한국원자력의학원
KOREA INSTITUTE OF RADIOLOGICAL & MEDICAL SCIENCES

의료 RI와 방사성의약품의 임상 활용 및 전망

Korean Institute of Radiological & Medical Sciences (KIRAMS)
Division of Applied-RI

Jung Young Kim, Ph.D.

2018.10.24

인터뷰

[방사선의학의 창]
한국원자력안전아카데미 이승구 이사장님
원로의 혜안,
'식지 않는 원자력사랑'으로 고견 제시

[말랑말랑 인터뷰]
오승록 서울 노원구청장
자연과 문화 속 힐링도시를 꿈꾸는 노원에는
현장에서 답을 찾는 '감동' 구청장이 있다

[이달의 방사선의학 연구자]
[방사선생물학 분야]
한국원자력연구원 김인규 박사님,
한국생명공학연구원 조은위 박사님

칼럼

[X선생의 과학레시피]
유도진화(Directed evolution)에게 갈채를!
2018년 노벨화학상 길라잡이

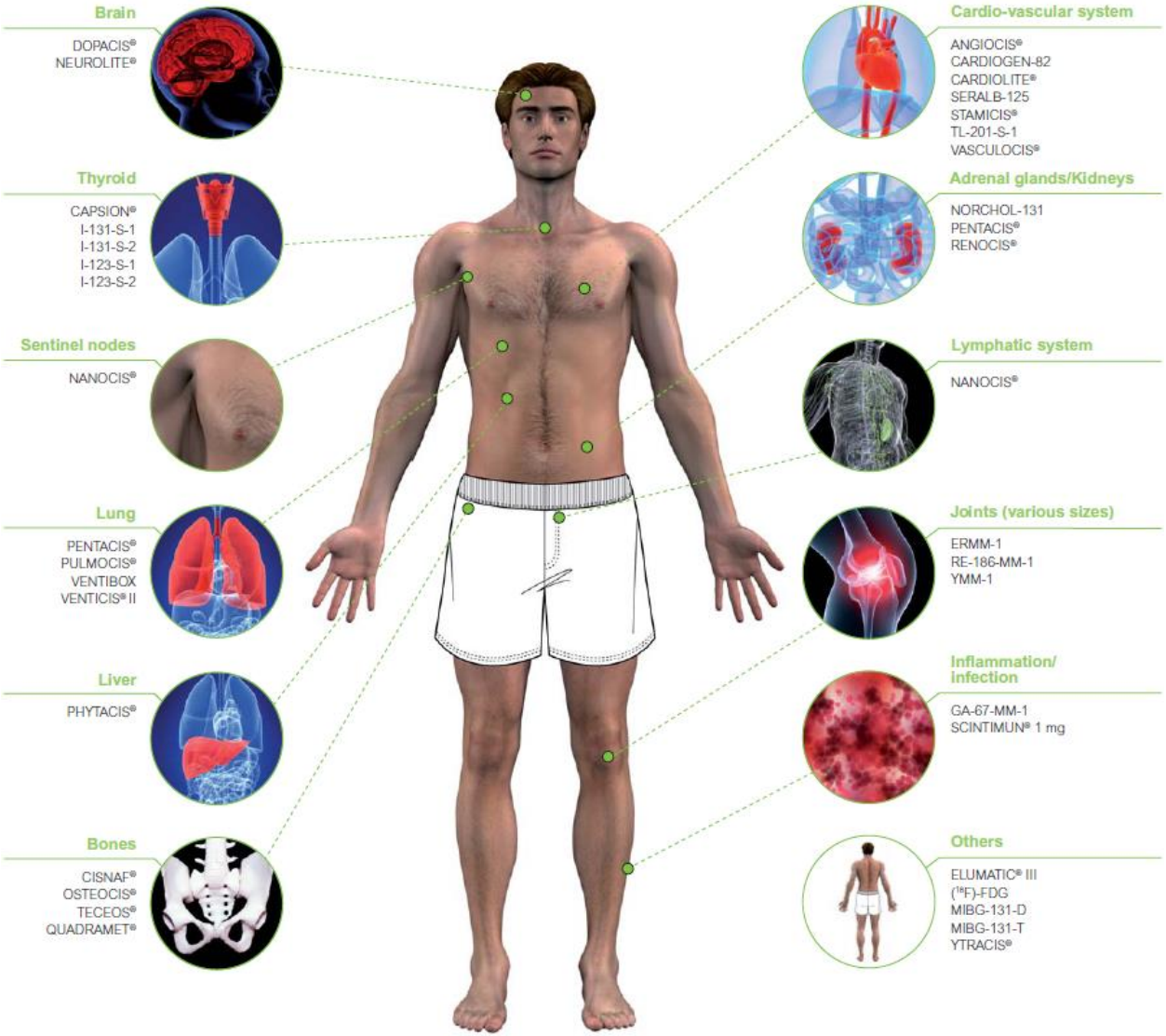
[편집위원노트]
제3의 항암제에는 제3의 눈이 필요하다

트렌드

[방사선의학 동향리포트]
국가 의생명연구를 선도하는
'한국원자력의학원'의 역할과 책임

[방사선의학 동향리포트]
북한의 방사선의학 인프라 현황

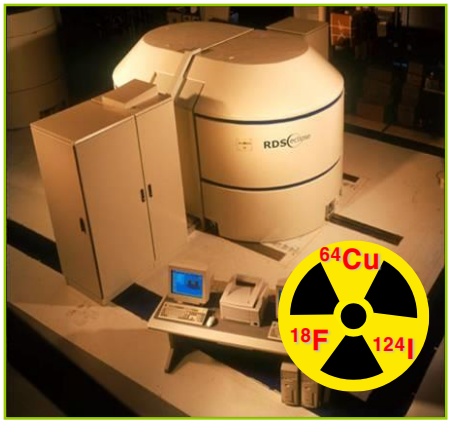
01 How Many Radiopharmaceuticals?



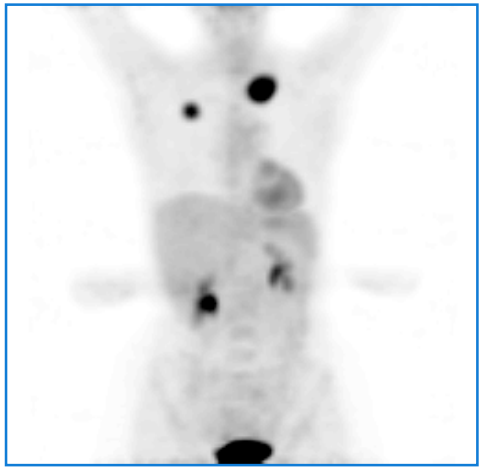
Product Catalogue, IBA (2013)

GMP Rules of Radiopharmaceuticals

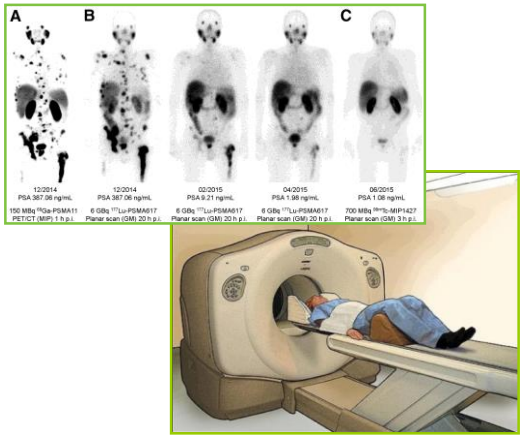
Medical cyclotron
(Production of medical radioisotopes)



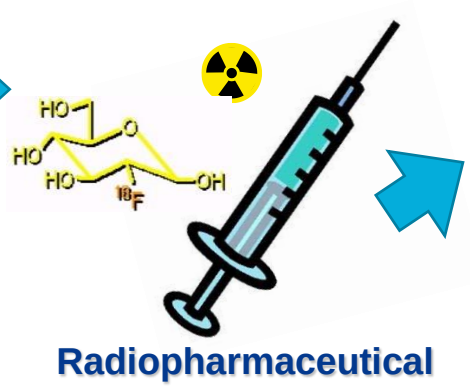
Tumor Images
(Early tumor-diagnosis, biological size & position for in vivo tumor, dementia, epilepsy, Parkinson's disease, etc.)



Nuclear Medicine Imaging (NMI) & Targeted-Radionuclide Therapy (TRT)



- Preparation by GMP (cGMP) rule
- Daily production & Immediately use



Radiopharmaceutical

Injection for human
(Waiting time for uptake & background excretion of radiopharmaceuticals; FDG scan after 40-50 mins)

03 Medical RI & Nuclear Medicine in KIRAMS

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Cyclotron-based RI & RP Production

- 50 MeV cyclotron (IBA, 1985)
- 30 MeV cyclotron (IBA, 2000)
- 16.5 MeV cyclotron (IBA, 2018)

- I-123, [I-123]MIBG, [I-123]FPCIT
- Tl-201
- [C-11]PIB, [C-11]Methionine
- [F-18]FDG, [F-18]FPCIT
- Cu-64, Zr-89, I-124

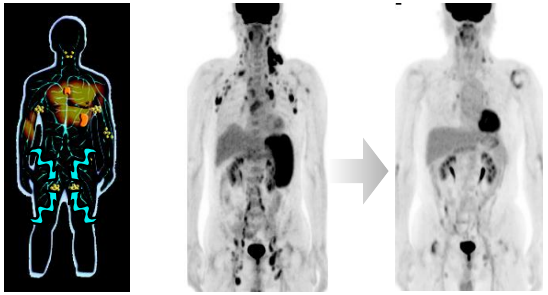
- KIRAMS RI Production System
- GE MX, FASTlab2, FX2 (C&N)
- E&Z Modular Lab

Molecular Imaging & Pre-clinic Study

- MicroPET/CT
- Optical Imaging
- BAS/ Whole Body Autocrytome
- MicroMRI (9.4 T)/ NMR (600 MHz)
- GLP Facility
- LC-QTOF
- AMS (C-14 Analysis)

Department of Nuclear Medicine

- SPECT
- PET/CT, PET/MRI
- Targeted Radionuclide Therapy



- Clinical Study for New Drug
- Multi-center or Multi-country

04 3R One-Stop KIRAMS! (Fast Bench to Bed)

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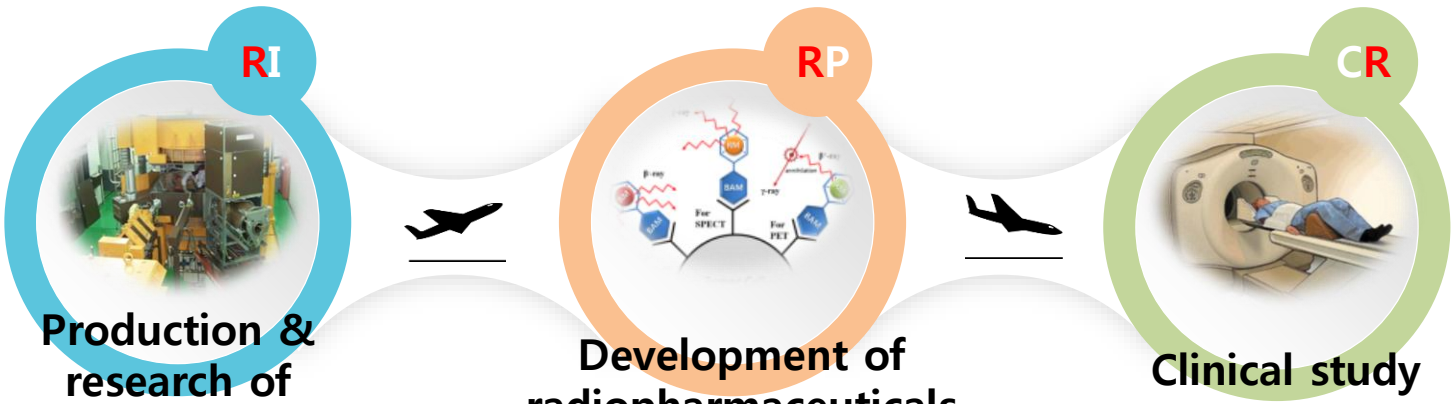


Medical Radioisotope

- Medical cyclotron-based
- National RI supply system

Radiopharmaceuticals

- New radiopharmaceuticals
- Precision medicine

Clinical Research

- Medical application
- Improvement of medical tech
- Multi-center clinical trial

- New research center open, from 2019
- GMP facility : 6 cleanrooms for radiopharmaceuticals
- GE cyclotron (16.5 MeV, F-18 & C-11)
- GLP animal study
- Recent Q.C. system
- Research room for basic sciences

Mongolian PET Center supported by KIRAMS

Medical Instruments in Nuclear Medicine (Sam Sung co. & GE Healthcare China)

Cyclotron : Minitracer (GE), 1 Set

Module : FASTlab 2 (GE, not confirmed), 2 Set

Hot Cell : Production cell (dual), Dispenser cell (Comecer, not confirmed)

Dispenser : Timotheo LT (not confirmed)

PET : PET/CT Discovery IQ-3 ring, 1 Set

SPECT : SPECT/CT is not confirmed

Auto-injector : Model is not confirmed

Q.C. :

(1) RadioTLC scanner

(2) Gas chromatography

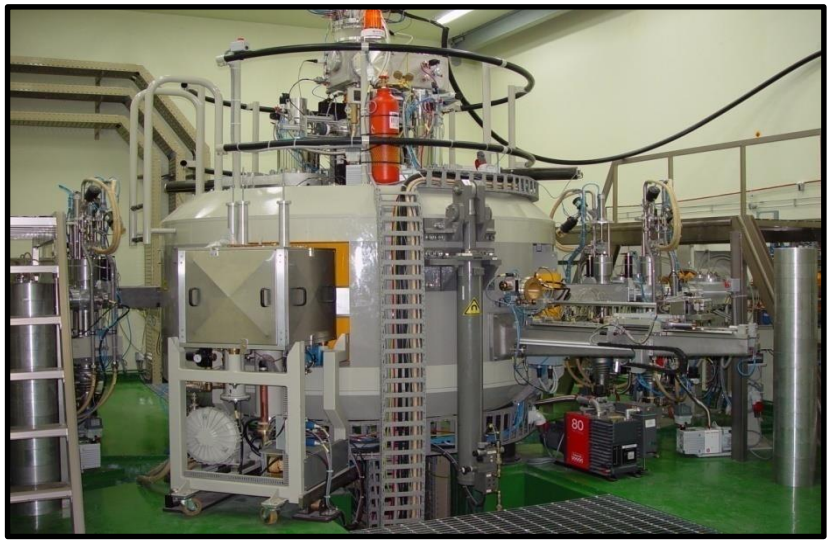
(3) MCA …

Target Radiopharmaceuticals : FDG, NaF, FLT, etc.

