Radiopharmaceuticals

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Question to ask

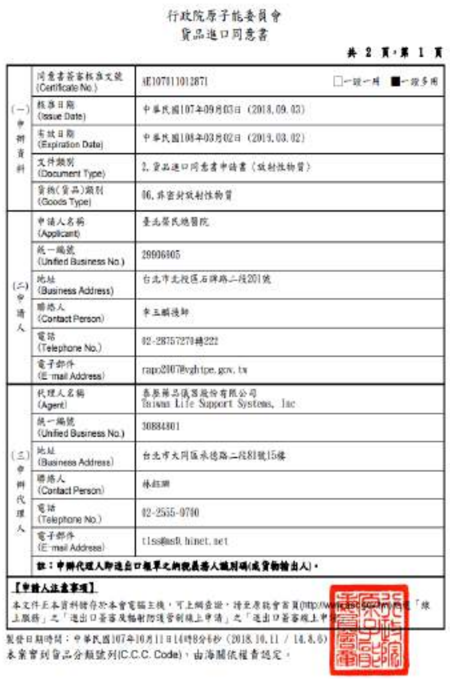
- What is Nuclear Pharmacy ?
- Radiopharmaceuticals VS. Traditional pharmaceuticals.
- Will the radiation from the nuclear medicine test be harmful?
- How does a SPECT / PET scan work?
- Why will I receive radioiodine treatment?

Agencies that regulate the use and distribution of radiopharmaceutical

- Taiwan Food and Drug Administration
  - Drug or medical device license
  - Application for import certification
  - PIC/S：Guide to Good Manufacturing Practice for Medicinal Products (Annexes 3)

- Atomic Energy Council
  - Ionizing Radiation Protection Act
  - E-Trade Facilitation for Radioactive Materials and Radiation Equipments

Agencies that regulate the use and distribution of radiopharmaceutical



行政院原子能委員會
貨品進口同意書

共 2 頁，第 1 頁

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放射性物質或可發生游離輻射設備操作人員輻射安全證書

輻安證字第　　號

姓名：

身分證編號：

出生日期：

頒證依據：依游離輻射防護法第卅一條之規定發給證書

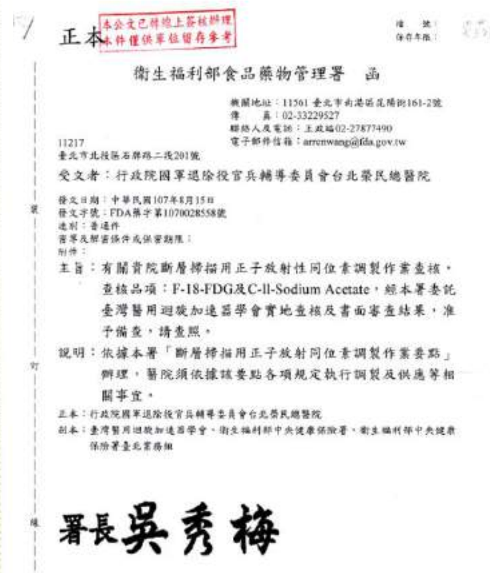
原發照日期：一〇二年十二月十二日

有效期限：一〇八年十二月十一日

附註：操作之物質、設備或作業涉及醫用者，應符合中央衛生法規之規定。

行政院原子能委員會 主任委員 蔡春鴻

中華民國 一〇二年十二月十三日



正本

衛生福利部食品藥物管理署 函

受文者：行政院國軍退除役官兵輔導委員會台北榮民總醫院

主旨：有關貴院斷層掃描用正子放射性同位素調製作業查核，查核品項：F-18-FDG及C-11-Sodium Acetate，經本署委託臺灣醫用迴旋加速器學會實地查核及書面審查結果，准予備查，請查照。

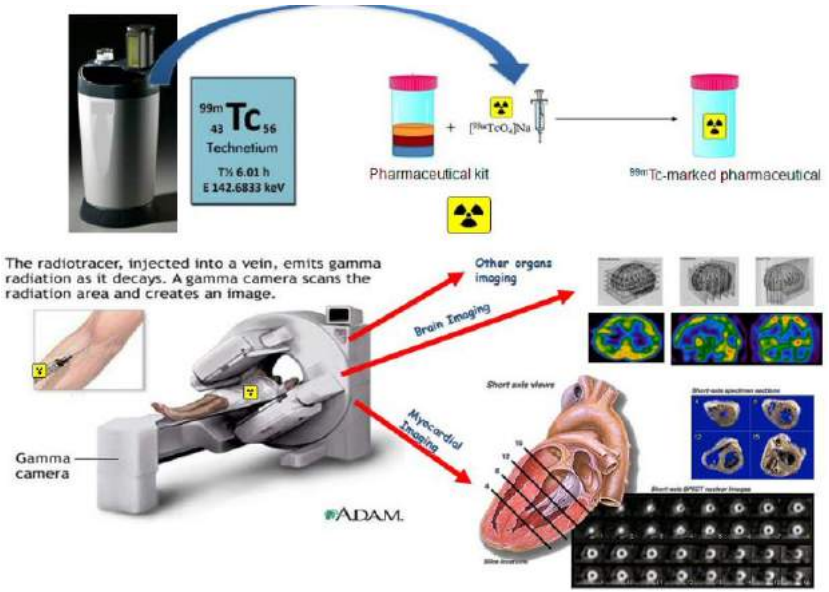
說明：依據本署「斷層掃描用正子放射性同位素調製作業要點」辦理，醫院須依據該要點各項規定執行調製及供應等相關事宜。

署長 吳秀梅

Predict → Diagnose → Inform → Treat

Radiopharmaceuticals

- A radiopharmaceutical is a radioactive drug used for diagnosis or therapy in a tracer quantity, masses so small that they do not produce pharmacologic effects , It is composed of two parts ; a radionuclide and a pharmaceutical.



Ex : Tc-99m 5270mCi/ μg → Tc-99m 1.8×10^{-4} μg/mCi

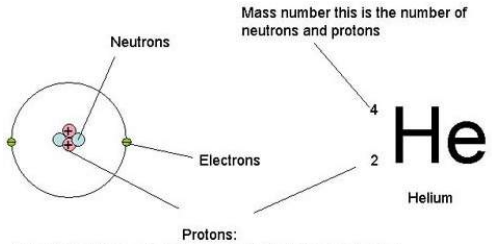
I-131 5mCi / 0.04μg → I-131 100mCi / 0.8μg

MDP kit 7.5mg

Phytate kit 2.9mg

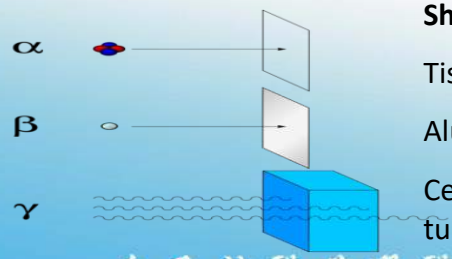
DMSA kit1.4mg

Frequency of Adverse Reactions and Death Related Drugs		
Drug Category	Adverse Reactions	Death
Radiopharmaceuticals	~ 3 /100,000	< 1/10,000,000
Iodine contrast media,ionic	3.8 ~ 12.7%	~ 1/ 75,000
Iodine contrast media,nonionic	0.6 ~ 3.1%	~ 1/ 75,000
Pharmacologic drugs	0.6 ~ 6%	~ 1/ 7,500



Types of Particles in Nuclear Reactions

Name	Symbol(s)	Representation	Description
Alpha particle	${}^4_2\mathrm{He}$ or ${}^4_2\alpha$		(High-energy) helium nuclei consisting of two protons and two neutrons
Beta particle	${}^0_1\mathrm{e}$ or ${}^0_{-1}\beta$		(High-energy) electrons
Positron	${}^0_{+1}\mathrm{e}$ or ${}^0_{+1}\beta$		Particles with the same mass as an electron but with 1 unit of positive charge
Proton	${}^1_1\mathrm{H}$ or ${}^1_1\mathrm{p}$		Nuclei of hydrogen atoms
Neutron	${}^1_0\mathrm{n}$		Particles with a mass approximately equal to that of a proton but with no charge
Gamma ray	γ	γ	Very high-energy electromagnetic radiation



Shielded by:

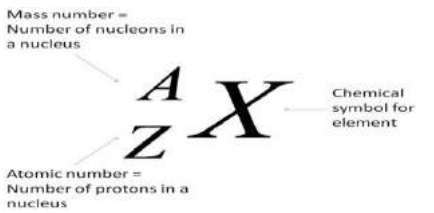
Tissue paper, skin

Aluminum foil, plastic

Centimeters - inches of lead, tungsten

https://opentextbc.ca/chemistry/chapter/21-2-nuclear-equations/

Notation of nuclear reactions – radioactive decays

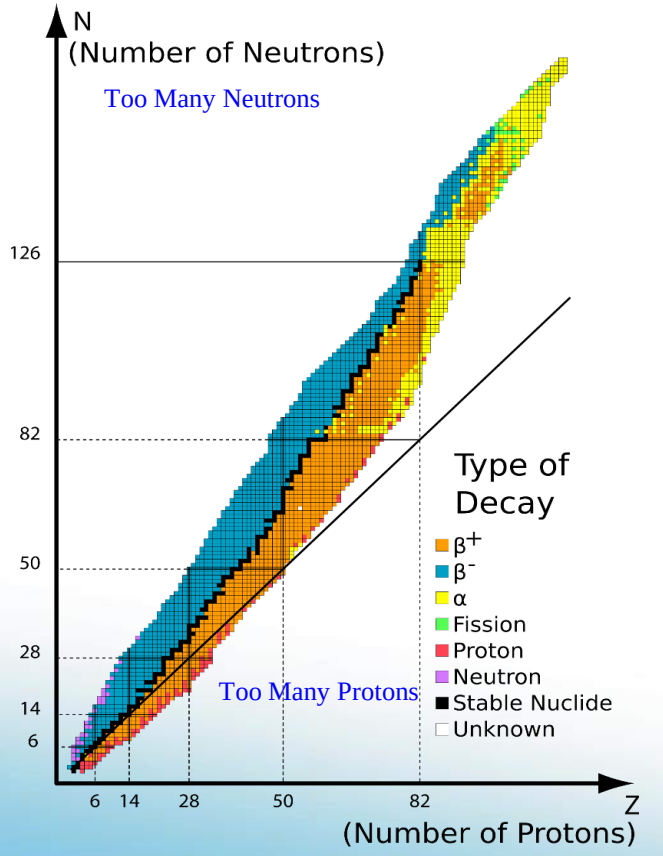


ISOTOPES

	^{9}C	^{10}C	^{11}C	^{12}C	^{13}C	^{14}C	^{15}C	^{16}C	^{17}C
Type of decay	EC	EC	$+\beta$ or EC	Stable	Stable	$-\beta$	$-\beta$	$-\beta$	$-\beta$
Half-life	0.127 s	19.3 s	20.3 min			5715 years	2.45 s	0.75 s	0.19 s

