(n,p)\rightarrow{}^{232}Ac$	β^-	119 s

Ac-225의 방사성의약품 응용

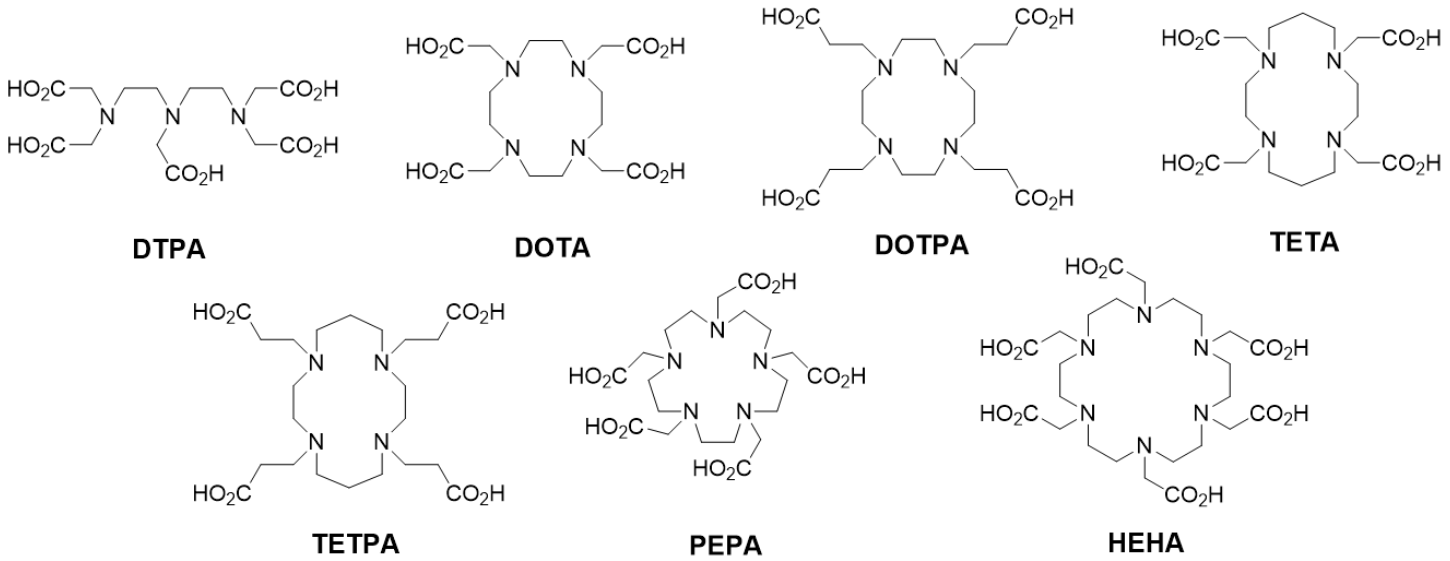


그림 1. ^{225}Ac 표지 연구에 사용되었던 킬레이터

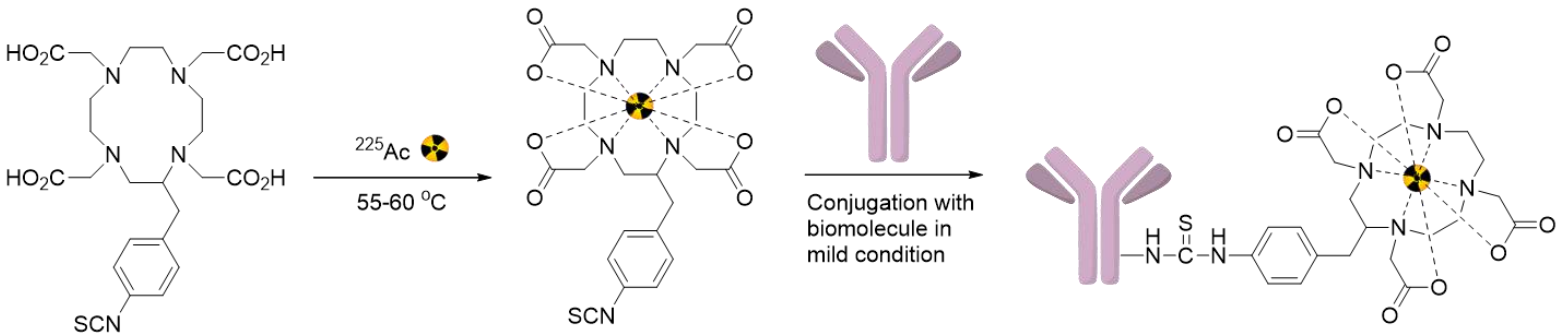
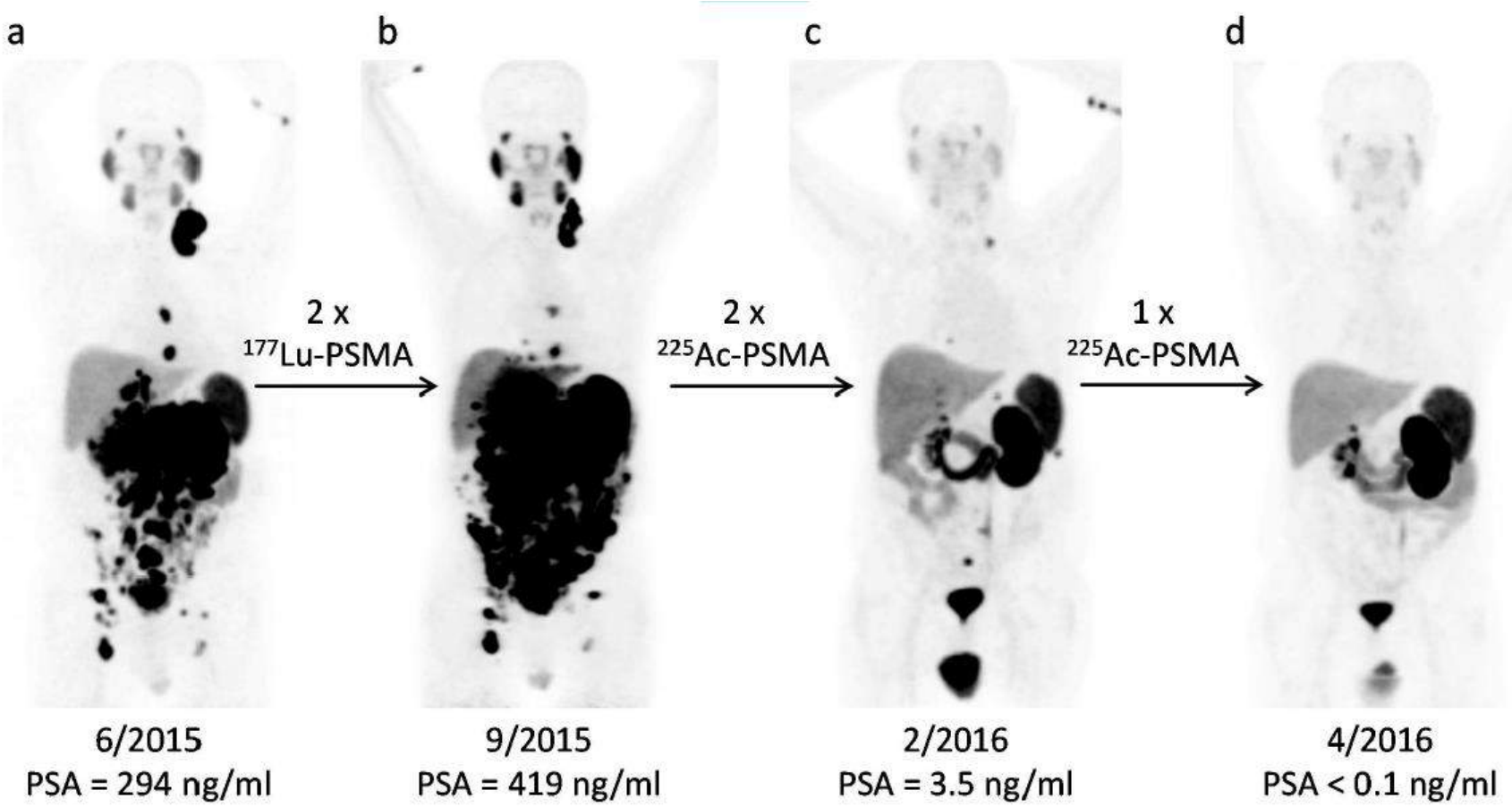


그림 2. ^{225}Ac를 생체분자에 표지 하기위한 두 단계 과정

PSMA 방사성의약품, 전립선암 치료 결과



전신 전이된 전립선암 환자를 ^{225}Ac-PSMA-617로 치료한 결과
(출처: Kratochwil C, Bruchertseifer F & Giesel FL et al., 2016: 1941-1944)

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We can look for good cooperation!
Please, don't hesitate to ask us!

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