Mongolia National Diagnosis & Treatment Center

Medical Cyclotrons in KIRAMS

Energy (Proton beam)	Producer	Beam	Target Isotopes
50 MeV	Scantronix (1985)	Alpha Deuteron Proton	^{64}Cu (PET), ^{124}I (PET), ^{89}Zr(PET), ^{18}F (PET), ^{44}Sc(PET), ^{117m}Sn(beta), ^{211}At(alpha), ^{67}Cu(beta)
30 MeV	IBA (2000)	Proton	^{18}F(PET), ^{11}C(PET), ^{123}I(SPECT), ^{201}Tl(SPECT)
16.5 MeV	GE (2018)	Deuteron Proton	^{18}F(PET), ^{11}C(PET)



07 Research History of KIRAMS-RI

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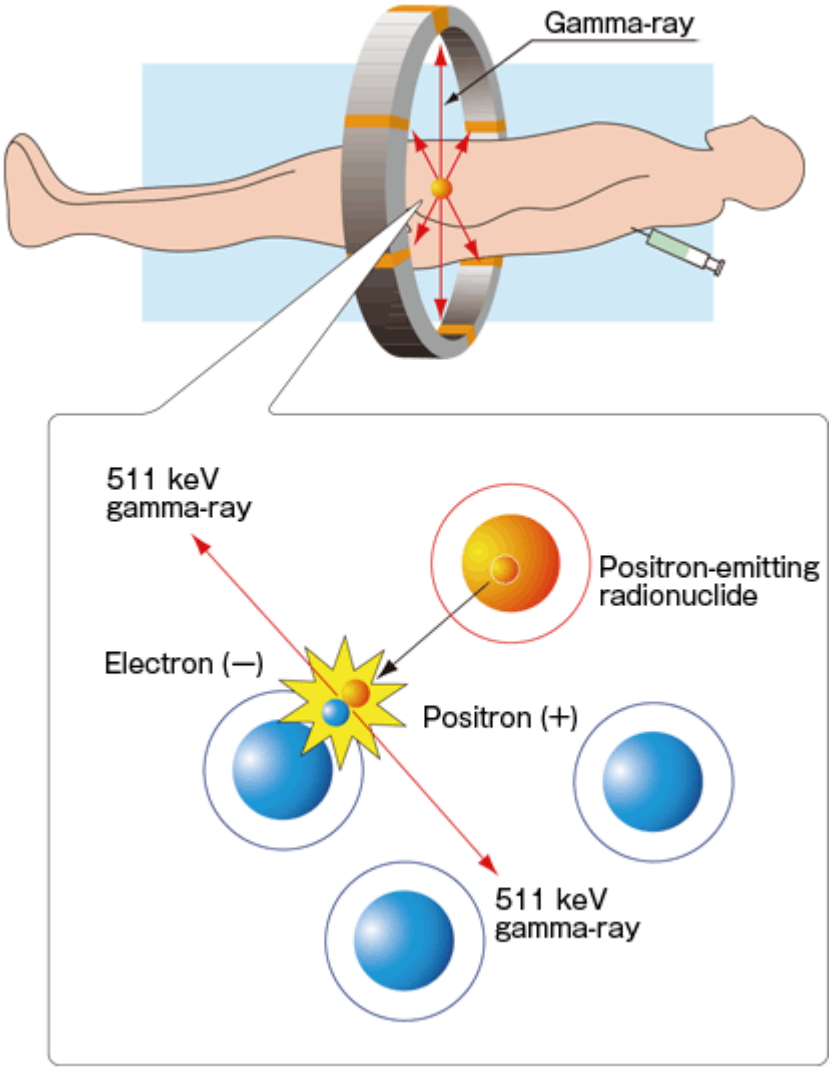
- 1986; Installation and operation of MC-50 cyclotron (Scanditronix co., Sweden)
- 1989; First production and clinic distribution of ^{67}Ga (SPECT, tumor) in Korea
- 1990; First production and clinic distribution of ^{201}Tl (SPECT, myocardiac) in Korea
- 1990; First production and clinic distribution of ^{123}I (SPECT, thyroid) in Korea
- 1992; First development of ^{111}In, ^{22}Na, ^{51}Cr in Korea
- 1995; First development and production of ^{18}F, ^{11}C in Korea
- 1995; First development and clinic production of [^{18}F]FDG, [^{11}C]methionine in Korea
- 2002; Installation and operation of Cyclone-30 (IBA co., Belgium)
- 2003; Mass production and clinic distribution of ^{67}Ga (Korea), ^{201}Tl (Korea), ^{123}I (Canada)
- 2003; First development and clinic distribution of [^{123}I]mIBG (SPECT, childhood cancer) in Korea
- 2005; First development and research distribution of ^{124}I (PET, thyroid, nanoparticle-labeling) in Korea
- 2006; First development of ^{103}Pd (prostate cancer, brackytherapy) in Korea
- 2007; First development and clinic distribution of ^{64}Cu (PET, tumor) in Korea
- 2007-13; First development and clinic study (low-level oxygen tumor) of [^{64}Cu]ATSM in Korea
- 2014; First development and research distribution of ^{89}Zr (PET, tumor) in Korea
- 2017; First development and clinic study (PET, breast cancer) of [^{64}Cu]Herceptin in Korea

PE Radioisotopes and PET System



Main Positron-Emitting Radioisotopes in Nuclear Medicine

Non-Metals

- ^{18}F (110 mins); good imaging & good half-life
- ^{11}C (20.4 mins); good imaging & natural carbon
- ^{13}N (9.96 mins); good imaging & natural nitrogen
- ^{15}O (2 mins); good imaging & natural oxygen
- ^{76}Br (16.1 hrs); good match with nucleic acid
- ^{124}I (4.18 days); good match with nanoparticles

Metals

- ^{64}Cu (12.7 hrs); good imaging & match with peptides
- ^{89}Zr (78.4 hrs); good match with antibodies
- ^{68}Ga (68 mins); good imaging & match with peptides
- ^{44}Sc (3.97 hrs); good in vivo stability & match with peptides

BASIC SCIENCES

RADIOCHEMISTRY
AND RADIOPHARMACEUTICALS

[18F]-Labeled 3-Deoxy-3-Fluoro-D-Glucose: Synthesis and Preliminary Biodistribution Data

Timothy J. Tewson, Michael J. Welch, and Marcus E. Raichle

Mallinckrodt Institute of Radiology, St. Louis, Missouri

A cyclotron target system for the production of anhydrous [18F] fluoride ion has been developed and used for the synthesis of carrier-free [18F]-3-deoxy-3fluoro-D-glucose (3-FDG). The synthesis is sufficiently rapid and efficient to allow production of usable amounts of 3-FDG with a 6-MeV cyclotron. Preliminary animal studies show that 3-FDG is in fact a glucose analog.

J Nucl Med 19: 1339–1345, 1978

The development of positron-emission tomography, coupled with the synthesis of biologic substrates containing positron-emitting nuclides, makes it possible to study local metabolism in vivo by noninvasive techniques. Carbon-11-labeled glucose has been used to determine local glucose metabolism in the brain (*1*), but the rapid metabolic turnover leads to the egress of $^{11}CO_2$. A glucose analog that would be transported like glucose and enter but not complete the metabolic cycle would be desirable. The synthesis of such a compound has recently been published, [18F]-2-deoxy-2-fluoro-D-glucose (2-FDG) (*2*). It is available only with a large cyclotron.

Of the possible isomers of deoxy-fluoro-glucose, the 6-fluoro cannot be phosphorylated at C-6, the 5-fluoro prevents the formation of the pyranose ring, and the 4-fluoro rapidly loses fluoride ion in vivo (*3*), as do the alpha and beta glucosyl fluorides with fluorination at C-1 (*4*).

Controlled transport across cell membranes involves either "active transport" or "facilitated diffusion" (*5*). Both processes involve a carrier and have a significant activation energy (10–12 kcal/mole). For a given concentration gradient, facilitated diffusion is considerably faster than would be expected from a passive mechanism. Active transport is an energy-consuming process, moving the substrate against a concentration gradient. The in vitro studies of these two transport systems have been performed on the hamster intestine for active transport (*6*) and on the human erythrocyte for facilitated diffusion (*7*). The blood-brain barrier is extremely difficult to study in vitro. There is, however, considerable in vivo evidence, both direct and indirect, that transport of glucose across the blood-brain barrier is similar to that in the human erythrocyte—that is, a facilitated diffusion. Both systems are sodium-independent, are insensitive to insulin, and respond like transport inhibitors such as phloretin, phlorizin, and cytochalasin B (*8*). Both systems also respond in a similar quantitative fashion to a variety

Received March 22, 1978; revision accepted July 5, 1978.

For reprints contact: T. J. Tewson, Div. of Radiation Sciences, Mallinckrodt Institute of Radiology, 510 South Kingshighway, St. Louis, MO 63110.

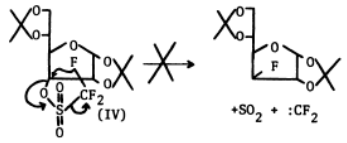


FIG. 3. Possible route for introduction of F-19 in synthesis of [18F]-3-FDG.

tained at A (Fig. 2). This initial estimate of the extraction fraction of [18F]-3-FDG is high because of the presence of significant recirculating tracer in the field of view of the detector. Correction for this recirculating tracer is made in the following manner. A second injection of labeled deoxyglucose is injected into the venous outflow of the brain by way of the catheter in the right jugular bulb. The quantity of tracer injected is normalized first to the amount injected into the carotid artery, and second to the first estimate of the nonextracted fraction as detailed above. The tracer curve generated from this injection (Fig. 2) is then used to subtract a first approximation of the amount of tracer present due to recirculation from the arterial tracer curve. From this corrected arterial curve the venous data are renormalized and the subtraction procedure repeated. After three iterations of this procedure it can be shown (unpublished) that the true extraction fraction of a tracer such as 3-FDG can be determined from the arterial curve. The final extrapolated value (Fig. 2) is used to compute the actual fractional extraction of the tracer.

The cerebral metabolic rate for glucose was computed from the arteriovenous glucose difference and the CBF as measured by $H_2{}^{15}O$.

In order to assess the behavior of [18F]-3-FDG in brain following its i.v. administration, 1 mCi was injected into a peripheral vein in an animal prepared and monitored in the manner described above.

Whole-body distribution data were obtained using a similarly anesthetized and paralyzed monkey, and injection of 6.5 mCi of [18F]-3-FDG. Scintigrams (200k counts/image) were obtained using a scintillation camera with a 550-keV-rated collimator, and the time taken for accumulation was recorded in each case. The results are shown in Fig. 4. The experiment was repeated with carrier-free material and the distribution was very similar.

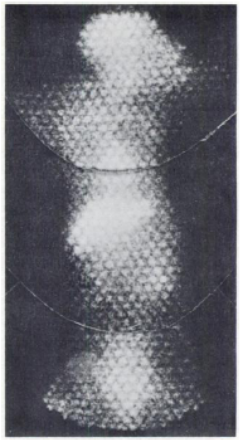


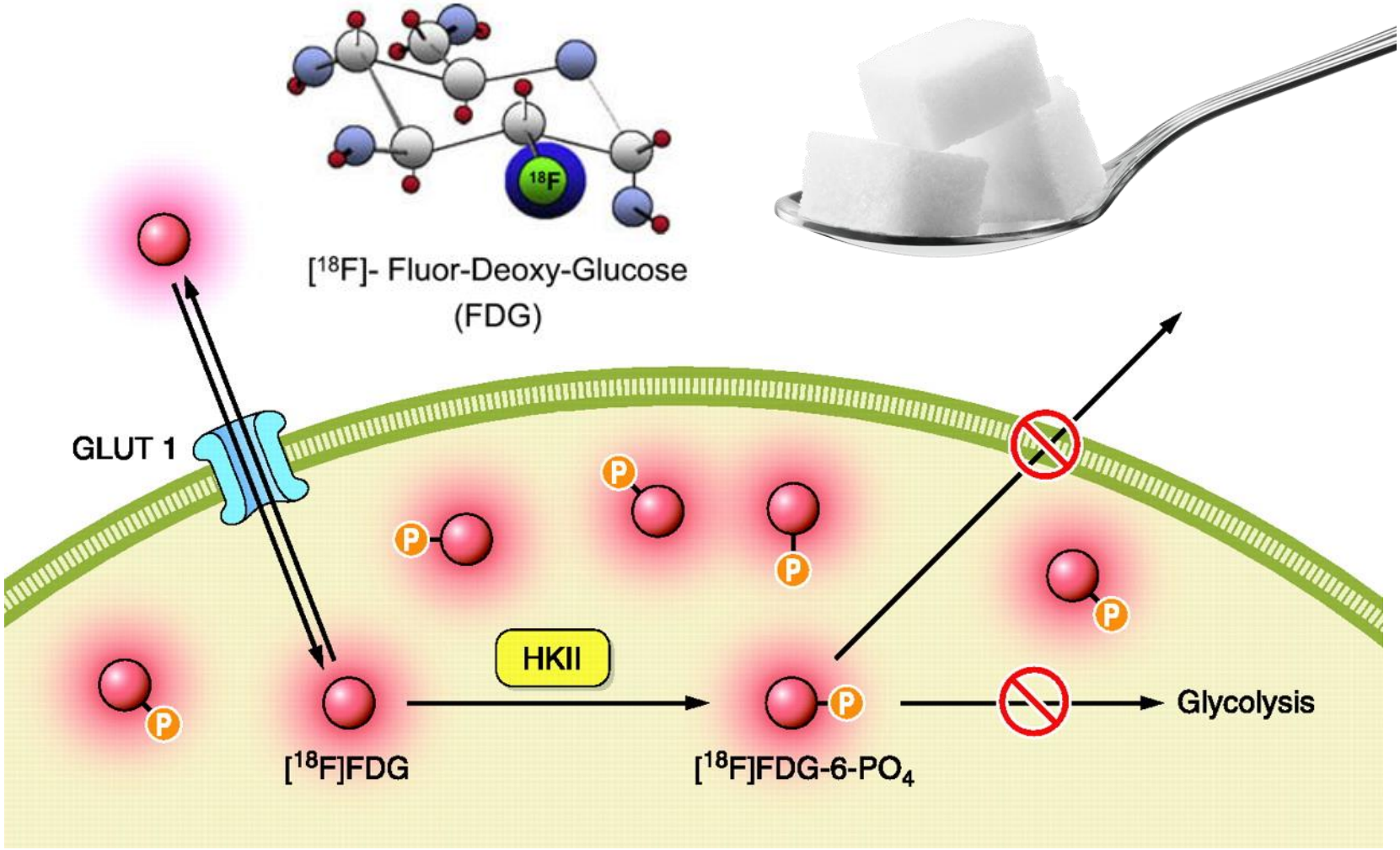
FIG. 4. Fluorine-18 distribution in rhesus monkey 30 minutes after injection of 6.5 mCi of [18F]-3-FDG.

RESULTS AND DISCUSSION

Radiochemistry. The reaction between cesium fluoride and the allose trifluoromethane sulfonate (IV) is close to quantitative with respect to both the ester and the fluorine ion (*19*), but with the radiotracer considerably less than 100% is incorporated. The primary variable is in the washoff from the glass wool plug. This is not surprising. Cesium fluoride is known to react with glass in the presence of water to produce fluorinated silicone derivatives, which can either be freed from the surface or remain in the polymeric structure of the glass. There is a rough correlation between the activity washed off the glass wool and that lost from the ether layer by the aqueous wash. Consequently the activity remaining in the ether layer is fairly constant, being 15% of the starting activity without correction for decay. This is consistent with increased removal of silicone fluorides rather than free fluoride ion. There is also the possibility of fluoride exchange with the trifluoromethane sulfonate anion. This occurs to a small extent with the ester (VI), and might occur to a larger extent with the anion produced by the displacement reaction.