n/p ratio too low | n/p ratio too high

Decay Type	Radiation Emitted	Generic Equation	Model
Alpha decay	$^{4}_{2}\alpha$	$^{A}_{Z}X \longrightarrow {}^{A-4}_{Z-2}X' + {}^{4}_{2}\alpha$	Parent → Daughter + Alpha Particle
Beta decay	$^{0}_{-1}\beta$	$n \rightarrow p + \beta^-$; $^{A}_{Z}X \longrightarrow {}^{A}_{Z+1}X' + {}^{0}_{-1}\beta$	Parent → Daughter + Beta Particle
Positron emission	$^{0}_{+1}\beta$	$p \rightarrow n + \beta^+$; $^{A}_{Z}X \longrightarrow {}^{A}_{Z-1}X' + {}^{0}_{+1}\beta$	Parent → Daughter + Positron
Electron capture	X rays	$p + e^- \rightarrow n$; $^{A}_{Z}X + {}^{0}_{-1}e \longrightarrow {}^{A}_{Z-1}X' + X\text{ ray}$	Parent + Electron → Daughter + X ray
Gamma emission	$^{0}_{0}\gamma$	$^{A}_{Z}X^* \xrightarrow{\text{Relaxation}} {}^{A}_{Z}X' + {}^{0}_{0}\gamma$	Parent (excited nuclear state) → Daughter + Gamma ray
Spontaneous fission	Neutrons	$^{A+B+C}_{Z+Y}X \longrightarrow {}^{A}_{Z}X' + {}^{B}_{Y}X' + C\,{}^{1}_{0}n$	Parent (unstable) → Daughters + Neutrons + ENERGY



Graph of isotopes by type of nuclear decay

https://chem.libretexts.org/Textbook_Maps/General_Chemistry/Map%3A_Chemistry_(Averill_and_Eldredge)/20%3A_Nuclear_Chemistry/20.2%3A_Nuclear_Reactions

Units of Radiation Exposure and Dose

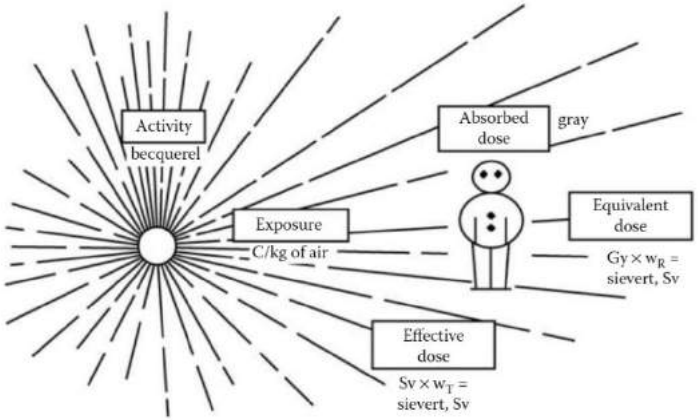


FIGURE 2.1 The five concepts that relate a radiation worker to a radioactive source: Activity, measured in becquerels; Exposure, measured in C/kg of air; Absorbed dose, measured in grays; Equivalent dose, measured in sieverts; and Effective dose, also measured in sieverts.

TABLE 2.3
Summary of Basic Concepts and Units

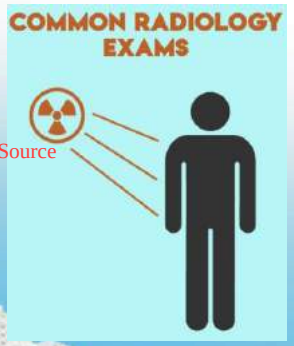
Concept	Unit and Definition
Activity (A)	becquerel (Bq) = 1 nt/s
	curie (Ci) = 3.7×10^{10} nt/s
Exposure (X)	1 C/kg of air at STP
	roentgen (R) = 2.58×10^{-4} C/kg of air at STP
Absorbed dose (D)	gray (Gy) = 1 J/kg in any material
	rad = 0.01 J/kg of any material = 100 ergs/g
Equivalent dose ($H_{T,R}$)	sievert (Sv) = Gy × w_R
	rem = rad × Q
Effective dose (E)	sievert (Sv) = Sv × w_T
	rem = rad × w_T

Radiation Weighting Factors

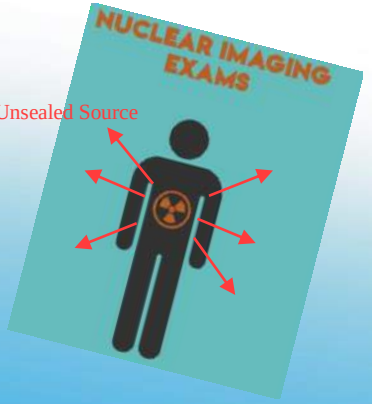
Radiation	w_R	Q
Beta, gamma, x-rays	1	1
Neutrons, <10 keV	5	2
>10-100 keV	10	2.5
>100 keV-2 MeV	20	
>2 MeV-20 MeV	10	
>20 MeV	5	
Protons, >2 MeV	2	10
Alpha, heavy ions	20	20

Tissue Weighting Factors

Tissue	w_T
Gonads	0.20
Bone marrow	0.12
Colon	0.12
Lung	0.12
Stomach	0.12
Bladder	0.05
Breast	0.05
Liver	0.05
Esophagus	0.05
Thyroid	0.05
Skin	0.01
Bone surface	0.01
Remainder	0.05
Total Body	**1.00**



Sealed Source



Unsealed Source

1nt/s =Nuclear transformation per second
rad = radiation absorbed dose
W_R = Radiation Weighting Factors
W_T = Tissue Weighting Factors

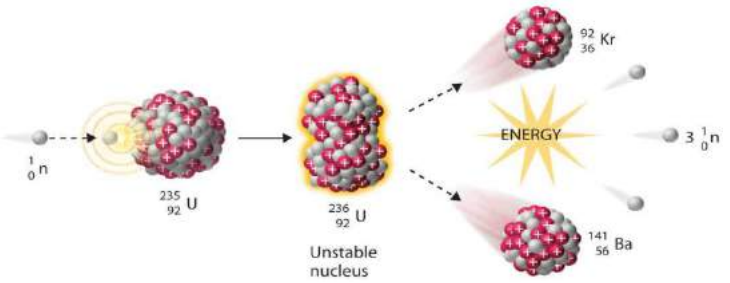
Production of radionuclides

- Reactor - produced radionuclides

  Fission or (n,f) Reaction

  $^{235}_{92}U + ^{1}_{0}n \rightarrow ^{236}_{92}U \rightarrow ^{92}_{36}Kr + ^{141}_{56}Ba + 3^{1}_{0}n$