Whether the silver-wool/cesium-hydroxide procedure truly produces carrier-free material or merely "no carrier added" is difficult to resolve fully. There are two possible sources of stable fluoride. The first is by thermal decomposition of the trifluoromethane sulfonate (IV) as shown in Fig. 3. This may oc-

Mechanism of [^{18}F]FDG Signal Amplification



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

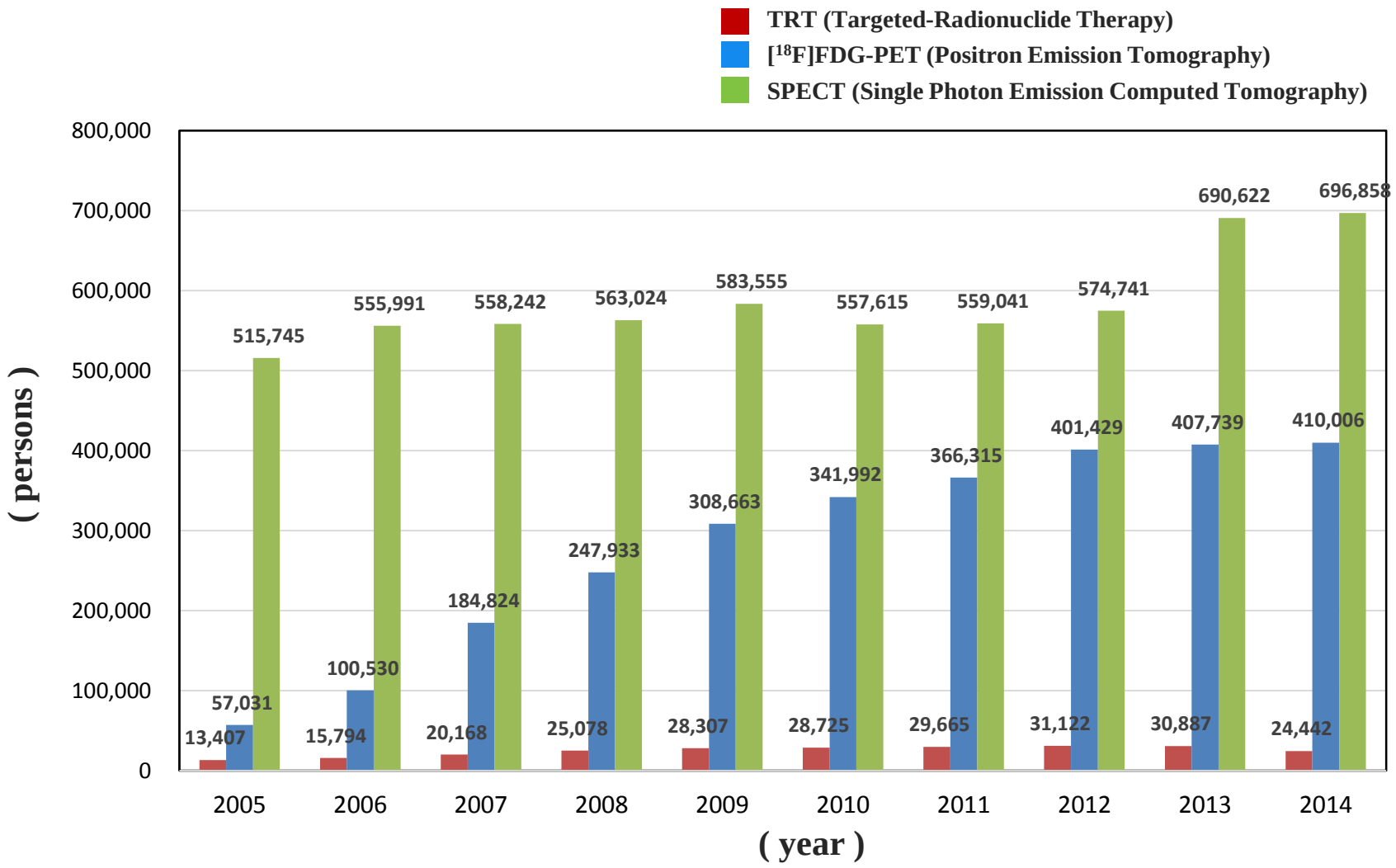
11 [^{18}F]FDG Role in Nuclear Medicine

***Oncology:** For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.

***Cardiology:** For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

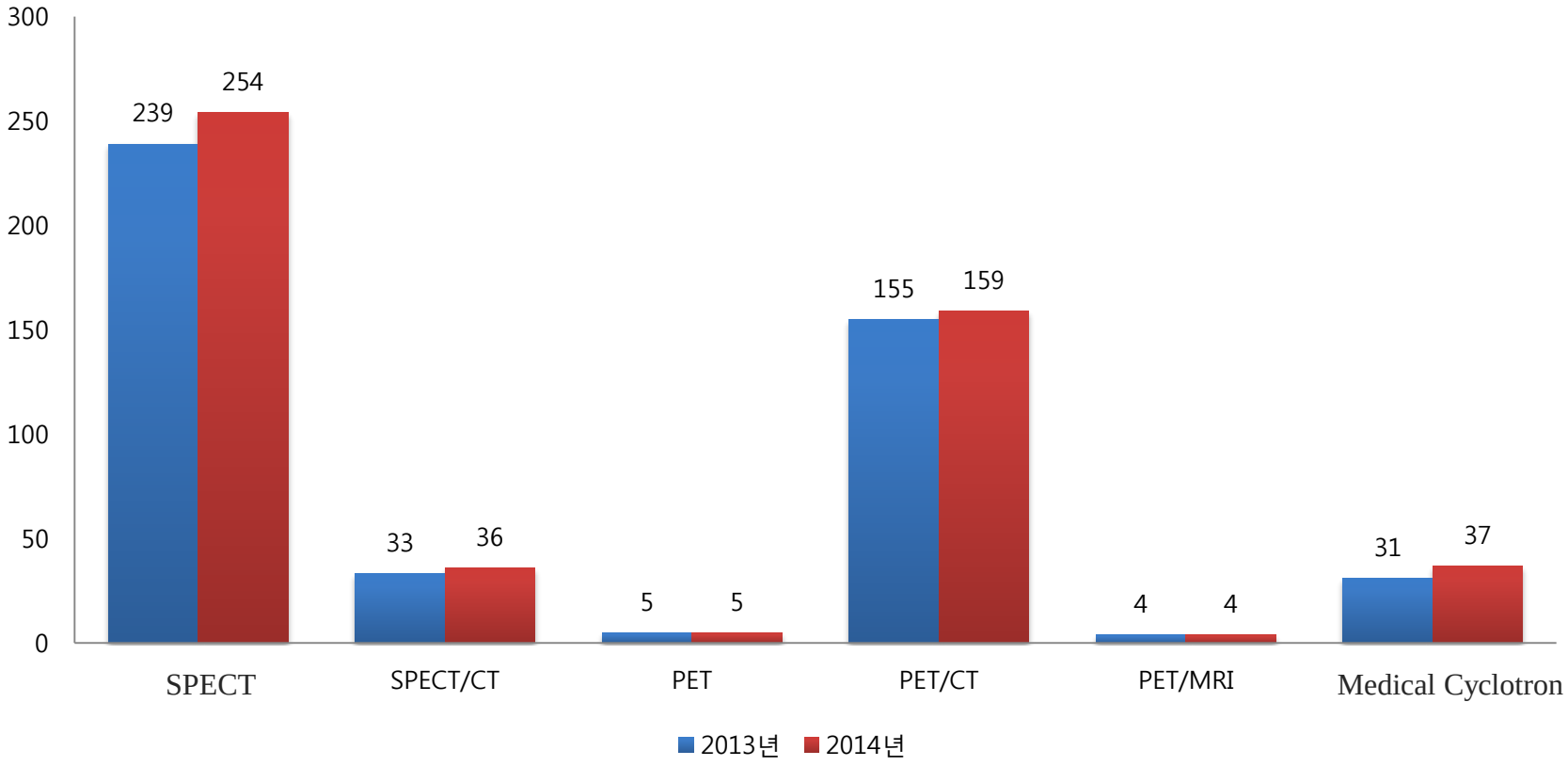
***Neurology:** For the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

12 [^{18}F]FDG-PET in Korean Nuclear Medicine

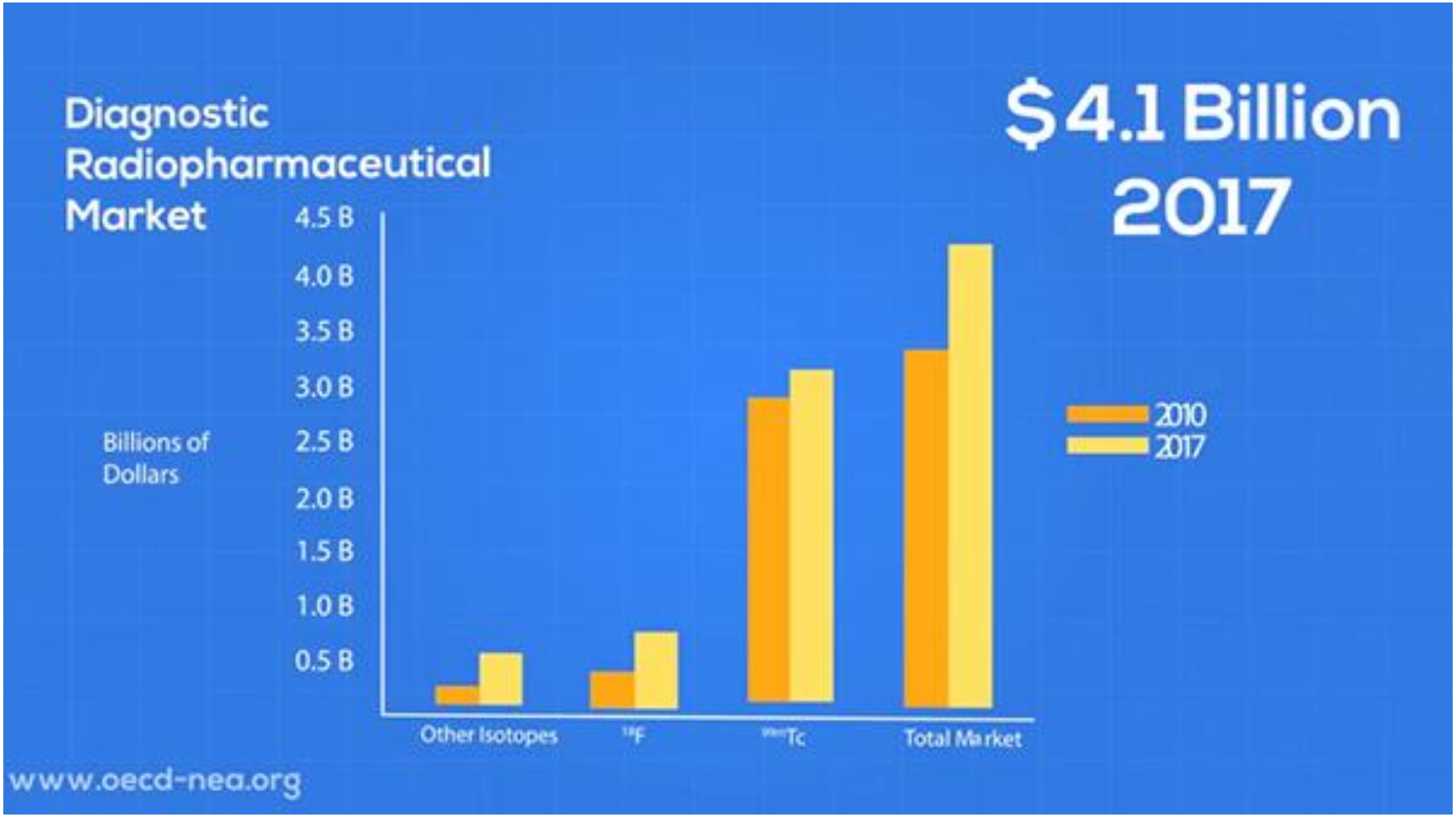


By The Korean Society of Nuclear Medicine, 2016

13 Korean Nuclear Medicine Infra



World Diagnostic Radiopharm. Market



15 FDA-Approved Radiopharmaceuticals

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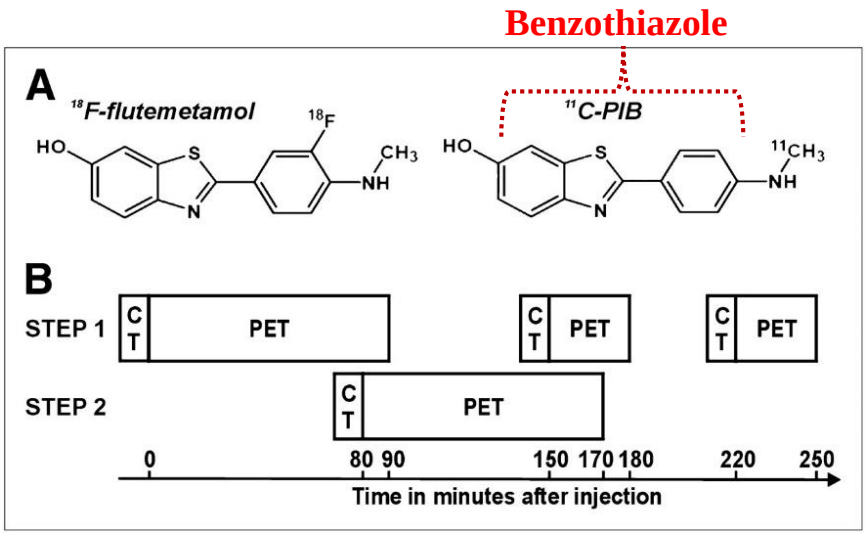
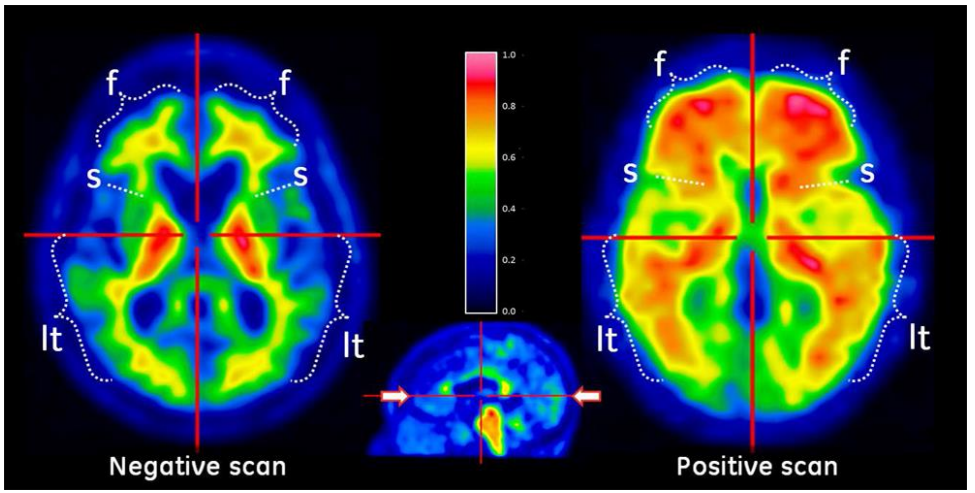
(U.S.A, 2016)

PET Radiopharm	Manufacturer	Medical Use in PET Imaging
^{11}C-choline	No patent	Prostate cancer
^{18}F-florberaben	Piramal Imaging	Alzheimer's disease (AD)
^{18}F-florbetapir	Eli Lilly	Alzheimer's disease (AD)
^{18}F-flucicovine	Blue Earth Diagnostics	Prostate cancer
^{18}F sodium fluoride	No patent	Bone imaging
^{18}F-fludexoyglucose (FDG)	No patent	Tumor, brain, myocardial perfusion
^{18}F-flutemetamol	GE Healthcare	Alzheimer's disease (AD)
^{68}Ga-DOTATATE	Advance Accelerator Applications	Neuroendocrine tumor
^{13}N-ammonia	No patent	Myocardial perfusion
^{82}Ru-rubidium chloride	Bracco Diagnostics, DRAXIMAGE	Myocardial perfusion

- Korean FDA was also approved for [^{18}F]FLT (Lung cancer), [^{18}F]MISO (Hypoxia tumor) [^{18}F]FP-CIT (Parkinson's disease) and [^{18}F]FC119S (Alzheimer's disease).

[^{18}F]Flutemetamol (GE Healthcare co.)





J Nucl Med August 2009 vol. 50 no. 8 1251-1259

17 [^{18}F]FC119S by Future Chem co. & KIRAMS

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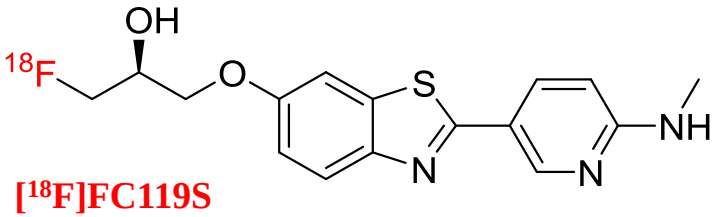
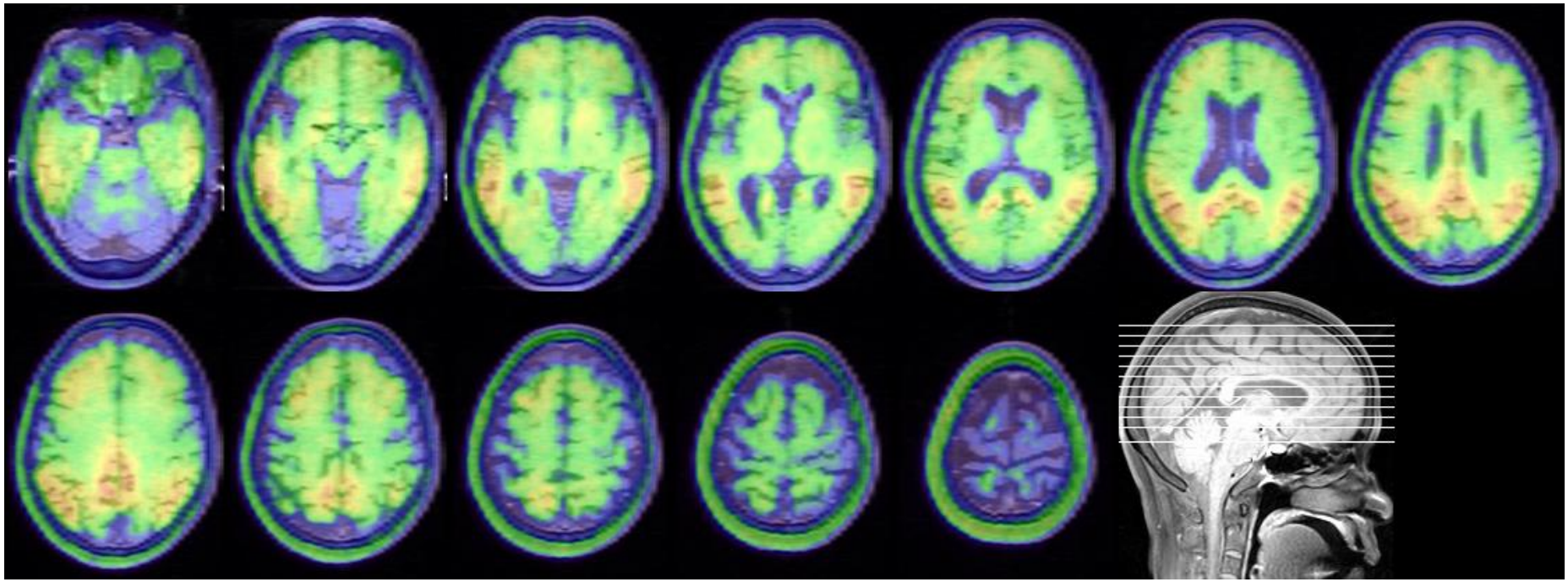
- Cooperation of KIRAMS and Future Chem co.
- With clinic study for about 150 persons
- Approved by KFDA (2018)

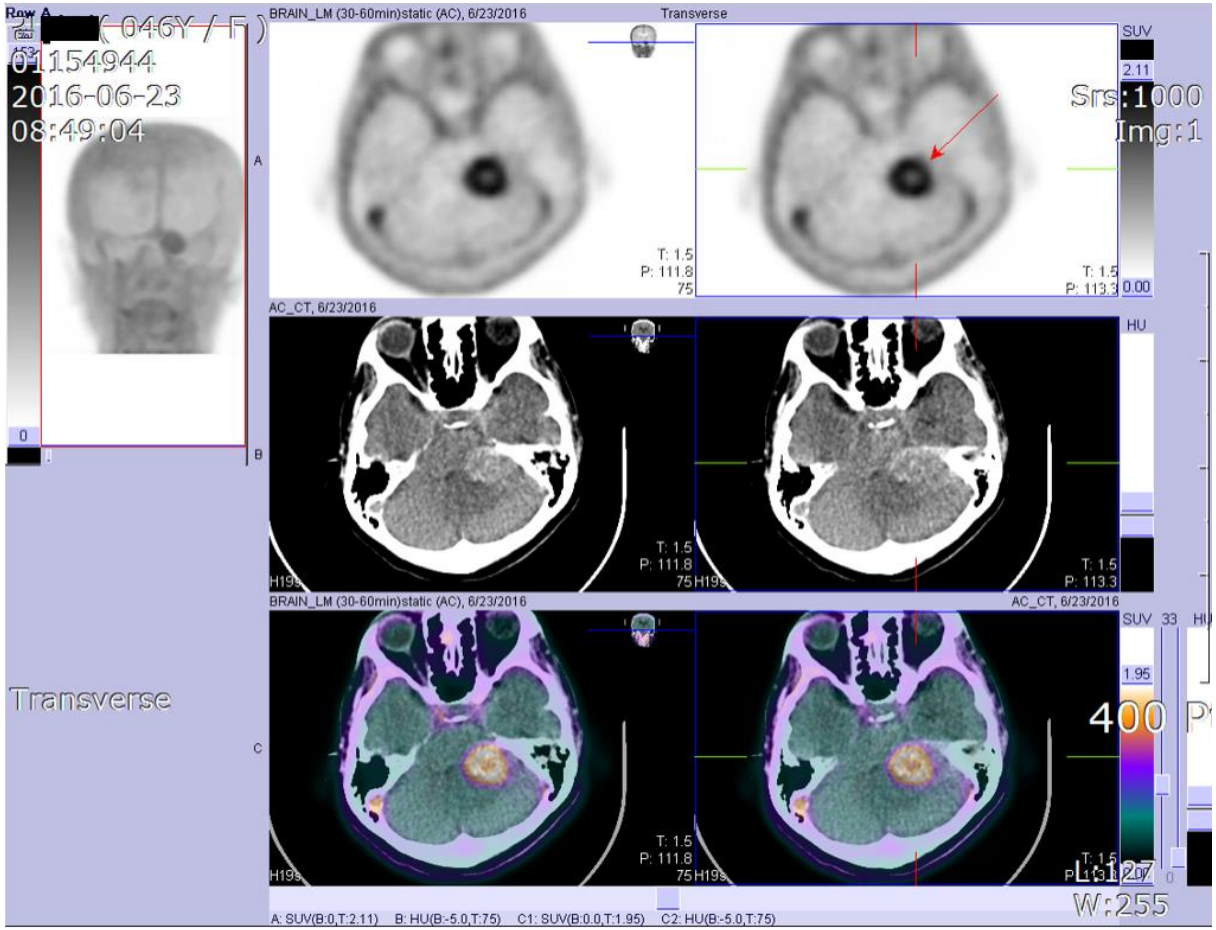


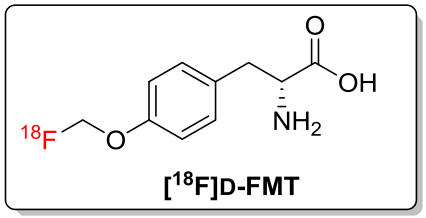
[^{18}F]FC119S



[^{18}F]FMT for Brain Cancer in KIRAMS

First Human Study of D-Isomers of ^{18}F-Fluoromethyl Tyrosine (10 persons, 2018)





[^{18}F]D-FMT

New PET-RI Project in KIRAMS

- **Positron-emitted radioisotope** → 511KeV of gamma ray
- **Physical half-life :** 12.7 hours
- **Medical applications :** Tumor diagnosis (ATSM, peptides & Ab, Monitoring of ^{67}Cu)

- **Positron-emitted radioisotope** → 511KeV of gamma ray (with other gamma ray)
- **Physical half-life :** 4.2 days
- **Medical applications :** Thyroid diagnosis, monitoring of nanoparticles & ^{131}I

- **Positron-emitted radioisotope** → 511KeV of gamma ray (with 908 KeV)
- **Physical half-life :** .3.3 days
- **Medical applications :** Monitoring & tumor diagnosis of anti-tumor antibody drug

- Above PET-RIs's price : about **€300/mCi** in only Europe
  (not included 'package and delivery charge', with radioactivity at department time)
  - 'ECA program of European Radiopharmaceuticals GMP Education Program', 2017

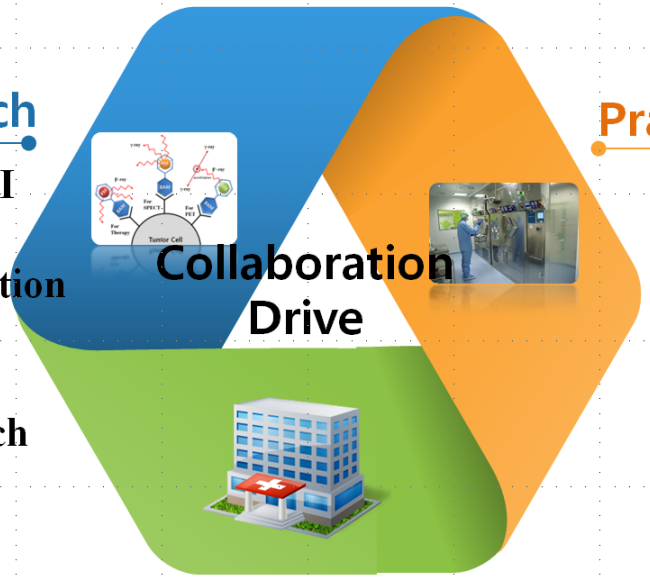
Scientific Project by National Fund

Technical Development and Practice of Future-oriented Radioisotopes for PET ('17.05-'21.01)

KIRAMS (Group 1)

Deuteron beam → *RI Tech

- Target & irradiation tech for RI production by D^+ beam
- Advanced ability for RI production
- Focused on ^{64}Cu, ^{89}Zr, ^{124}I
- Automation of RI purification
- Development of RI-labeling tech



Kaibiotech co. (Group 2)

Practice study for new RI

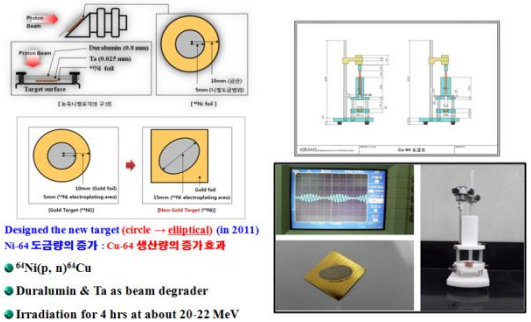
- Shielding tech
- Packaging tech
- GMP manuals
- Korean Approval
- Group organization of Korean user

Domestic Univ. & Medical Researches

- RI-Application supported by KIRAMS
- Clinical study by new RI-drug
- Sharing of RI-labeling tech
- Research collaboration

Development of PET-RI Tech by KIRAMS

^{64}Cu



Designed the new target (circle → elliptical) (in 2011)
Ni-64 도금량의 증가 : Cu-64 생산량의 증가 효과

- ^{64}Ni(p, n)^{64}Cu
- Duralumin & Ta as beam degrader
- Irradiation for 4 hrs at about 20-22 MeV

$^{64}CuCl_2$ Copper chloride

Copper-64
(Cu-64)
Copper-64 is a radiochemical
NOT FOR HUMAN USE, ONLY RESEARCH

Model	KIRAMS-Cu(II)
Package unit	5 mCi (1 vial)
Definition	Acidic solution containing copper-64 in the form of copper(II) chloride. Physical properties of copper-64 : Half life 12.7 hours, β⁻ 37.1%, β⁺ 17.9%
Production	Copper-64 is produced by proton irradiation of enriched nickel-64 (purity : 99%). No carrier copper is added.
Characters	Appearance : clear, colorless solution
Identification	Gamma-ray spectrometry : the most prominent gamma photon has an energy of 511 KeV.
Test	pH : lower than 3 Sterility : Not tested for. Bacterial endotoxins :Not tested for.
Radioactive concentration	> 5mCi/mL in glass vial
Radionuclidic purity	Copper-64 : > 99%
Radioactivity	Determine the radioactivity using a calibrated instrument.

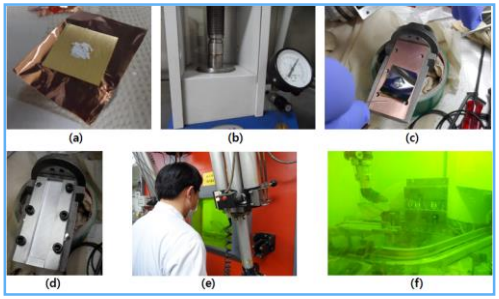
한국원자력의학원

^{124}I

▶ I-124 표적의 성능 향상에 의한 생산력 증가
- 내열성 강화, 냉각효과 상승, 생산수율 향상

▶ I-124 회수 장치의 안정화를 통한 생산력 증가
- 온도의 안정화 효과
- 작업자의 피폭 감소 효과
- 타겟 제작 및 I-124 회수의 안정화

<I-124 정제 및 회수 장치 제작>



^{89}Zr

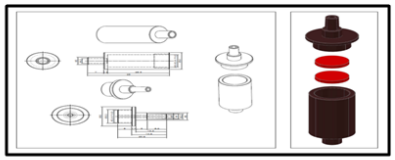
(1) 방사성동위원소 ^{89}Zr의 생산기술 개발

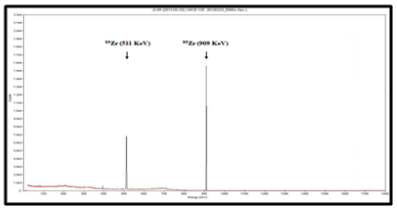
1 단계	2 단계	3 단계	4 단계
이트륨 표적의 제작	가속기에 의한 핵반응	방사화된 이트륨 표적 (^{89}Zr) 용해	^{89}Zr 분리 및 정제

(2) 농축 이트륨 표적의 제작 및 핵반응 조건
- 농축 ^{89}Y foil 방법으로 선정 및 제작
- 2.0cm×2.0cm×0.025mm (45mg)
- 양성자 빔 에너지 조사(16~18MeV, 20㎂)
- ^{89}Y(p,n)^{89}Zr 핵반응
- 월평균 1회 생산을 통해 대과제 연구 지원

연차별	1차 년도	2차 년도	3차 년도
빔조사 조건	1 uA/0.5h	20 uA/2h	20 uA/2h
Zr-89 수율	0.17 mCi/h	6.25mCi/h	7.5 mCi/h

▶ ^{89}Zr 정제를 위한 1회용 컬럼 제작 및 활용
- Hydroxylamate column 합성 → 1회용 컬럼화
- resin 내 금속의 킬레이터 결합 정도의 차이 이용
  (Y → 3+, Zr → 4+)





Official Production License by KIRAMS

한국원자력의학원
KOREA INSTITUTE OF RADIOLOGICAL & MEDICAL SCIENCES

$^{89}ZrCl_4$ Zirconium chloride

Zirconium-89
(Zr-89)

Zirconium-89 is a radiochemical

NOT FOR HUMAN USE, ONLY RESEARCH

Model	KIRAMS-Zr(IV)
Package unit	1-10 mCi (1 vial)
Definition	Acidic solution containing zirconium-89 in the form of zirconium(IV) chloride. Physical properties of zirconium-89 : Half life 3.27 days, β^+ 22.3%, EC 76.6%
Production	Zirconium-89 is produced by proton irradiation of enriched yttrium-89 (chemical purity : 99%). No carrier zirconium is added.
Characters	Appearance : clear, colorless solution
Identification	Gamma-ray spectrometry : the most prominent gamma photon has an energy of 511, 909 KeV.
Test	pH : lower than 3 Sterility : Not tested for. Bacterial endotoxins :Not tested for.
Radioactive concentration	> 10.0 mCi/mL in glass vial
Radionuclidic purity	Ziconium-89 : > 99%
Radioactivity	Determine the radioactivity using a calibrated instrument.