  $\rightarrow ^{131}_{53}I + ^{102}_{39}Y + 3^{1}n$

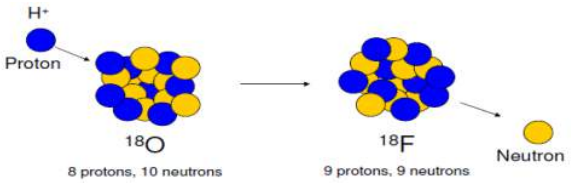


  Neutron Capture or (n, γ) Reaction

  $^{98}Mo(n, \gamma)^{99}MO$ 、$^{196}Hg\ (n, \gamma)^{197}Hg$

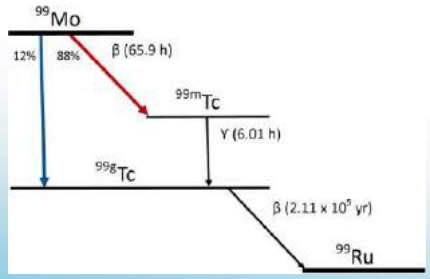
- Cyclotron - produced radionuclides

  $^{18}O(p, n)^{18}F$、$^{14}C(p, \alpha)^{11}C$ 、$^{66}Zn(d, n)^{67}Ga$



- Generator - produced radionuclides

  $^{99}Mo/^{99m}Tc$、 $^{68}Ge/^{68}Ga$ 、$^{113}Sn/^{113m}In$



Target Nucleus [Bombarding Particle , Product Emission] Product Nucleus

Characteristics of commonly used radionuclides

Nuclide	Physical half life	Mode of decay (%)	γ ray energy[a] (MeV)	Abundance (%)	Common production method
$^{3}_{1}H$	12.3 years	β (100)			$^{6}Li(n, \alpha)^{3}H$
$^{11}_{6}C$	20.4 min	β^{+}(100)	0.511 (annihilation)	200	$^{10}B(d, n)^{11}C$ $^{14}N(p, \alpha)^{11}C$
$^{13}_{7}N$	10 min	β^{+}(100)	0.511 (annihilation)	200	$^{12}C(d, n)^{13}N$ $^{16}O(p, \alpha)^{13}N$ $^{13}C(p, n)^{13}N$
$^{14}_{6}C$	5,730 years	β (100)			$^{14}N(n, p)^{14}C$
$^{15}_{8}O$	2 min	β^{+}(100)	0.511 (annihilation)	200	$^{14}N(d, n)^{15}O$ $^{15}N(p, n)^{15}O$
$^{18}_{9}F$	110 min	β^{+}(97) EC(3)	0.511 (annihilation)	194	$^{18}O(p, n)^{18}F$
$^{32}_{15}P$	14.3 days	β (100)			$^{32}S(n, p)^{32}P$
$^{51}_{24}Cr$	27.7 days	EC(100)	0.320	9	$^{50}Cr(n, \gamma)^{51}Cr$
$^{52}_{26}Fe$	8.3 h	β^{+}(56) EC(44)	0.165 0.511 (annihilation)	100 112	$^{55}Mn(n, 4n)^{52}Fe$ $^{50}Cr(\alpha, 2n)^{52}Fe$
$^{57}_{27}Co$	271 days	EC(100)	0.014 0.122 0.136	9 86 11	$^{56}Fe(d, n)^{57}Co$
$^{58}_{27}Co$	71 days	β^{+}(14.9) EC(85.1)	0.811	99.5	$^{55}Mn(\alpha, n)^{58}Co$
$^{59}_{26}Fe$	45 days	β (100)	1.099 1.292	56 43	$^{58}Fe(n, \gamma)^{59}Fe$
$^{60}_{27}Co$	5.2 years	β (100)	1.173 1.332	100 100	$^{59}Co(n, \gamma)^{60}Co$
$^{62}_{28}Zn$	9.3 h	β^{+}(8) EC(92)	0.420 0.511 0.548 0.597	25 31 15 26	$^{63}Cu(p, 2n)^{62}Zn$
$^{62}_{29}Cu$	9.7 min	β^{+}(97) EC(3)	0.511 (annihilation)	194	$^{62}Ni(p, n)^{62}Cu$ $^{62}Zn \xrightarrow[9.3h]{\beta^{+}, EC} {}^{62}Cu$
$^{67}_{29}Cu$	2.6 days	β (100)	0.185	49	$^{67}Zn(n, p)^{67}Cu$
$^{201}_{81}Tl$	73 h	EC(100)	0.167 x ray (0.069 0.083)	9.4 93	$^{203}Tl(p, 3n)^{201}Pb$ $^{201}Pb \xrightarrow[9.3\ hr]{EC} {}^{201}Tl$

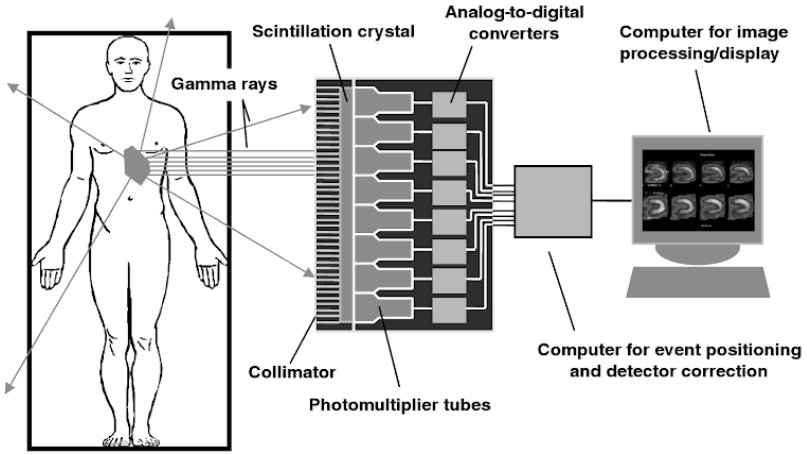
Nuclide	Physical half life	Mode of decay (%)	γ ray energy[a] (MeV)	Abundance (%)	Common production method
$^{67}_{31}Ga$	78.2 h	EC(100)	0.093 0.184 0.300 0.393	40 20 17 5	$^{68}Zn(p, 2n)^{67}Ga$
$^{68}_{31}Ga$	68 min	β^{+}(89) EC(11)	0.511 (annihilation)	178	$^{68}Zn(p, n)^{68}Ga$
$^{68}_{32}Ge$	270.8 days	EC(100)			$^{66}Zn(\alpha, 2n)^{68}Ge$
$^{82}_{37}Rb$	75 s	β^{+}(95) EC(5)	0.511 (annihilation) 776	190 13	$^{82}Sr \xrightarrow[25.5\ days]{EC} {}^{82}Rb$
$^{82}_{38}Sr$	25.5 days	EC(100)			$^{85}Rb(p, 4n)^{82}Sr$ $Mo(p, spallation)^{82}Sr$
$^{89}_{38}Sr$	50.6 days	β (100)			$^{88}Sr(n, \gamma)^{89}Sr$
$^{90}_{38}Sr$	28.6 years	β (100)			$^{235}U(n, f)^{90}Sr$
$^{90}_{39}Y$	2.7 days	β (100)			$^{89}Y(n, \gamma)^{90}Y$ $^{90}Sr \xrightarrow[\beta]{28.6y} {}^{90}Y$
$^{99}_{42}Mo$	66 h	β (100)	0.181 0.740 0.780	6 12 4	$^{98}Mo(n, \gamma)^{99}Mo$ $^{235}U(n, f)^{99}Mo$
$^{99m}_{43}Tc$	6.0 h	IT(100)	0.140	90	$^{99}Mo \xrightarrow[66\ hr]{\beta} {}^{99m}Tc$
$^{111}_{49}In$	2.8 days	EC(100)	0.171 0.245	90 94	$^{111}Cd(p, n)^{111}In$
$^{113m}_{49}In$	100 min	IT(100)	0.392	64	$^{112}Sn(n, \gamma)^{113}Sn$ $^{113}Sn \xrightarrow[117\ days]{EC} {}^{113m}In$
$^{123}_{53}I$	13.2 h	EC(100)	0.159	83	$^{121}Sb(\alpha, 2n)^{123}I$
$^{124}_{53}I$	4.2 days	β^{+}(23) EC(77)	0.511 (annihilation)	46	$^{124}Te(p, n)^{124}I$
$^{125}_{53}I$	60 days	EC(100)	0.035 x ray (0.027 0.032)	7 140	$^{124}Xe(n, \gamma)^{125}Xe$ $^{125}Xe \xrightarrow[17\ hours]{EC} {}^{125}I$
$^{131}_{53}I$	8.0 days	β (100)	0.284 0.364 0.637	6 81 7	$^{130}Te(n, \gamma)^{131}Te$ $^{235}U(n, f)^{131}Te$ $^{131}Te \xrightarrow[25\ min]{\beta} {}^{131}I$ $^{235}U(n, f)^{131}I$
$^{133}_{54}Xe$	5.3 days	β (100)	0.081	37	$^{235}U(n, f)^{133}Xe$
$^{137}_{55}Cs$	30.0 years	β (100)	0.662	85	$^{235}U(n, f)^{137}Cs$
$^{153}_{62}Sm$	1.9 days	β (100)	70 103	5 28	$^{152}Sm(n, \gamma)^{153}Sm$
$^{186}_{75}Re$	3.8 days	β (92) EC(8)	137	9	$^{185}Re(n, \gamma)^{186}Re$

Classification

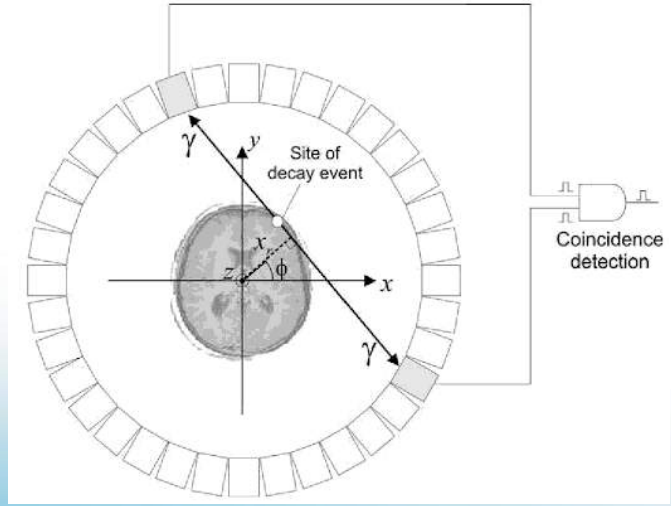
- Radiopharmaceuticals
  - Diagnosis
    - SPECT
      - ^{99m}Tc kits
      - ^{67}Ga-citrate
      - ^{201}Tl-chloride
      - ^{133}Xe gas
      - ^{111}In-Pentetreotide
      - ^{131}I-NP59
      - ^{131}I-NaI
    - PET
      - ^{18}F-FDG
      - ^{13}N-Ammonia
      - ^{11}C-Sodium Acetate
      - ^{18}F-NaF
      - ^{18}F-Florbetaben
      - ⋮
  - Therapy
    - ^{131}I-NaI
    - ^{90}Y-Resin Microspheres (SIR-Spheres®)
    - ^{90}Y-Glass Microspheres (Thera-Spheres®)
    - ^{90}Y-Zevalin
    - ^{223}Ra-Dichloride (Xofigo®)
    - ^{153}Sm-EDTMP
    - ^{186}RE-HEDP
    - ^{89}Sr-Chloride (Metastron®)

SPECT vs PET

- In **SPECT** (Single Photon Emission Tomography), the emitted radiation already is a Gamma ray, which is then directly used to create the camera mages. **SPECT** cameras use collimators to help localizing with precision the direction of the incoming ray.