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$^{64}CuCl_2$ Copper chloride

Copper-64
(Cu-64)

Copper-64 is a radiochemical

NOT FOR HUMAN USE, ONLY RESEARCH

Model	KIRAMS-Cu(II)
Package unit	1-50 mCi (1 vial)
Definition	Acidic solution containing copper-64 in the form of copper(II) chloride. Physical properties of copper-64 : Half life 12.7 hours, β^- 37.1%, β^+ 17.9%
Production	Copper-64 is produced by proton irradiation of enriched nickel-64 (purity : 99%). No carrier copper is added.
Characters	Appearance : clear, colorless solution
Identification	Gamma-ray spectrometry : the most prominent gamma photon has an energy of 511 KeV.
Test	pH : lower than 3 Sterility : Not tested for. Bacterial endotoxins :Not tested for.
Radioactive concentration	> 5mCi/mL in glass vial
Radionuclidic purity	Copper-64 : > 99%
Radioactivity	Determine the radioactivity using a calibrated instrument.

한국원자력의학원

$Na^{124}I$ Sodium Iodide

Iodine-124
(I-124)

Iodine-124 is a radiochemical

NOT FOR HUMAN USE, ONLY RESEARCH

Model	KIRAMS-Na[^{124}I]
Package unit	1-20 mCi (1 vial)
Definition	A dilute solution of NaOH containing I-124 in the chemical form of iodide ($^{124}I^-$). Physical properties of I-124 : Half life 4.18 days, β^+ 25.6%, EC 74.4%
Production	Iodine-124 is produced by proton irradiation of enriched tellurium-124 or tellurium-125 (chemical purity : over 98%). No carrier iodine (or iodide) is added.
Characters	Appearance : clear & colorless solution
Identification	Gamma-ray spectrometry : the most prominent gamma photon has an energy of 27, 31, 511(major), 603, 723, 1691 KeV.
Test	pH : higher than 9 Sterility : Not tested for. Bacterial endotoxins : Not tested for.
Radioactive concentration	> 2.0 mCi/mL in glass vial
Radionuclidic purity	Iodine-124 : > 99%
Radioactivity	Determine the radioactivity using a calibrated instrument.

한국원자력의학원

New PET-RI User Meeting in Korea

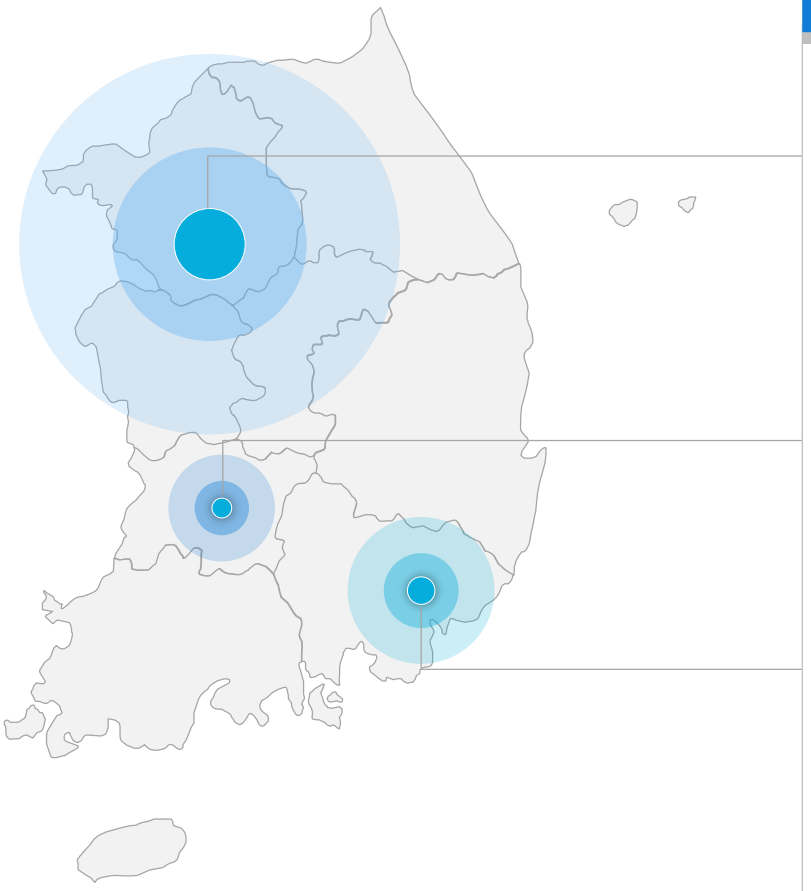
PET-RI 사용자 그룹 유저미팅 개최

- 2017 미래선도 PET-RI 사용자 그룹 유저미팅 개최(2017.07.28)
- 참석기관: 한국원자력의학원, 경북대학교, 동아대학교병원, 삼성서울병원, 한국원자력연구원, 분당서울대병원, 서울대병원, 아주대병원, 퓨처켐, 새한산업, 카이바이오텍
- 11개 기관, 과제책임자 및 담당실무자 30여 명 참석

PET-RI 사용자 그룹 유저미팅 주요 내용

- 과제 간 또는 과제, 연구주제간 공동연구협약서 체결
- PET-RI 동위원소(Cu-64, Zr-89, I-124) 사용신청서 작성
- 과제 책임자 및 실무자간 메일 전송
- PET-RI 생산회의에 의해 공급량 조절(cyclotron 및 target의 상태에 따라 공급량 변동 가능)
- 공급지원은 2세부 카이바이오텍이 지원(포장 및 운송)
- 동위원소 운송내역 KINS 보고 및 생산자, 사용자 각각 KINS 보고체계 확립

PET-RI Supply by KIRAMS Project



Partner Institutes by RI-MOU

(1) Seoul National Univ. Hospital (2)

(2) Seoul Asan Hospital

(3) Seuol Sam-Sung Hospital (2)

(4) Severance Hospital

(5) A-Ju Univ. Hospital

(6) Kyungpook National Univ. Hospital

(7) Kyungook Univ.

(8) Chonnam National Univ. Hosptial

(9) Yonsei Univ.

(10) KIRAMS researchers

(11) Singapore Univ. (International co-work)

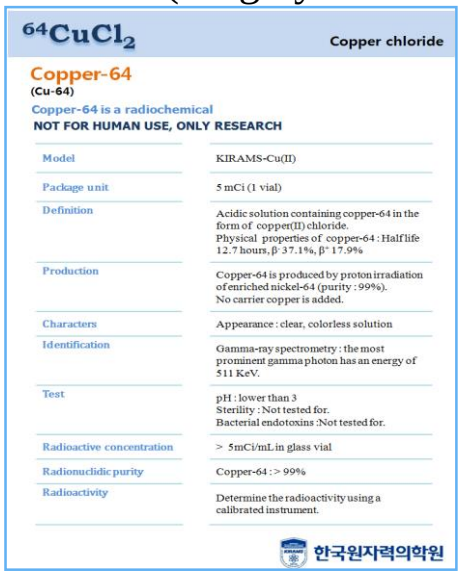
Major Results by KIRAMS PET-RI Project

Clinical Study

▶ **^{64}Cu-ATSM** (FDA approved, research); 5 persons,
Diagnostic study of tumor bearing low level oxygen (KIRAMS)

▶ **^{64}Cu-DOTA-Trastuzumab & ^{64}Cu-NOTA-Trastuzumab** (FDA approved, research) ; 15 persons, Metastatic breast cancer (Surgery-Nuclear medicine, KIRAMS)

Production License by KINS



$^{64}CuCl_2$ Copper chloride

Copper-64
(Cu-64)
Copper-64 is a radiochemical
NOT FOR HUMAN USE, ONLY RESEARCH

Model	KIRAMS-Cu(II)
Package unit	5 mCi (1 vial)
Definition	Acidic solution containing copper-64 in the form of copper(II) chloride. Physical properties of copper-64 : Half life 12.7 hours, β- 37.1%, β+ 17.9%
Production	Copper-64 is produced by proton irradiation of enriched nickel-64 (purity : 99%). No carrier copper is added.
Characters	Appearance : clear, colorless solution
Identification	Gamma-ray spectrometry : the most prominent gamma photon has an energy of 511 KeV.
Test	pH : lower than 3 Sterility : Not tested for. Bacterial endotoxins :Not tested for.
Radioactive concentration	> 5mCi/mL in glass vial
Radionuclidic purity	Copper-64 : > 99%
Radioactivity	Determine the radioactivity using a calibrated instrument.

한국원자력의학원

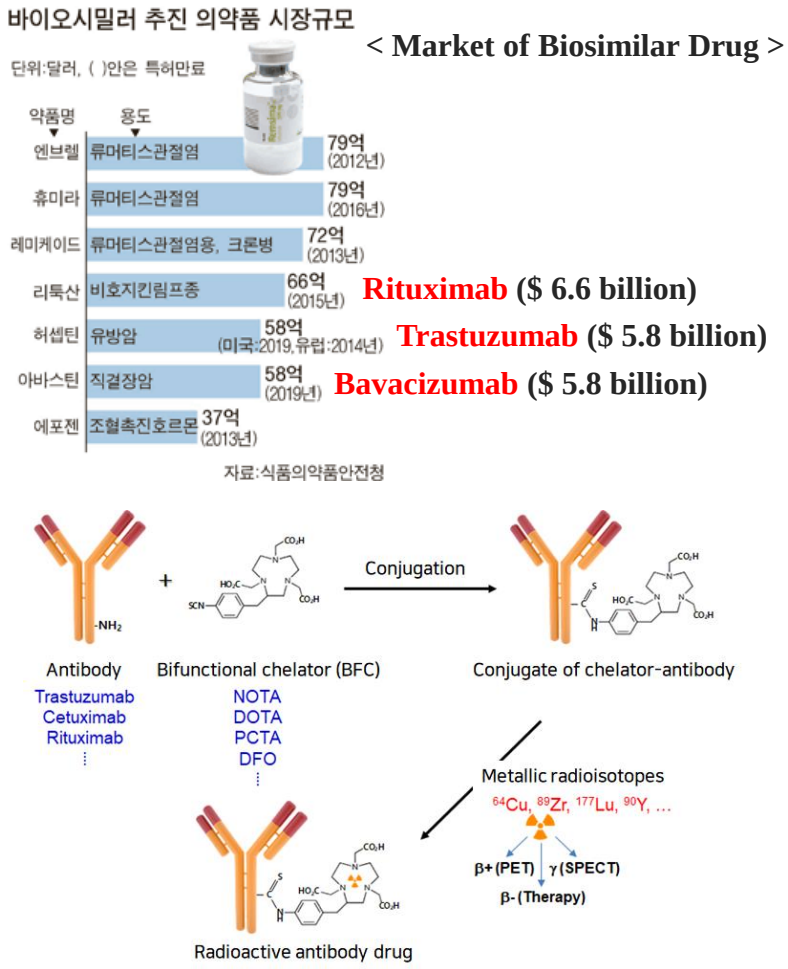
SCI Journal

PET-RI	Cu-64 (32)	I-124 (11)	Zr-89 (2)
2016년 (13)	Amino Acids(2) J. Nucl. Med.(2) Nucl. Med. Commun.(1) Biochem. Biophy. Res. Comm.(1) Nucl. Eng. Tech. (1) Nucl. Med. Commun.(1) Cancer Biother. Radiopharm. (2)	Appl. Radiat. Isot. (1) Mol. Imaging Biol. (1)	Mol Pharm.(1)
2015년 (9)	EANMMI Res, (1) PloS One (1) Nucl. Med. Commun.(1) Int. J. Oncol.(1) Inorg. Chem. (1) ACS Med. Chem. Lett.(2)	Biochem. Biophy. Res. Comm.(1)	Cancer Biother. Radiopharm. (1)
2014년 (6)	J. Nucl. Med.(1) Nucl. Med. Biol. (1) J. Med. Chem. (1) ACS Med. Chem. Lett.(1) Bioconjug. Chem.(1)	ACS Med. Chem. Lett.(1)	
2013년 (4)	Nucl. Med. Biol. (1) Biomaterials(2) Bioconjug. Chem.(1) ACS Med. Chem. Lett.(1)		
2012년 (5)	Nucl. Med. Biol. (1) Bioconjug. Chem.(2)	Bioorg. Medi. Chem.(1) J. Korean Med. Sci (1)	
2010년 (3)	Nucl. Med. Mol. Imaging(1) Appl. Radiat. Isot. (1)	Appl. Radiat. Isot. (1)	
2008년 (1)		Angewandte Chemie(1)	
2007년 (2)		J. Med. Chem. (1) J. Label. Como. Radiopharm(1)	
2005년 (1)		J. Nucl. Med.(1)	
RI 개발 년도	2009년	2005년	2014년

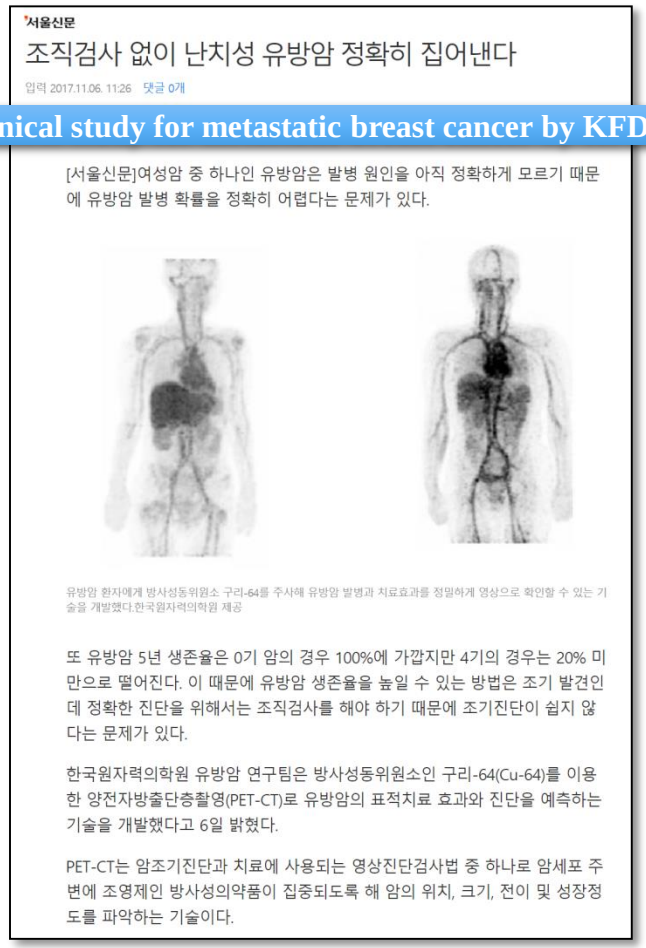
Clinic Study of ^{64}Cu-Trastuzumab

- Clinical study for metastatic breast cancer using radioactive trastuzumab

Preparation of RI-antibody conjugate



^{64}Cu-DOTA (or NOTA)-trastuzumab,2017


서울신문

조직검사 없이 난치성 유방암 정확히 집어낸다

입력 2017.11.06. 11:26 댓글 0개

Clinical study for metastatic breast cancer by KFDA

[서울신문]여성암 중 하나인 유방암은 발병 원인을 아직 정확하게 모르기 때문에 유방암 발병 확률을 정확히 어렵다는 문제가 있다.