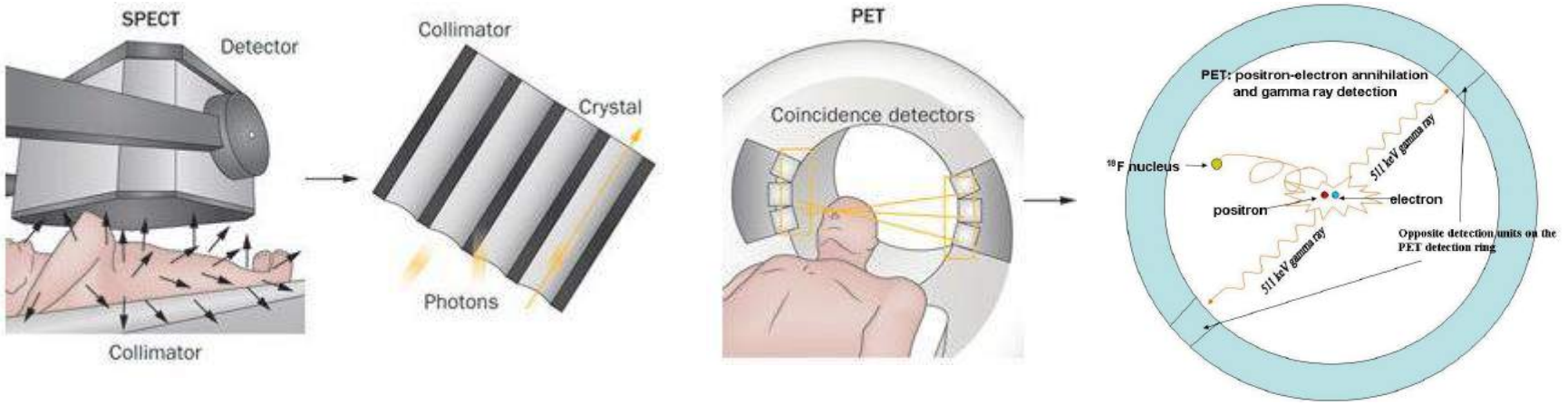


- In **PET** (Positron Emission Tomography), the emitted radiation is a positron which, when interacting with the tissues around the radiopharmaceutical, creates 2 rays, one opposite the other. The rays hit a camera and the two signals taken in coincidence allow a precise localization of the emission point .

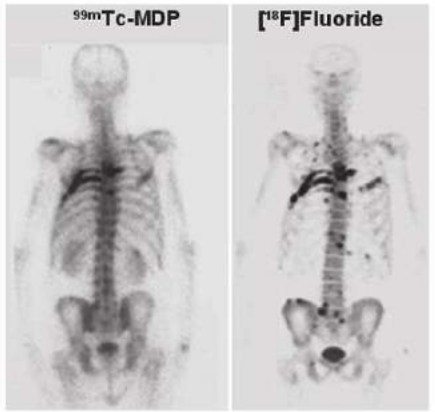


Emission Tomography: The Fundamentals of PET and SPECT.p16-17

SPECT Scanner vs. PET, Which is Best?



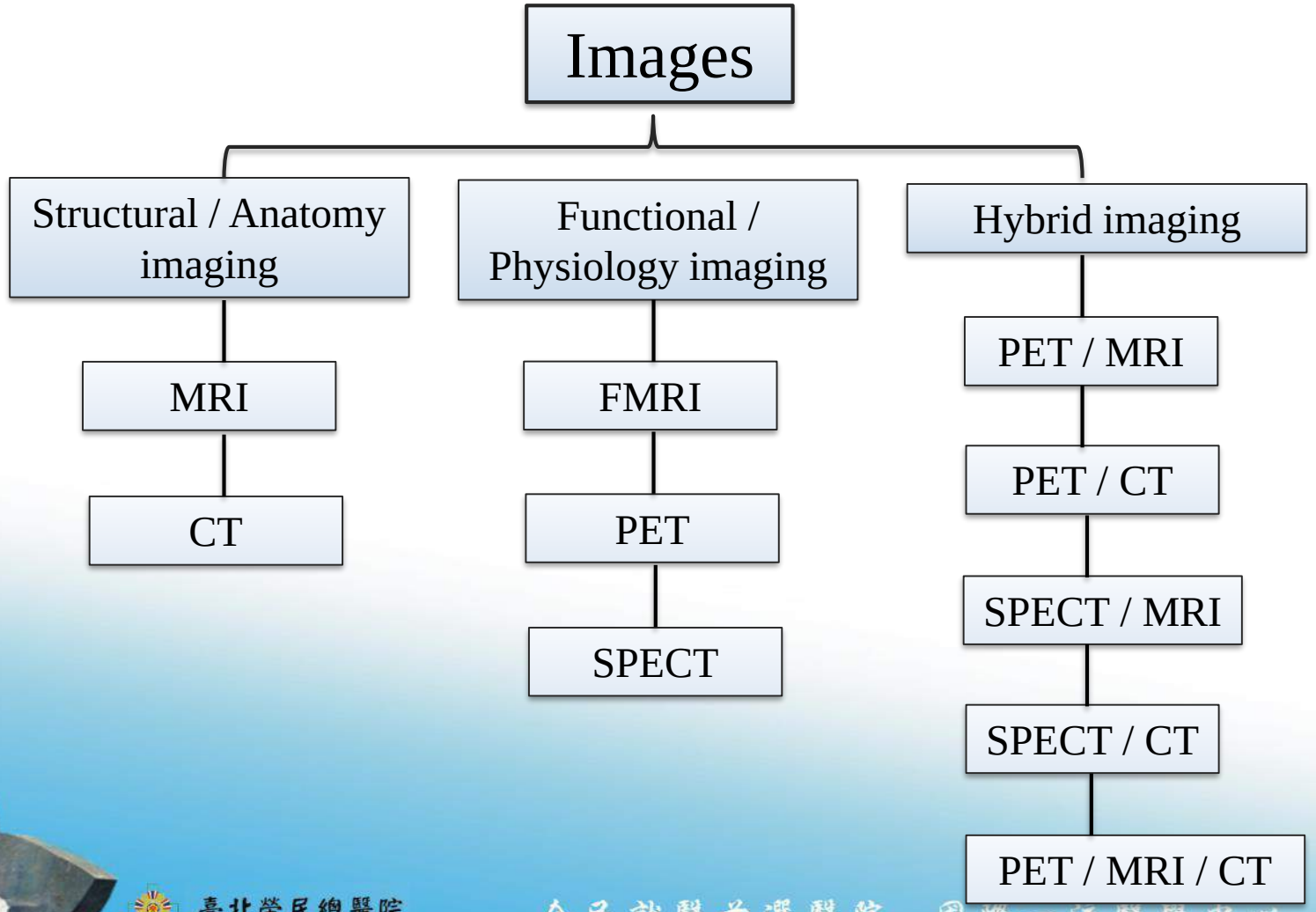
SPECT	PET
Emits gamma radiations	Emits positrons
More than one detector around the patient	Ring of detectors
Poor resolution	Good resolution
Low sensitivities	High sensitivity
Less capital intensive scanner	Costlier scanner
Longer lived radioisotopes	Shorter lived radioisotopes



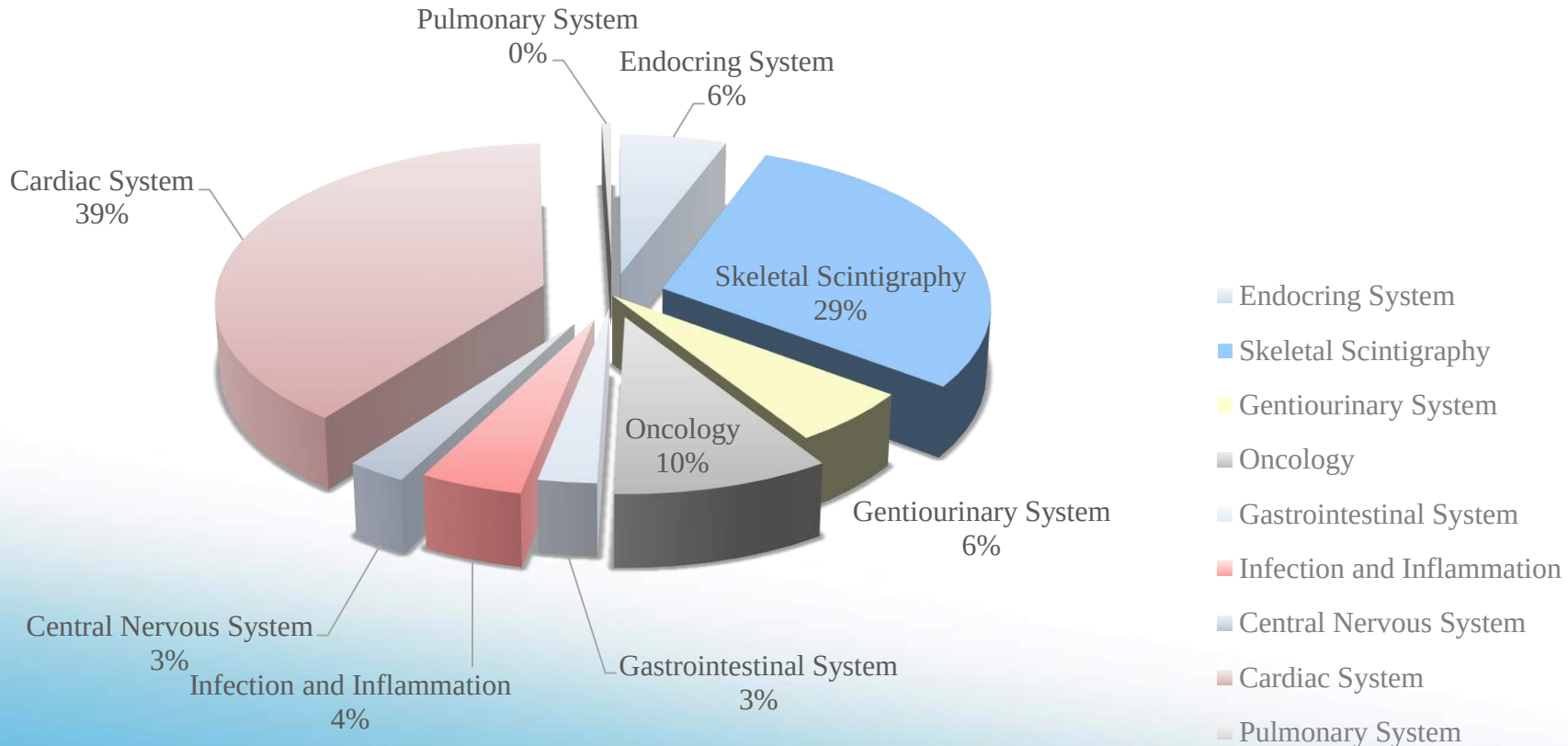
Comparison of [^{18}F]fluoride-PET (**b**) and ^{99m}Tc-MDP planar scintigraphy (**a**) results in a patient with bone metastases. Fluoride-PET shows more bone lesions with significantly greater spatial resolution compared to planar bone scan (Schwaiger 2003)