유방암 환자에게 방사성동위원소 구리-64를 주사해 유방암 발병과 치료효과를 정밀하게 영상으로 확인할 수 있는 기술을 개발했다.한국원자력의학원 제공

또 유방암 5년 생존율은 0기 암의 경우 100%에 가깝지만 4기의 경우는 20% 미만으로 떨어진다. 이 때문에 유방암 생존율을 높일 수 있는 방법은 조기 발견인데 정확한 진단을 위해서는 조직검사를 해야 하기 때문에 조기진단이 쉽지 않다는 문제가 있다.

한국원자력의학원 유방암 연구팀은 방사성동위원소인 구리-64(Cu-64)를 이용한 양전자방출단층촬영(PET-CT)로 유방암의 표적치료 효과와 진단을 예측하는 기술을 개발했다고 6일 밝혔다.

PET-CT는 암조기진단과 치료에 사용되는 영상진단검사법 중 하나로 암세포 주변에 조영제인 방사성의약품이 집중되도록 해 암의 위치, 크기, 전이 및 성장정도를 파악하는 기술이다.

^{89}Zr Production & Its Applications (2014)

Success of ^{89}Zr-PET imaging & Diagnosis for Rheumatoid Arthritis using ^{89}Zr oxalate

First Production of ^{89}Zr in Korea

암 진단용 방사성동위원소, 국내 생산 가능해졌다

[2017-09-28 10:26:35] 목록 | 프린트

국내 연구진이 그동안 수입에 의존했던 암 치료용 방사성동위원소의 국내 양산 시스템을 구축하는 데 성공했습니다.

한국원자력의학원은 지르코늄-89 양산시스템을 구축하고, 다음 달부터 국내 의료기관에 공급할 예정이라고 밝혔습니다.

지르코늄-89는 다른 방사성동위원소와 달리 반감기가 3.3일로 길어 정확한 암 진단이나 장시간의 약물반응 관찰이 가능하지만, 대량생산이 어려워 그동안 수입에 의존해왔습니다.

연구팀은 특수 흡착제를 이용해 불순물을 제거하는 방식으로 순도 99.9%의 지르코늄-89를 분리 정제하는 데 성공했다고 설명했습니다.

의학원은 사전 수요조사를 통해 서울대병원 등 14개 연구팀에 다음 달부터 지르코늄-89를 제공하기로 했습니다.

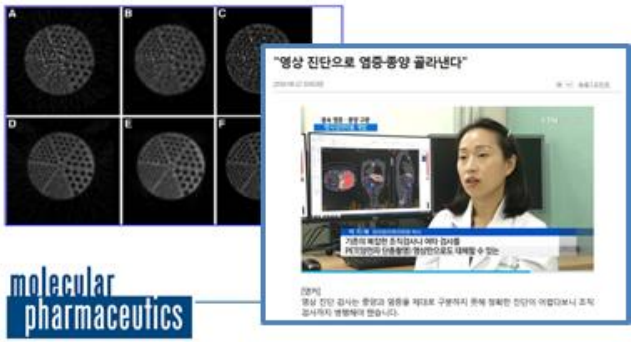
양훼영 [hwe@ytn.co.kr]

Rheumatoid Arthritis, ^{89}Zr oxalate

CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS
Volume 30, Number 1, 2015
© Mary Ann Liebert, Inc.
DOI: 10.1089/cbr.2014.1709

Spatial Resolution and Image Qualities of Zr-89 on Siemens Biograph TruePoint PET/CT

Young Sub Lee,[1,2] Jin Su Kim,[1] Jung Young Kim,[1] Byung Il Kim,[1] Sang Moo Lim,[1] and Hee-Joung Kim[2]

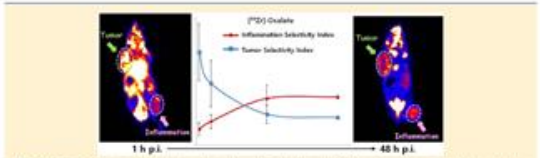


molecular pharmaceutics

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
[‡]Department of Nuclear Medicine, Korea Institute of Radiological and Medical Sciences, Seoul 139-706, Republic of Korea



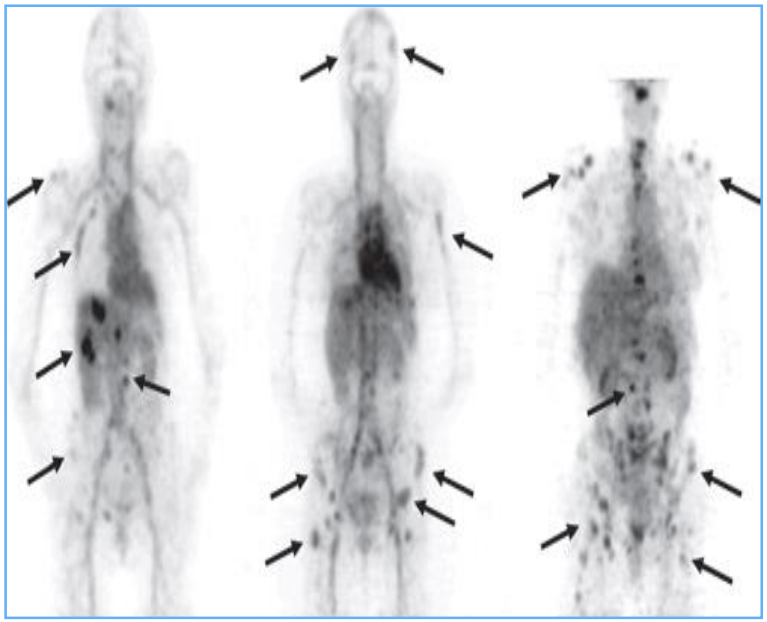
ABSTRACT: To obtain an additional pharmacological agent for the diagnosis of inflammation, we investigated the medical use of ^{89}Zr-oxalate as a positron emission tomography (PET) probe for the in vivo imaging of inflammation and compared its efficacy to that of 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) 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

Pre-Clinic Study of ^{89}Zr-Trastuzumab

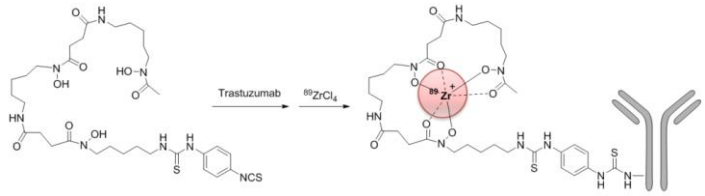
- Good PET imaging agent for metastatic breast cancer, ^{89}Zr-DFO-trastuzumab

^{89}Zr-DFO-trastuzumab in Holland

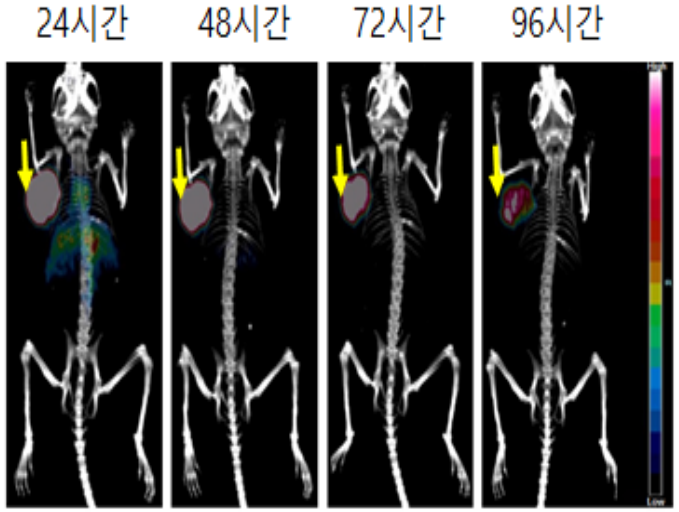


Biodistribution of ^{89}Zr-trastuzumab and PET Imaging of HER2-Positive Lesions in Patients With Metastatic Breast Cancer, ***Clinical Pharmacology & Therapeutics 87(5) 2010***

^{89}Zr-DFO-trastuzumab in KIRAMS



^{89}Zr-Df-trastuzumab 종양 진단 PET 영상

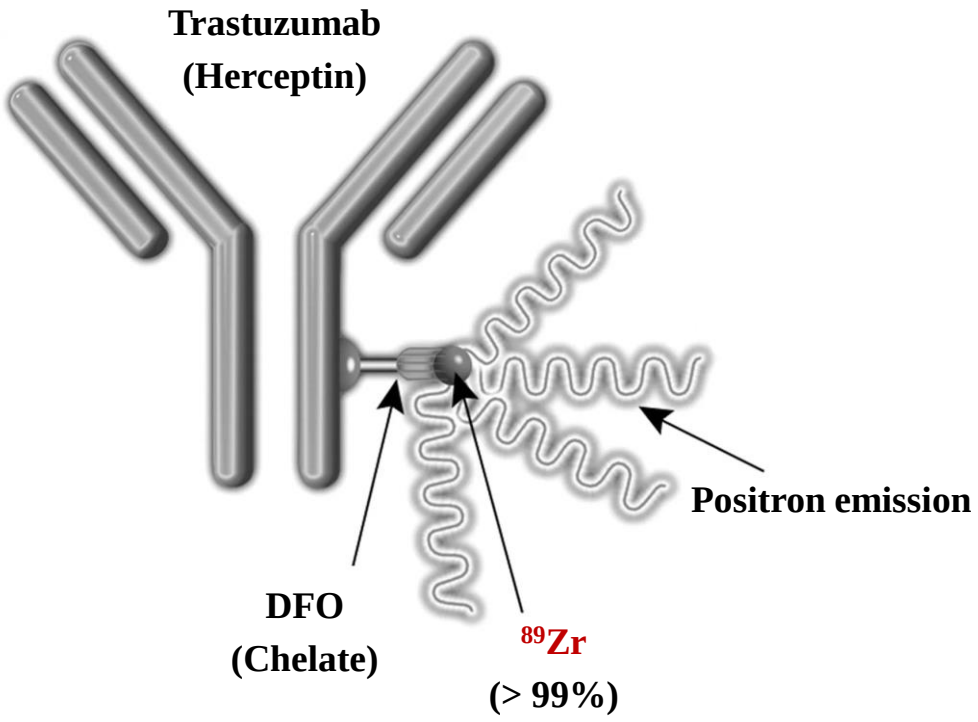


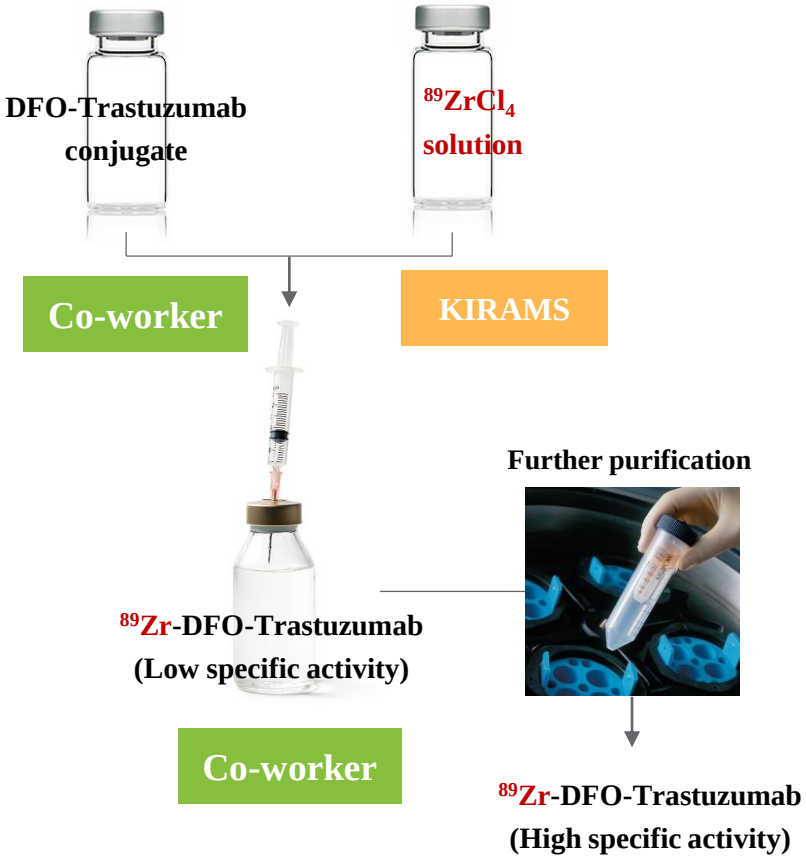
사람표피성장인자수용체 2 고발현 유방암 세포주를 이식한 동물모델의 면역 PET 영상(화살표: 종양)

Co-Work by Chelate-Kit Radiochemistry

- Preparation of new radiopharmaceuticals by Chelate-Kit

^{89}Zr-DFO-Trastuzumab





How to Delivery ^{89}Zr

- **Development and KINS's approval of tungsten vial-shield for exclusive ^{89}Zr, by co-work of Kaibiotech co. and KIRAMS**

NUCLEAR LIGHT INDUSTRY

NLI-RIC-^{89}Zr

Type "A" Tungsten Shielded Container
for radioactive substances transportation

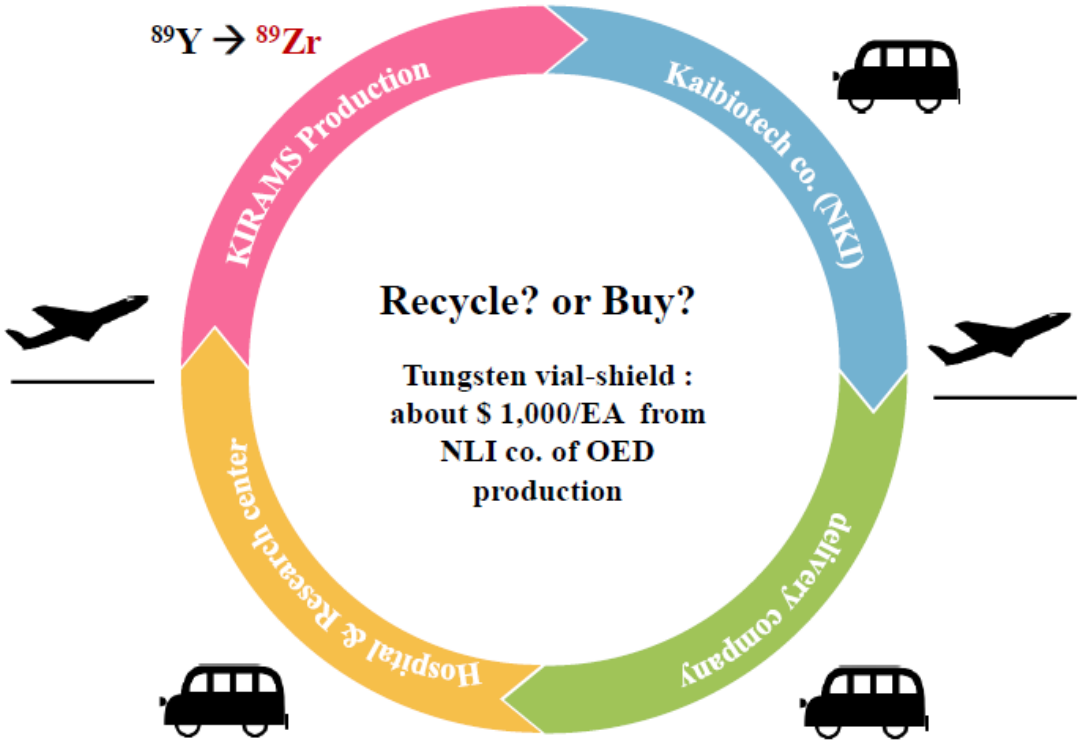
Features

- Manufactured in conformity with the law of Korean Nuclear Safety and Security, "Technical Standards according to Regulations on Packaging and Transportation of Radioactive Materials, etc."
- Air-tight ensured by O-ring sealing device on the top of container
- Three types of containers available for optimum shielding effect depending on each nuclide.
- Minimized pollution possibility with neat finish and easy-to-open structure by rotating the cap on the top of container
- Provided with Certificate for Type A Container
- Shielding evaluation method in accordance with MCNP code