Molecular Imaging: Radiopharmaceuticals for PET and SPECT ,p6

Comparison of CT、MRI、SPECT and PET

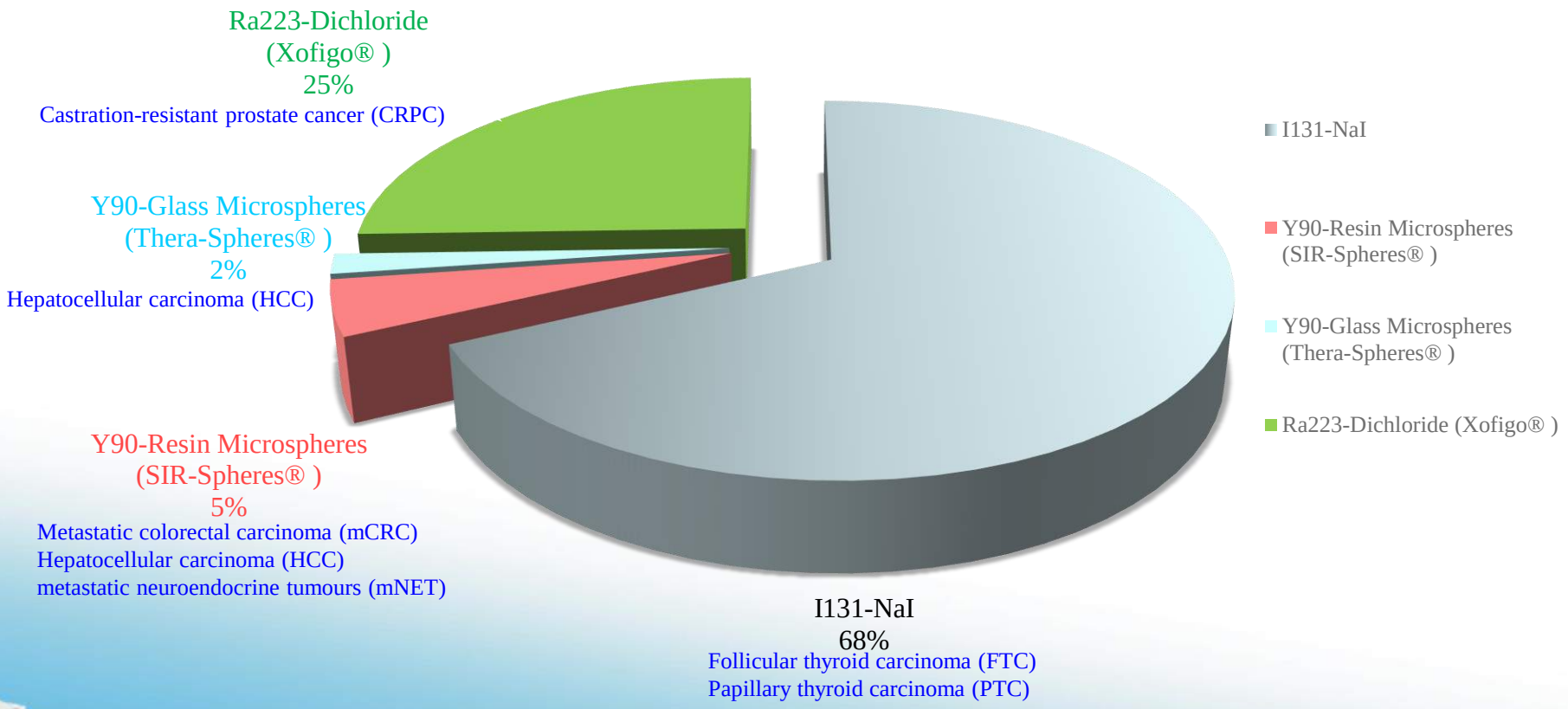


Current Status of Nuclear Medicine in VGHTPE 2018 ~ 2019



Percentage distribution of Diagnosis

Current Status of Nuclear Medicine in VGHTPE 2018 ~ 2019



Percentage distribution of Radionuclide Therapy

Radiopharmaceuticals used in nuclear medicine

Radionuclide	Symbol	Physical half-life	Chemical form	Diagnostic use
Chromium	^{51}Cr	27.8 days	Sodium chromate	Red blood cell volume and survival
			Albumin	Gastrointestinal protein loss
Cobalt	^{57}Co	270 days	Cyanocobalamin (vitamin B_{12})	Vitamin B_{12} absorption
Fluorine	^{18}F	110 min	Fluorodeoxyglucose	Oncology and myocardial hibernation
Gallium	^{67}Ga	77 hr	Gallium citrate	Inflammatory process and tumor imaging
Indium	^{111}In	67.4 hr	DTPA	Cerebrospinal fluid imaging
			Ibritumomab tiuxetan	Localization of tumor
			OctreoScan (pentetreotide)	Neuroendocrine tumors
			ProstaScint (capromab-pendetide)	Prostate cancer
			Oxine	White blood cell/abscess imaging
Iodine	^{123}I	13.3 hr	Sodium iodide	Thyroid function and imaging
			Human serum albumin	Plasma volume
	^{131}I	8 days	Sodium iodide	Thyroid function, imaging, and therapy
			Hippurate (馬尿酸)	Renal function
Nitrogen	^{13}N	10 min	Ammonia	Myocardial perfusion
Rubidium	^{82}Rb	75 sec	Rubidium chloride	Cardiovascular imaging
Technetium	^{99m}Tc	6 hr	Sodium pertechnetate	Imaging of brain, thyroid, scrotum, salivary glands, renal perfusion, and pericardial effusion; evaluation of left-to-right cardiac shunts
			Sulfur colloid	Imaging of liver and spleen and renal transplants, lymphoscintigraphy
			Macroaggregated albumin	Lung imaging
			Sestamibi	Cardiovascular imaging, myocardial perfusion
			DTPA	Brain and renal imaging
			DMSA	Renal imaging
			MAG3	Renal imaging
			Diphosphonate	Bone imaging
			Pyrophosphate	Bone and myocardial imaging
			Red blood cells	Cardiac function imaging
			HMPAO	Functional brain imaging and white blood cell/abscess imaging
			Iminodiacetic derivations	Liver function imaging
			Neurolite (Bicisate)	Brain imaging
			Myoview (Tetrofosmin)	Myocardial perfusion
			CEA-scan (Arcitumomab)	Gastrointestinal tract
			Cardiolite (Sestamibi)	Myocardial perfusion
			Apcitide (AcuTect)	Acute venous thrombosis
Thallium	^{201}Tl	73.5 hr	Thallous chloride	Myocardial imaging
Xenon	^{133}Xe	5.3 days	Xenon gas	Lung ventilation imaging

https://radiologykey.com/nuclear-medicine-3/

Radiopharmaceuticals used in nuclear medicine

Table 1. Available radionuclide therapy in oncology

Radionuclide	Physical half-life (days)	Emission	Maximum range (mm)	Radiopharmaceutical	Targeting mechanism	Indications
I-131	8.04	Beta, gamma	4	I-131 as iodide	Thyroid hormone synthesis	Differentiated thyroid cancer
Lu-177	6.7	Beta, gamma	1	Lu-177 DOTATATE	Somatostatin-receptor binding	Neuro-endocrine tumours
Y-90	2.7	Beta	12	Y-90 DOTATATE	Somatostatin-receptor binding	Neuro-endocrine tumours
Y-90	2.7	Beta	12	Y-90 microspheres, SIR-Spheres or TheraSpheres	Intravascular trapping	Liver metastases Hepatocellular carcinoma
Y-90	2.7	Beta	12	Y-90 ibritumomab tiuxetan (Zevalin)	CD20 antigen binding	Non-Hodgkin's lymphoma
I-131	8.04	Beta, gamma	4	I-131 tositumomab (Bexxar)	CD20 antigen binding	Non-Hodgkin's lymphoma
I-131	8.04	Beta, gamma	4	I-131 MIBG	Active transport and intracellular storage	
Sm-153	1.95	Beta, gamma	3.1	Sm-153 EDTMP	Chemo-adsorption	Bone pain palliation
Sr-89	50.5	Beta	8	Sr-89 chloride	Calcium analogue	Bone pain palliation

MIBG = meta-iodobenzylguanidine; EDTMP = ethylene-diamine-tetramethylene-phosphonic acid.

Ideal Properties of SPECT Radionuclides for Diagnostic Imaging

- Decay mode:

  Electron capture or isomeric transition from metastable states ; no particulate radiation; gamma or x-ray only.

- Photon energy :

  100 ~ 200 keV is ideal

  Below 100 keV = tissue absorption and scatter (decreases resolution)

  Above 200 keV there is low detection efficiency. (decreases sensitivity)

- Half-life :

  Effective half-life equal to 1 to 1.5 times the imaging time.

- Chemical properties:

  Can be compounded into different chemical forms.

^{99m}Tc-labeled radiopharmaceuticals

- Pulmolite ® MAA kit
- Techne ® MDP kit
- Techne ® Pyrophosphate kit
- Techne ® DTPA kit
- Techne ® DMSA kit
- Techne ® Phytate kit
- GMS Trodat-1 kit
- Ceretec ® HMPAO kit
- Neurolite ® ECD kit
- Cardiolite ® MIBI kit
- INER MAG_3 Kit

Preparation of a Technetium-99m labeled radiopharmaceutical

Tc-99m as sodium Pertechnetate is added to the reaction vial

↓

Reduced ^{99m}Tc + chelating agent ⇌ ^{99m}Tc-chelate

Tc-99m radiopharmaceutical is ready for dispensing

↓

The patient dose is withdrawn from the vial

↓

Each dose is measured in the dose calibrator before it dispensed

Radiopharmaceutical kit

- Ligand :

  The properties of the ligand are primarily responsible for dictating how the product will behave in the body.

- Reducing agent :

  Stannous ion ..

Reduction of $^{99m}Tc^{7+}$ to an oxidation state that binds to chelating molecule of interest.

Oxidation State of Technetium in Various Compounds	
Oxidation State	Chemical Form
Tc(VII)	Pertechnetate , Sulfur Colloid
Tc(V)	DMSA(high pH) , ECD , HMPAO ,MAG_3
Tc(IV)	DTPA , MDP , PYP
Tc(III)	DMSA(low pH) , HIDA analogues
Tc(I)	Sestamibi

- Other agent :

  Stabilizers , transfer ligands ,

  buffer , solubilizing agent ..