Specifications

- External dimensions : Ø46 x H79 mm
- Internal dimensions : Ø26 x H57 mm
- Weight : 1.75Kg
- Tungsten shielding : 10mm (W:94.83%, Ni:3.15%, Fe:2.02%)
- Density : 18.05g/cm³
- Maximal transportable activity : 10mCi
- Max dose ratio on the surface : 0.23mSv/hr (Distance 20cm)

NUCLEAR LIGHT INDUSTRY CO., LTD.
Majung4-ro Seo-gu, Incheon, Republic of Korea
Tel : +82 2 2682 6571 Fax : +82 2 2682 4929 E-mail : info@nlik.com Web : http://www.nlik.com



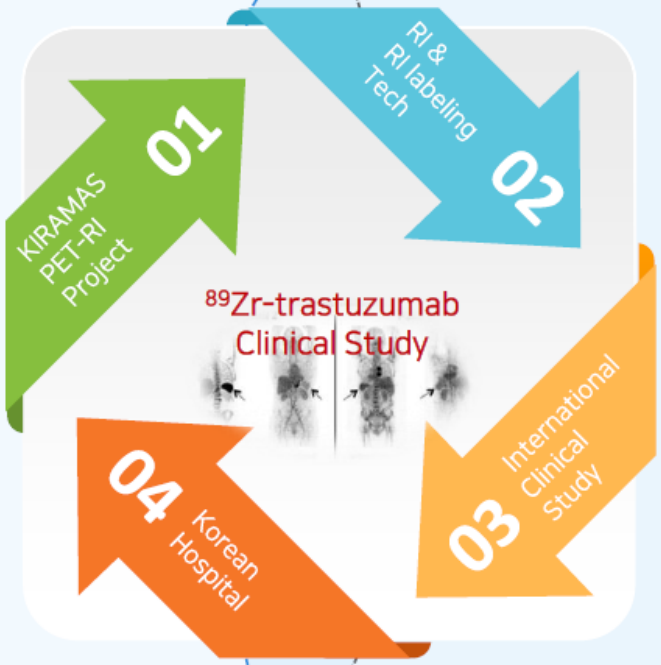
International Project for Clinical Study!

한국원자력의학원 KOREA INSTITUTE OF RADIOLOGICAL & MEDICAL SCIENCES

Suggestion of internationally a joint research for ^{89}Zr-DFO-trastuzumab, with KIRAMS

KIRAMS PET-RI Project
Medical RI, ^{89}Zr Delivery
^{89}Zr-labeling Technique
^{89}Zr-trastuzumab
Immino-PET Technique
Quality Control Technique

Hospital & Research in Korea
KIRAMS approved from KFDA
Supplying to Korean Hospital
Clinical Study & Practical use
Korea-Vietnam Medical Relationship



RI & RI-labeling Tech
Drug Delivery for RI
Labeling Tech for RI
Preparation of ^{89}Zr-trastuzumab
Quality Control
^{89}Zr-labeling Researches

IAEA
International Atomic Energy Agency
Atoms for Peace

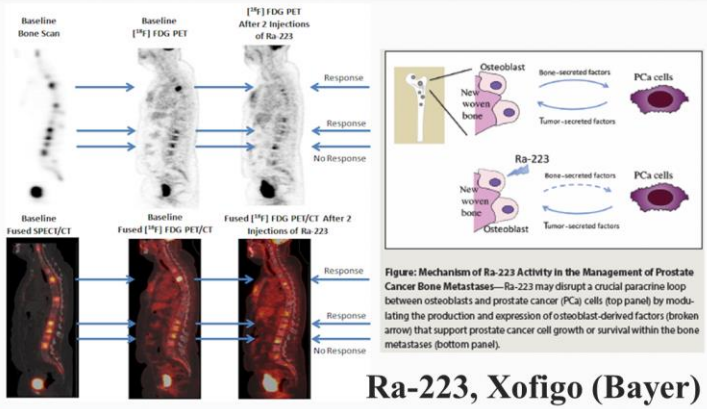
International Clinical Study
^{89}Zr-trastuzumab Clinical Study
Nuclear Medicine Imaging
(Target : Breast Cancer etc.)
Development of Medical Tech

- ^{89}Zr can be a good delivery due to half-life 3.3 days, and be freely received from KIRAMS for project period.
- In addition, KIRAMS & KaiBiotech were successful to develop a specific vial-shield for ^{89}Zr.
  - It was approved by Korean government
- This shield ($ 1,000) was made of tungsten material, which was cheaper than ^{18}F vial-shield.
  - If don't want to buy vial-shield, we can be shared one shield with give and take.

Fourth Way (TRT) for Tumor Therapy

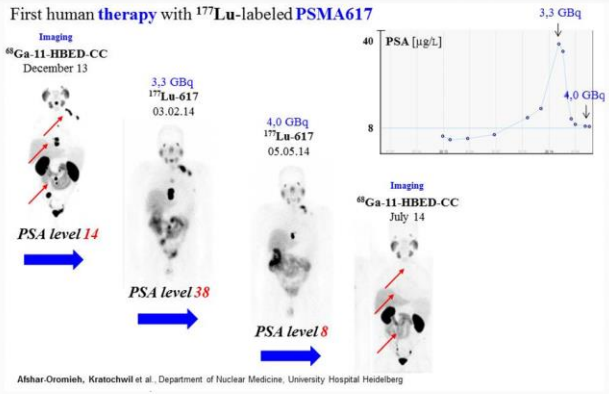
TRT : Targeted-Radionuclide Therapy

Bone metastases & pain palliation

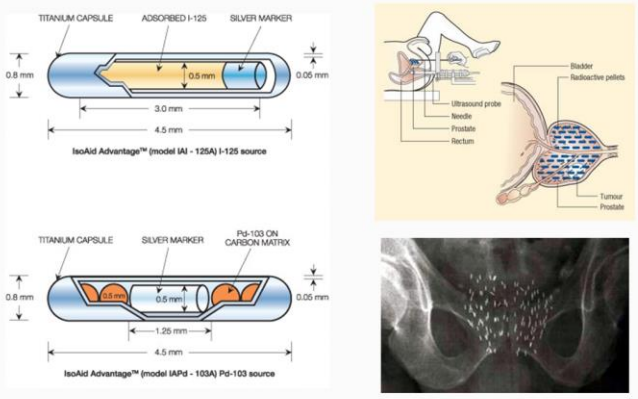


Ra-223, Xofigo (Bayer)

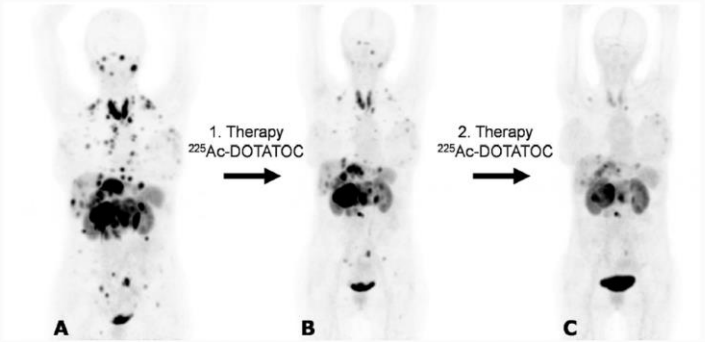
Metastatic prostate cancer



Brachytherapy, prostate cancer

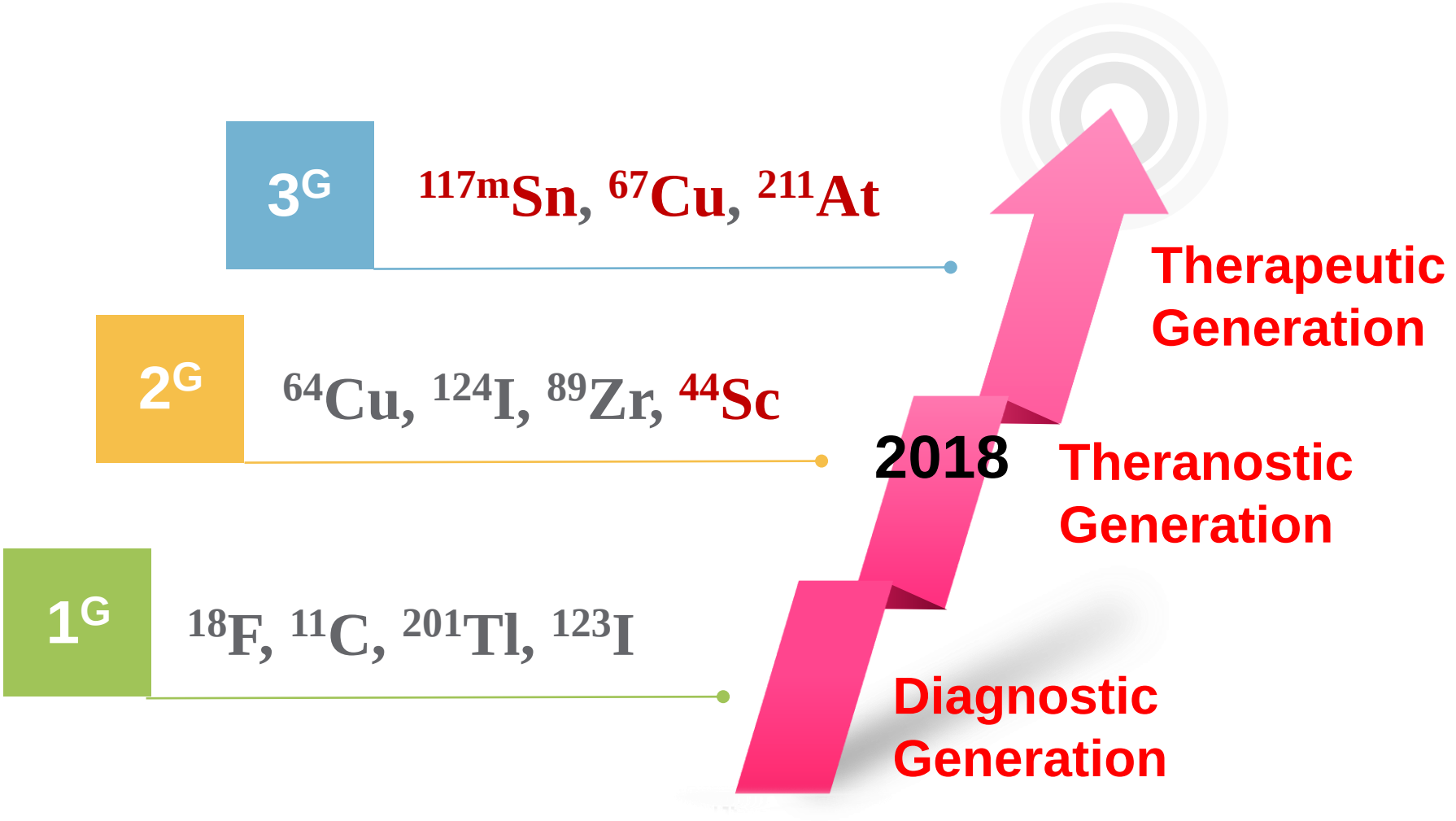


Tumor-targeting agent, alpha ray



Na[^{18}F]-PET & Xofigo Therapy in KIRAMS

Cy-RI Research Trend in Nuclear Medicine



KIRAMS Research Plans for Therapeutic RI

50 MeV Cyclotron

Proton Beam
(H^+)

^{18}F, ^{11}C, ^{44}Sc*

^{64}Cu, ^{124}I, ^{89}Zr

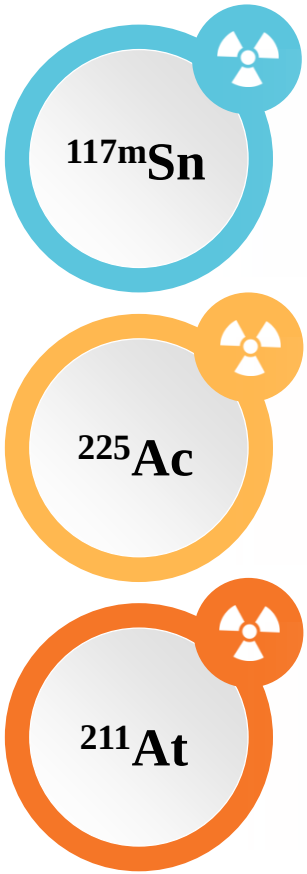
Deuteron Beam
(D^+)

Alpha Beam
(He^{2+})

^{117m}Sn*, ^{211}At*, ^{67}Cu*

KIRAMS Future Plan for TRT

TRT : Targeted-Radionuclide Therapy



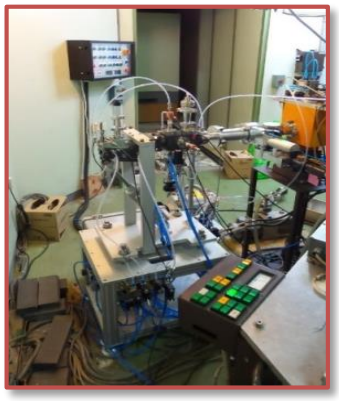
- **Therapy by conversion electron & SPECT**
- **Physical half-life :** 14 days, **Nuclear reaction :** ^{116}Cd(α,3n)^{117m}Sn
- **Target disease :** arthritis of cat, horse and dog

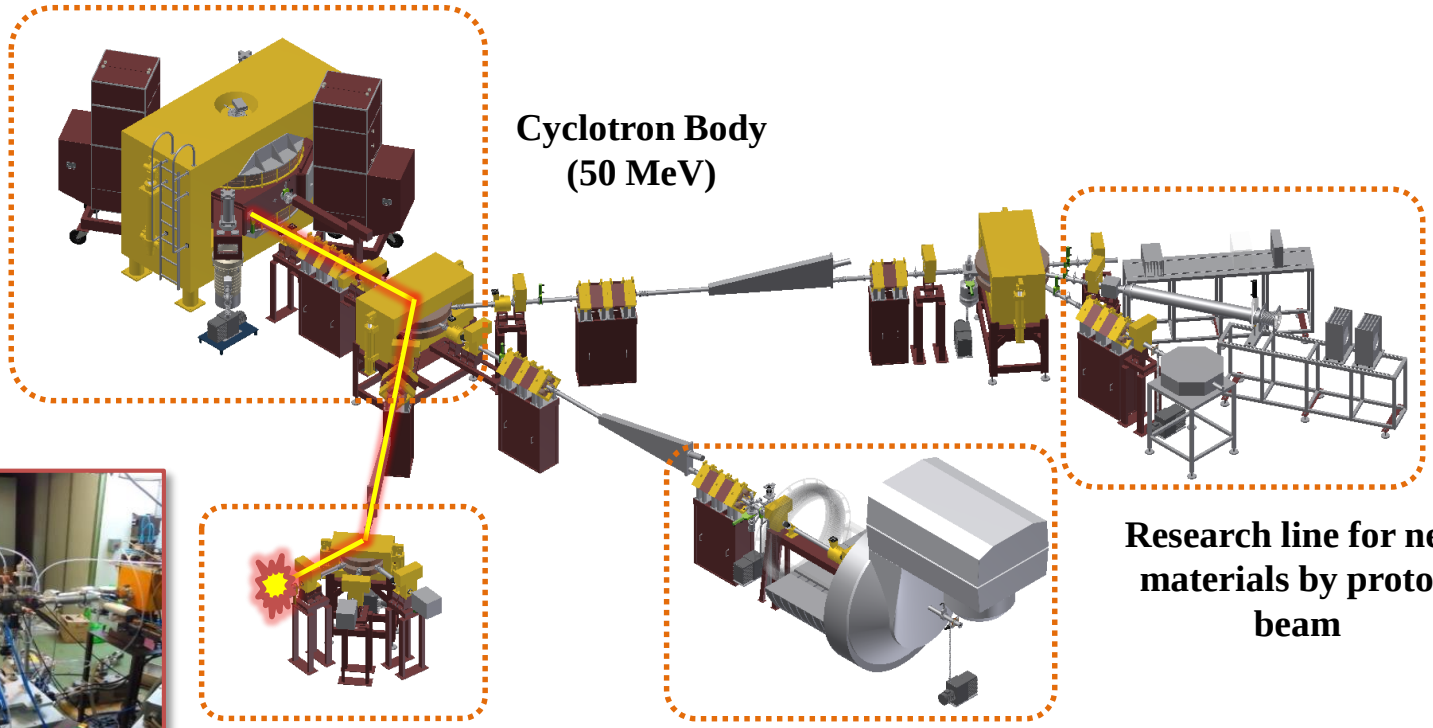
- **Therapy by alpha & beta ray**
- **Physical half-life :** 10 days, **Nuclear reaction :** ^{226}Ra(p,2n)^{225}Ac
- **Target disease :** prostate cancer therapy by ^{225}Ac-labeled PMSA ligands