Exchange reaction	
Radiopharmaceutical	Transfer ligand
^{111}In-Ibritumomab tiuxetan	Acetate
^{90}Y-Ibritumomab tiuxetan	
^{99m}Tc-Sestamibi	Citrate
^{111}In-Pentetreotide	
^{99m}Tc-ECD	EDTA
^{99m}Tc-MAG_3	Tartrate
^{99m}Tc-Trodat-1	Glucoheptonate

- Expiration time = Physical half-life (most)

Labeling with ^{99m}Tc

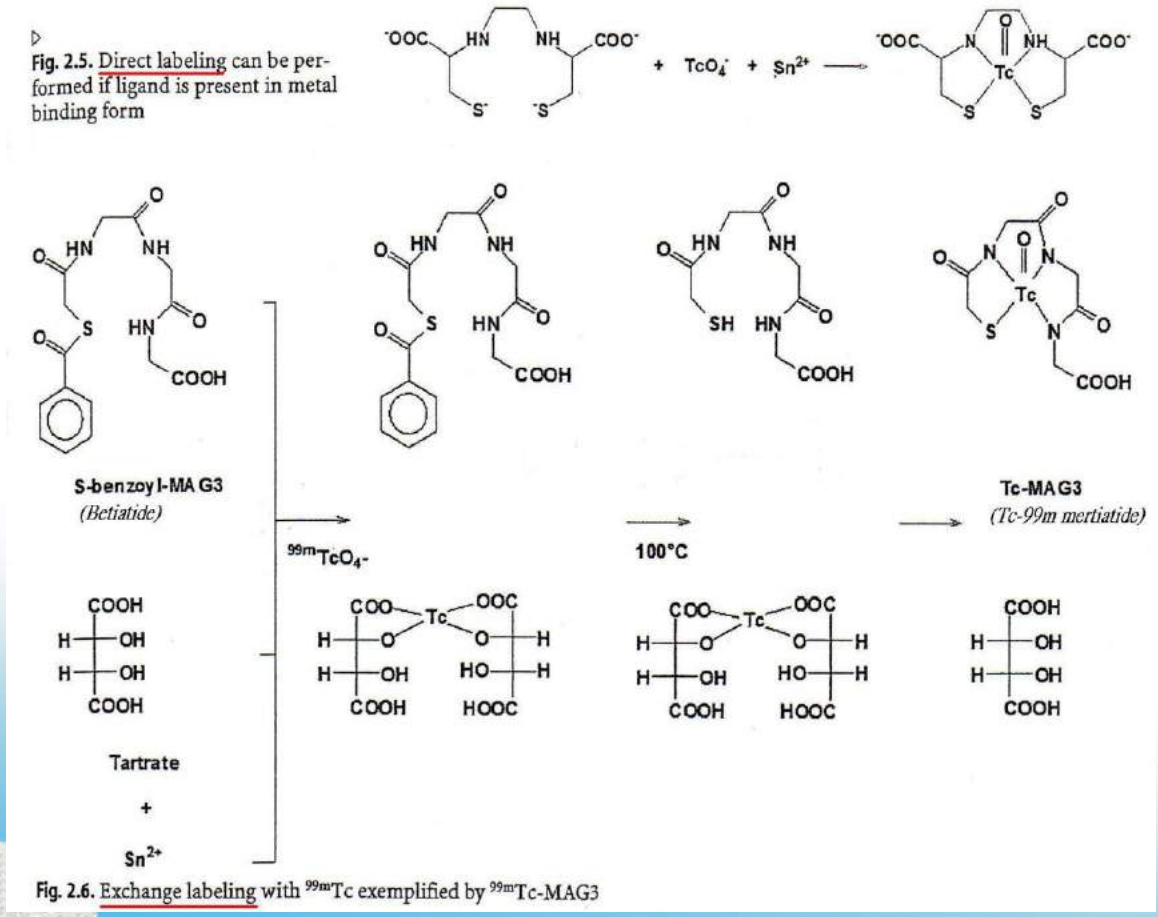


Fig. 2.5. Direct labeling can be performed if ligand is present in metal binding form

Fig. 2.6. Exchange labeling with ^{99m}Tc exemplified by ^{99m}Tc-MAG3

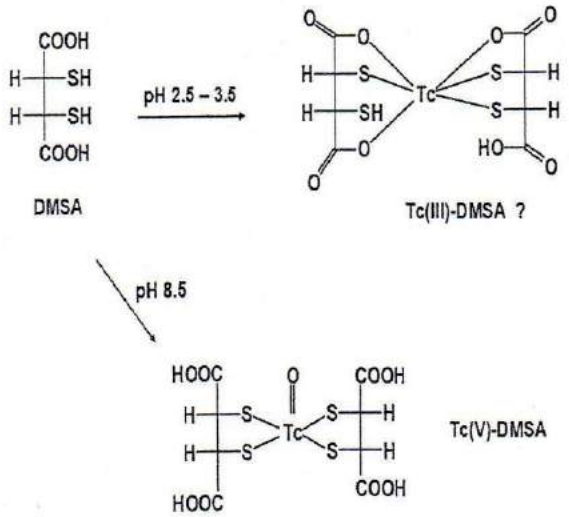


Fig. 2.4. pH determines valence of reduced Tc and nature of formed complex in the case of [^{99m}Tc]DMSA (the structure of Tc(III)-DMSA is a proposed structure)

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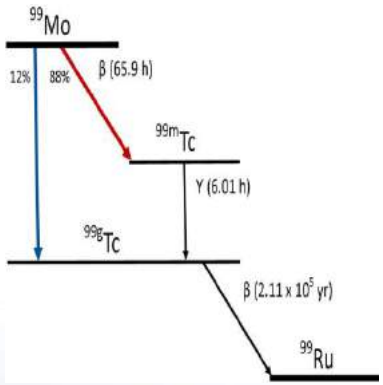
Labeling with ^{99m}Tc

- Common problems associated with preparative manipulations :

1. Improper mixing order
2. Improper heating
3. Incubation /time delays
4. Component concentration
5. Radiolytic effects
6. Excessive ^{99m}Tc
7. Excessive ^{99}Tc
8. Radiolytic oxidants
9. Inadequate stannous ion



Particle Size Distribution of ^{99m}Tc-Sulfur Colloid	
Particle Size (nm)	% of Total
Standard Preparation method (5 minute heating)	
< 100	15 ~ 20
100 ~ 600	70 ~ 80
700 ~ 5000	2 ~ 4
> 5000	0.5 ~ 1.5
Modified Preparation method (3 minute heating)	
< 30	47
30 ~ 50	0
50 ~ 80	1
80 ~ 200	5
200 ~ 400	21
400 ~ 800	16
800 ~ 2000	5
2000 ~ 5000	1
5000 ~ 10000	0
> 10000	5

Positron Emission Tomography

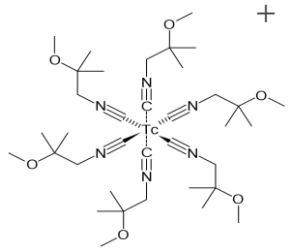
Agent	Mechanism	use
[^{18}F] FDG	Accumulates as sugar phosphate	Glucose utilization rate
[^{13}N] Ammonia	Accumulates as tissue amino acids	Myocardial perfusion
[^{11}C] Acetate	Incorporation in intermediary metabolites	Krebs cycle activity
[^{11}C] Raclopride	Dopamine D_2 receptor ligand	Receptor availability
[^{18}FNaF	Incorporation into bone	Bone scanning
[^{11}C]Palmitate	Incorporation in intermediary metabolites	Fatty acid metabolism

Cyclotron → Synthesis → Quality Control

Radiopharmaceuticals in Nuclear Pharmacy

- Tc-99m Sestamibi (Cardiolite ®)
- Tc-99m Mertiatide (MAG_3)
- Tc-99m Sulfur Colloid
- Tc-99m ECD (Neurolite ®)
- ^{201}Tl-Thallium Chloride
- ^{67}Ga-Gallium Citrate
- ^{111}In-Pentreotide (OctroScan®)
- ^{131}I- NP-59 (Adosterol ®)
- ^{90}Y-Microspheres (SIR-Spheres®)
- ^{90}Y-Ibritumomab tiuxetan (Zevalin ®)
- ^{223}Ra-Dichloride (Xofigo®)
- ^{123}I /^{131}I- Sodium Iodide
- ^{18}F-FDG
- ^{13}N-Ammonia
- ^{11}C-Acetate
- ^{18}F-NaF

Tc-99m Sestamibi (Cardiolite ®)



Formulation

$Cu(MIBI)_4.BF_4$	1mg
L-Cysteine hydrochloride hydrate	1mg
Stannous chloride	0.075mg
Mannitol	20mg
Sodium citrate dihydrate	2.6mg

Prior to adding the Sodium Pertechnetate Tc99m Injection to the vial, inspect the vial carefully for the presence of damage, particularly cracks, and do not use the vial if found. Tear off a radiation symbol and attach it to the neck of the vial.

Remove the vial from the lead shield and place upright in an appropriately shielded and contained boiling water bath, such that the vial is suspended above the bottom of the bath, and boil for 10 minutes. Timing for 10 minutes is begun as soon as the water begins to boil again. Do not allow the boiling water to come in contact with the aluminum crimp.

Remove the vial from the water bath, place in the lead shield and allow to cool for fifteen minutes.

■ Pharmacokinetic：

chemical class/charge	isonitrile cation
mechanism of uptake	passive diffusion
	negative electrical potential
myocyte localization	mitochondria
intracellular state	bound
first pass extraction fraction	66%
myocardial clearance	minimal
body clearance	hepatic

■ Clinical application:

Myocardial perfusion scan

Parathyroid scan

breast image (Miraluma ®)

Biochemical Properties of SPECT and PET Myocardial Perfusion Imaging Agents

Property	^{201}Tl-Chloride	^{99m}Tc-Sestamibi	^{99m}Tc-Tetrofosmin	^{82}Rb-Chloride	^{13}N-ammonia
Molecular	+1 Cation	+1 Cation	+1 Cation	+1 Cation	Neutral
Charge	Hydrophilic	Lipophilic	Lipophilic	Hydrophilic	Lipophilic
Uptake mechanism	Active transport Na-K ATPase	Passive diffusion	Passive diffusion	Active transport Na-K ATPase	Passive diffusion $NH_4^+ \rightarrow NH_3 + H^+$ (19 μsec equilibrium)
First-pass extraction (at resting blood flow)	~85 % Diffusion limited > 2.5ml / min /gram	~66 % Diffusion limited > 2.0ml / min /gram	~54 % Diffusion limited > 1.7ml / min /gram	~59 % Diffusion limited > 1ml / min /gram	~82% Diffusion limited > 2ml / min /gram
Heart uptake (% injected dose at rest)	~ 4%	~ 1.2%	~ 1.0%		
Heart retention	Redistributes	Bound in mitochondria	Bound in mitochondria	Redistribution (not possible) (rapid physical Half-life = 76 sec)	$^{13}NH_3$+Glutaminic acid → ^{13}N-Glutamine Biologic Half-life = 1 ~ 2hr Physical Half-life = 10min

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Contraindications for use of pharmacologic agents in stress testing

Contraindications	Dipyridamole	Adenosine	Dobutamine
Unstable angina or resting ischemia	X	X	X
Poor LV function (EF<15%)	X	X	X
Hypertension (> 200mm Hg systolic)		X	X
Hypotension (< 90mm Hg systolic)	X	X	
Severe aortic stenosis			X
History of asthma	X	X	
Active bronchospastic disease	X	X	
History of tacharrhythmias			X
Second-degree AV block		X	
Oral dipyridamole		X	
Xanthine compounds	X	X	
Atrial fibrillation with rapid ventricular response			X

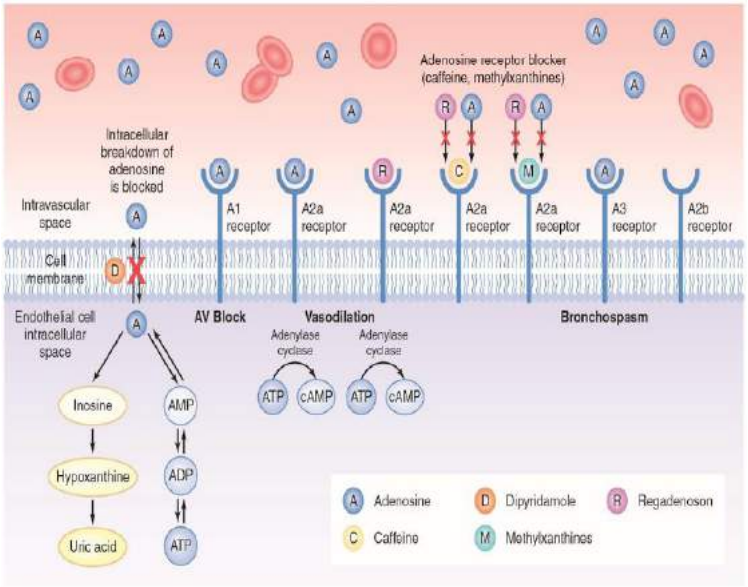
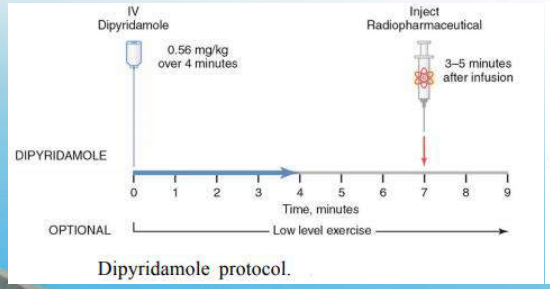
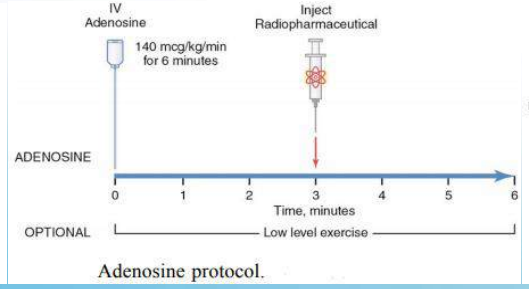


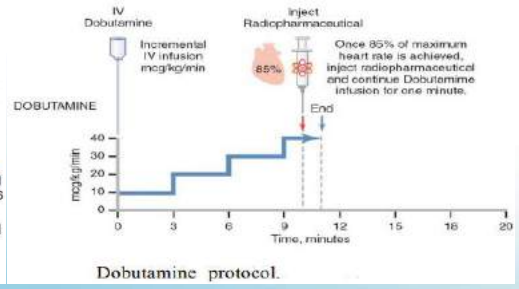
Figure 1. Mechanism of action of coronary vasodilators. *ADP*, Adenosine diphosphate; *AMP*, adenosine monophosphate; *ATP*, adenosine triphosphate; *AV*, atrioventricular; and *cAMP*, cyclic adenosine monophosphate.



Dipyridamole protocol.



Adenosine protocol.



Dobutamine protocol.

Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine ,p463 ~ 465

ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress、protocols、tracers

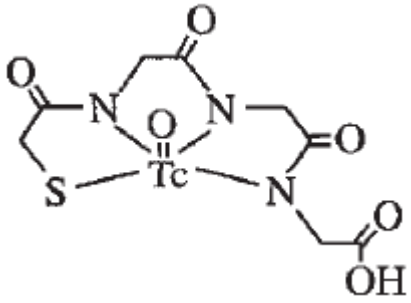
Current SPECT myocardial perfusion imaging protocols: recommended radiopharmaceutical activities and their corresponding radiation effective doses

	First injection				Second injection				Total Dose (mSv)	Total dose if Stress only (mSv)
	Given at	Activity (mCi)	Activity (MBq)	Dose (mSv)	Given at	Activity (mCi)	Activity (MBq)	Dose (mSv)		
Tc-99m protocols										
Tc-99m one-day stress-first/ stress-only	Stress	8–12	296–444	2.0–3.0	(Rest)	24–36	888–1332	7.0–10.5	9.0–13.5	2.0–3.0
Tc-99m one-day rest/stress	Rest	8–12	296–444	2.3–3.5	Stress	24–36	888–1332	6.1–9.1	8.4–12.6	n/a
Tc-99m two-day stress/rest	Stress	8–12	296–444	2.0–3.0	(Rest)	8–12	296–444	2.3–3.5	4.3–6.5	2.0–3.0
Tc-99m two-day stress/rest—large patient	Stress	18–30	666–1110	4.5–7.6	(Rest)	18–30	666–1110	5.2–8.7	9.8–16.3	4.5–7.6
Tc-99m two-day rest/stress	Rest	8–12	296–444	2.3–3.5	Stress	8–12	296–444	2.0–3.0	4.3–6.5	n/a
Tc-99m two-day rest/stress large patient	Rest	18–30	666–1110	5.2–8.7	Stress	18–30	666–1110	4.5–7.6	9.8–16.3	n/a
Tl-201 protocols										
Tl-201 stress/redistribution rest	Stress	2.5–3.5	92.5–129.5	10.9–15.3	n/a	n/a	n/a	n/a	10.9–15.3	10.9–15.3
Tl-201 stress/redistribution rest/ reinjection	Stress	2.5–3.5	92.5–129.5	10.9–15.3	Rest	1–2	37–74	4.4–8.8	15.3–24.1	n/a
Tl-201 rest/redistribution	Rest	2.5–3.5	92.5–129.5	10.9–15.3	n/a	n/a	n/a	n/a	10.9–15.3	n/a
Dual-isotope Tl-201 rest/Tc-99m stress	Rest	2.5–3.5	92.5–129.5	10.9–15.3	Stress	8–12	296–444	2.0–3.0	13.0–18.3	n/a
Dual-isotope Tl-201 rest/Tc-99m stress—large patient	Rest	3.0–3.5	111–129.5	13.1–15.3	Stress	18–30	666–1110	4.5–7.6	17.7–22.9	n/a
I-123 protocol										
*m*IBG	Rest	10	370	4.6	n/a	n/a	n/a	n/a	4.6	n/a
Newer technology reduced-dose protocols										
Tc-99m one-day stress-first/ stress-only	Stress	4–6	148–222	1.0–1.5	(Rest)	12–18	444–666	3.5–5.2	4.5–6.7	1.0–1.5
Tc-99m one-day rest/stress	Rest	4–6	148–222	1.2–1.7	Stress	12–18	444–666	3.0–4.5	4.2–6.3	n/a
Tc-99m two-day stress/rest	Stress	4–6	148–222	1.0–1.5	(Rest)	4–6	148–222	1.2–1.7	2.2–3.3	1.0–1.5
Tc-99m two-day stress/rest—large patient	Stress	9–15	333–555	2.3–3.8	(Rest)	9–15	333–555	2.6–4.4	4.9–8.1	2.3–3.8
Tc-99m two-day rest/stress	Rest	4–6	148–222	1.2–1.7	Stress	4–6	148–222	1.0–1.5	2.2–3.3	n/a
Tc-99m two-day rest/stress—large patient	Rest	9–15	333–555	2.6–4.4	Stress	9–15	333–555	2.3–3.8	4.9–8.1	n/a
Tl-201 stress/redistribution rest	Stress	1.3–1.8	48.1–66.6	5.7–7.9	n/a	n/a	n/a	n/a	5.7–7.9	5.7–7.9
Dual-isotope Tl-201 rest/Tc-99m stress	Rest	1.3–1.8	48.1–66.6	5.7–7.9	Stress	4–6	148–222	1.0–1.5	6.7–9.4	n/a
Dual-isotope Tl-201 stress/Tc-99m rest	Stress	1.3–1.8	48.1–66.6	5.7–7.9	(Rest)	4–6	148–222	1.2–1.7	6.9–9.6	5.7–7.9

Tc-99m Mertiatide (MAG_3)

Formulation

	European	U.S
Betiatide	1mg	1mg
Disodium tartrate	16.9mg	40mg
Stannous chloride	40μg	200μg
Lactose	None	20mg



Immediately following the addition of sodium pertechnetate Tc 99m solution to the reaction vial, withdraw the syringe plunger to a volume of 2 mL, thus removing 2 mL of argon gas and adding 2 mL of filtered air to the vial. The air is required to oxidize excess stannous ion. Remove both needles from the vial.