- **Therapy by alpha ray & electron capture**
- **Physical half-life :** 7.2 hrs, **Nuclear reaction :** ^{209}Bi(α,2n)^{211}At
- **Target disease :** micro-metastatic neuroblastoma by ^{211}At-labeled MABG

Application to MC-50 for Therapeutic RI

Spec.	Company	Particle Beam	Therapeutic radioisotopes
50 MeV (max. 60 μA)	Scanditronix (1985)	Alpha Deuteron Proton	^{117m}Sn(beta), ^{211}At(alpha), ^{67}Cu(beta), …





J Radioanal Nucl Chem (2017) 314:1653–1658
https://doi.org/10.1007/s10967-017-5557-7

CrossMark

Development of new ^{116}Cd/Pt target for cyclotron produced ^{117m}Sn as a medical radiometal

Seyoung Oh[1,2] · Byungil Kim[1] · Jung Young Kim[3] · Mitra Ghergherehchi[4] · Ho Seung Song[5] · Seung-wook Shin[2] · Jong Seo Chai[4]

Received: 19 June 2017 / Published online: 8 November 2017

Abstract The radioisotope ^{117m}Sn has recently attracted considerable attention because of its application in theranostics and its imaging using 159-keV γ-photons. In this study, we developed a target system that yielded ^{117m}Sn via a ^{116}Cd(α, 3n)^{117m}Sn nuclear reaction. A separable Pt substrate was utilized to prepare the enriched ^{116}Cd target to be irradiated, and the enriched ^{116}Cd in a cadmium acetate solution was electroplated onto the Pt substrate. The substrate was thermally analyzed via ANSYS simulations, and the plating thickness was optimized through calculations with TALYS code. The production of ^{117m}Sn was confirmed through the emission measurement of inherent gamma rays.

Keywords ^{117m}Sn · Solid target · Medical radioisotopes · Conversion electrons · Cyclotron · Alpha irradiation

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Introduction

In nuclear medi
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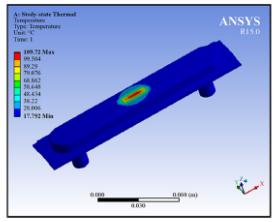

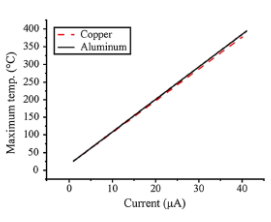

Fig. 4 **a** Thermal analysis results of the target using aluminum as the frame material under irradiation of alpha particles with energy of 45 MeV and current of 10 μA performed with the ANSYS simulation, and **b** comparison of the maximum temperature of copper and aluminum frames as a function of alpha-beam current

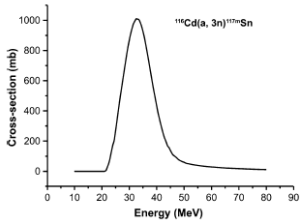

Fig. 5 Cross-section as a function of energy of ^{116}Cd(α,3n)^{117m}Sn

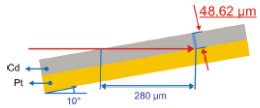

Fig. 6 Plating thickness of ^{116}Cd target at a 10° angle

Gamma-spectrum analysis with multichannel analyzer

To investigate the ^{117m}Sn production after irradiation of the enriched ^{116}Cd target with the alpha beam, we used an HPGe detector for the γ-spectrum analysis (Fig. 9). The production of ^{117m}Sn was confirmed with the observation of gamma rays with an energy of 158.6 keV and half-life of

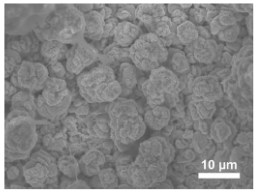

Fig. 7 SEM picture of plated ^{116}Cd on Pt

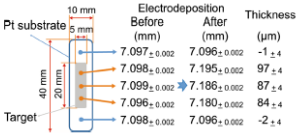

Fig. 8 Measured ^{116}Cd thickness as plated on the Pt substrate

13.8 days. In addition to the ^{117m}Sn peak, energy peaks corresponding to ^{115m}In, ^{115g}Cd (three peaks), and ^{117g}In with energies of 336.2, 492.3, 527.9, and 552.9 keV, respectively, were observed. The isotopes ^{115m}In and ^{117g}In exhibited short half-lives of 4.5 h and 43.2 min, respectively, as listed in Table 1 [15].

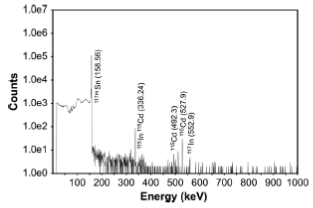

Fig. 9 Gamma spectrum obtained with HPGe detector after irradiation of the ^{116}Cd target with an alpha beam (energy of 45 MeV and current of 10 μA)

Table 1 Results of γ-spectrum analysis

	Nuclide	T1/2	E_γ (keV)	Reactions
1	^{117m}Sn	13.8 days	158.6	^{116}Cd(α, 3n)^{117m}Sn
2	^{115m}In	4.5 h	336.2	^{116}Cd(α, 4np)^{115m}In
3	^{115g}Cd	53.5 h	336.2	^{116}Cd(α, 3n2p)^{115g}Cd
4	^{115g}Cd	53.5 h	492.3	^{116}Cd(α, 3n2p)^{115g}Cd
5	^{115g}Cd	53.5 h	527.9	^{116}Cd(α, 3n2p)^{115g}Cd
6	^{117g}In	43.2 min	552.9	^{116}Cd(α, 2np)^{117g}In

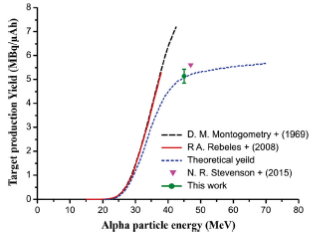

Fig. 10 Target yield for production of ^{117m}Sn via (a, 3n) reaction with ^{116}Cd

Production yield of ^{117m}Sn target

The ^{117m}Sn target production yield was calculated using Eq. (1) and presented in Fig. 10. The experimental cross-section values reported by Montgomery and Porile, and Rebeles et al. for the ^{116}Cd(α, 3n)^{117m}Sn reaction was used [15, 17]. The production yield from Montgomery and Porile reached 7.2 MBq/μAh at 42.5 MeV and the maximal energy available with the experimental data from Adam Rebeles et al. reached 5.3 MBq/μAh at 38 MeV. The value from the Clear Vascular company, over the energy range from 47 to 20 MeV is reported to be 5.6 MBq/μAh [6]. The theoretical yield is 5.1 MBq/μAh at 45 MeV and 5.67 MBq/μAh at 70 MeV. For the 45 MeV irradiation, our experimental target yield was 5.14 ± 0.29 MBq/μAh.

Conclusions

We demonstrated a new target system for generating ^{117m}Sn using an alpha particle beam, with a minimalized and recycled platinum substrate, compared with previously reported targets. In addition, we obtained a ^{117m}Sn production yield of 5.14 ± 0.29 MBq/μAh after irradiation of an alpha beam (10 μA, 45 MeV) for 30 min, and the production of ^{117m}Sn was confirmed by its intrinsic gamma energy and half-life.

Acknowledgements This work was funded by the Basic Science Research Program through the National Research Foundation of Korea and by the Ministry of Science, ICT & Future Planning Grant 1711045578.

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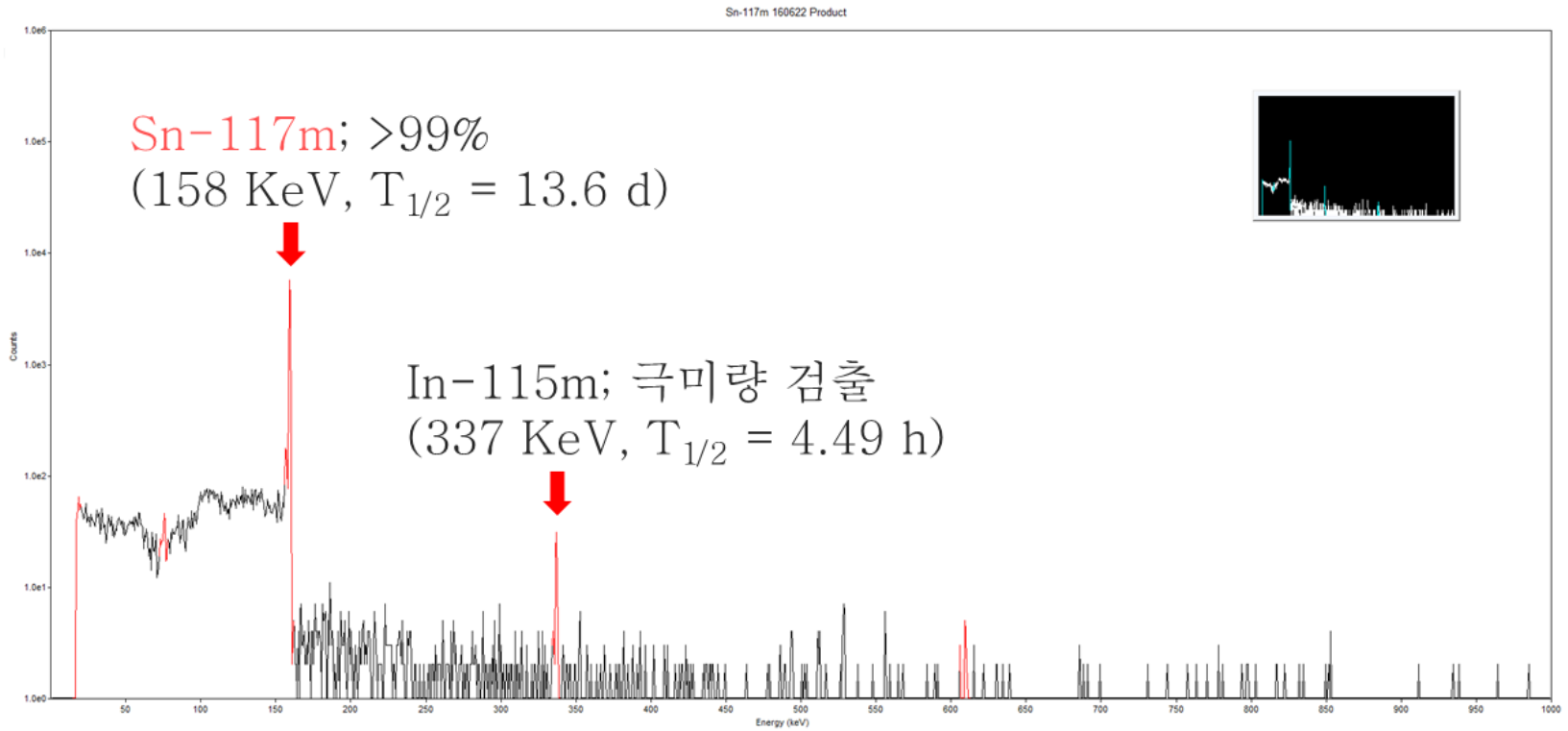
6. Krishnamurthy GT, Swailem FM, Srivastava SC, Atkins HL, Simpson LJ, Walsh TK, Ahmann FR, Meinken GE, Shah JH (1997) Tin-117 m(4+)DTPA pharmacokinetics and imaging

First Therapeutic RI in KIRAMS, ^{117m}Sn



- 알파빔 조사 조건: 10 μA, 30분
- 방사화학적 정제회수율: 약 10%
- 방사화학적 순도: >99% 이상, 극미량 In-115m 검출
- 방사화학적 생성수율: 평균 약 62 μCi/h (순도: >99%)
- Sn-117m 생산량 증가 계획: 정제회수율↑, 전류량↑, 조사시간↑

40 국가 의료 RI 치료기술혁신센터

한국원자력의학원 KOREA INSTITUTE OF RADIOLOGICAL & MEDICAL SCIENCES

국가 의료 RI 치료 인프라 연계 동위원소 생산기술 고도화

기술

핵종생산기술

- 표적기술
- 입자조사
- 분리정제
- 품질관리

대량,다핵종,고품질 RI

고부가가치 제품화

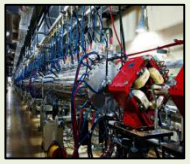
- RI 발생장치(기)/표지장치
- 밀봉선원
- 과학·분석기기

제품화 기술

시설


다목적 사이클로트론 (서울)


사이클로트론 (정읍)


양성자가속기 (경주)


하나로 (대전)

원료RI
원료의약품
선원 등
제품

동위원소 기초연구 진흥 및 기반기술 개발

활용진흥기술

- 공학활용
- 기초연구진흥
- 생명과학

응용 신기술

연구기반


RI이용 신약개발 플랫폼 (서울)


융합연구시설 (부산, 예정)

국가 의료 RI 기술 총합 추진

End User
병원
산업
연구
수출

41 국가 의료 RI 치료기술혁신센터

한국원자력의학원
KOREA INSTITUTE OF RADIOLOGICAL & MEDICAL SCIENCES

원천 **국가의료 치료용 방사성동위원소의 개발, 보급 및 통합 관리체계 실현**

- ✓ 첨단 의료 방사성동위원소 기술 개발에 따른 융합적 응용연구 활성화
- ✓ 치료용 동위원소에 대한 국가적 통합관리를 통한 효율성의 극대화
- ✓ 세계적으로 임상적 의의가 있는 치료용 동위원소 생산 및 보급을 통한 방사성의약품 시장 및 유관 기관의 활성화

임상 **미래의료의 핵심기술로서 방사선정밀의료기술 실현 & GMP/임상 전문 교육**

- ✓ 차세대 방사면역치료제 품목허가로 확대
- ✓ (전신 전이) 난치성 림프종, 신경내분비암, 전립선암 치료
- ✓ 국제적인 방사성의약품 GMP/임상 활용 전문(보수) 교육

국제 **국내 연구자네트워크 기반 국제 임상시험 추진**

- ✓ PET 진단 방사성의약품 신약 임상시험(7종, 2018년 현재)
- ✓ 종양치료 방사성의약품 신약 임상시험(2종, 2018년 현재)

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

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