↓

Invert the reaction vial several times to obtain complete mixing.

↓

Immediately transfer the reaction vial to the water bath. Place it inside the lead shield which has been equilibrated to the temperature of the boiling water bath. Allow the reaction vial to incubate for 10 minutes.

- Fractors that may cause radiochemical impurities :

1、 >100mCi ^{99m}Tc

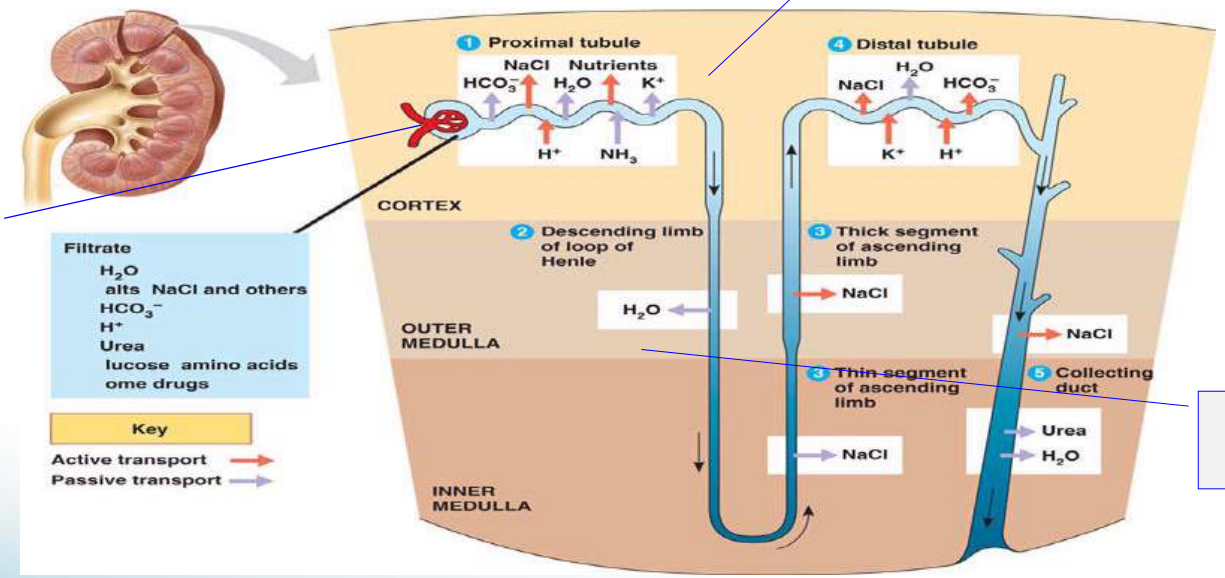
2、 Volume < 4ml

3、Waiting longer than 5min to place the vial into the boiling water bath .

4、Not adding air to the vial during radiolabeling .

Tc-99m Mertiatide (MAG_3)

- Different mechanisms of renal radiopharmaceutical



- Clinical application：

  Renal imaging / renography、 Effective renal plasma flow

  、 Urinary tract obstruction (Furosemide renal scan)

  、 Reno - vascular HTN (Captopril renal scan)

Captopril renogram for diagnosis of Renovascular hypertension (RVH)

- RVH refers to high blood pressure related to Renal Artery Stenosis (RAS).
- Renovascular hypertension . Because of reduced renal plasma flow , filtration pressure and GFR fall .Increased renin and resulting angiotensin II produces vasoconstriction of efferent glomerular arterioles , raising glomerular pressure and maintaining GFR.
- Captopril blocks the normal compensatory mechanism and GFR falls.
- Monitor and record blood pressure

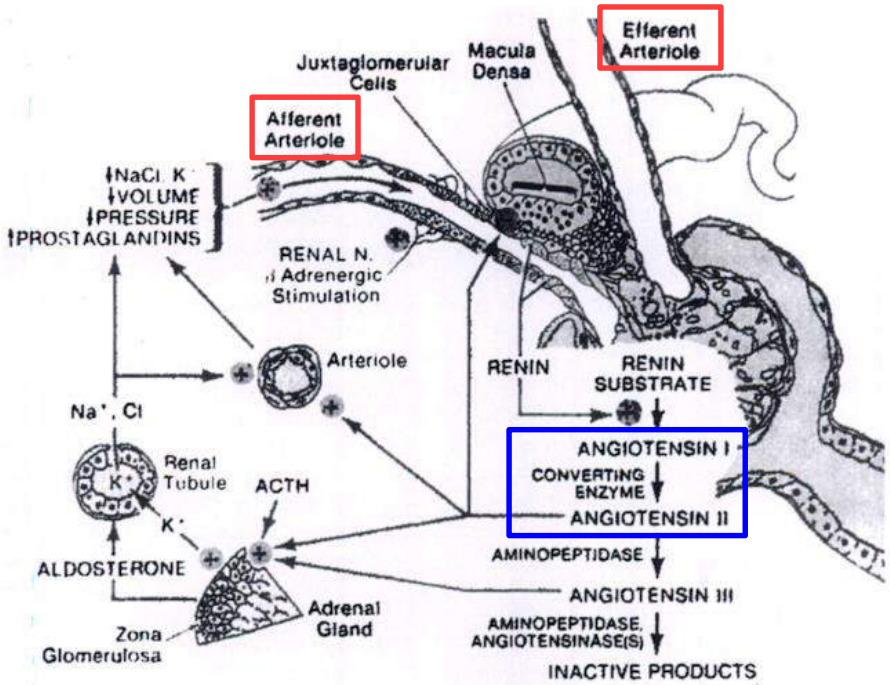


FIGURE 42.12. Diagram of renin-angiotensin pathway. (From Wyngaarden JB, Smith LH, Bennett JC, eds. *Cecil textbook of medicine*, vol 2, 19th ed. Philadelphia: WB Saunders, with permission.)

Tc-99m Sulfur Colloid

Formulation

Reaction vial

Anhydydrous Sodium thiosulfate 2mg - The source of sulfur

Disodium Edetate (Na^2EDTA) 2.3mg - Al^{3+} ion chelater

Gelatin 1.8mgmg - Protective colloid

Solution - A

1.8ml of 0.148N HCl

Solution - B

1.8ml of 24.6mg/ml anhydrous sodium biphosphate

7.9mg/m sodium hydroxide

Product	Particle size (um)	Property of before use	Prescribe procedure (boiling & cooling)
^{99m}Tc-Phytate	0.2 ~ 1	Non - colloid	No
^{99m}Tc-Sulfur colloid	0.1 ~1	Colloid	Yes
^{99m}Tc-Nanocolloid	0.1	Colloid	Yes
^{99m}Tc-MAA	10 ~ 90	Albumin	No

Tc-99m Sulfur Colloid

- Clinical application:

  Imaging areas of functioning retriculoendothelial cells in the liver, spleen and bone marrow

  It is used orally for:

  Esophageal transit studies 、Gastroesophageal reflux scintigraphy

  Aid in the evaluation of peritoneo-venous (LeVeen) shunt patency

Gastric Emptying Scintigraphy*

Mary Beth Farrell

Intersocietal Accreditation Commission

TABLE 2
Standardized Gastric Emptying Meal

120 g (4 oz.) of liquid egg whites (99% real eggs, cholesterol free, fat-free and low calorie)
2 slices of white bread 30 g strawberry jam 120 ml (4 oz.) water 18.5–37 MBq (0.5–1.0 mCi) ^{99m}Tc-SC

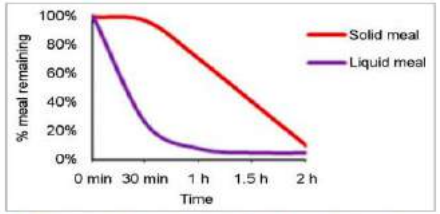


FIGURE 5. Normal gastric emptying curves. For solid meal (red), there is an initial 20-30 m lag period as the antrum reduces meal particle size and mixes with gastric acid. After the lag period, the solid material empties from the stomach in a linear fashion. The liquid meal (purple) immediately begins to leave the stomach and empties in an exponential pattern.

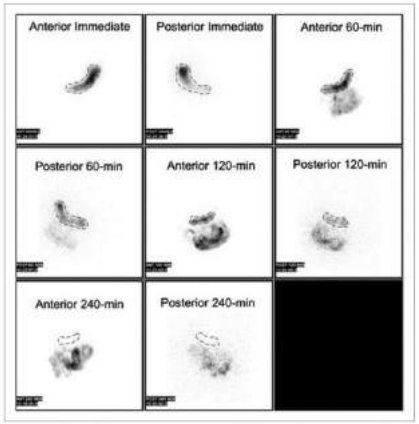


FIGURE 2. Normal gastric emptying study demonstrating correct regions of interest in both the anterior and posterior projections on initial, 1-hour, 2-hour, and 4-hour images. *This image was originally published in* JNMT. *Vijayakumar V. Assessment of the Practical Role of a Radionuclide Low-Fat-Meal Solid Gastric Emptying Study.* J Nucl Med Technol. *2006; 34:82–85. © SNMMI.*

In Vitro Evaluation of Tc-99m Radiopharmaceuticals for Gastric Emptying Studies

Dokuz Eylül University, Department of Nuclear Medicine, İzmir, Turkey

Table 1. Labeling efficiency at 90 minutes

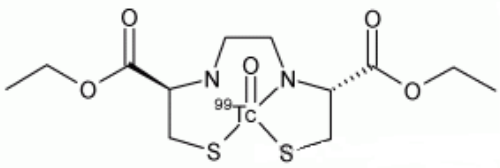
Radiopharmaceutical	mean±standard deviation
^{99m}Tc SC	95±5
^{99m}Tc Tin colloid	95±5
^{99m}Tc Nanocolloid	95±5
^{99m}Tc MAA	99±0.5
^{99m}TcO4 –	70±10
^{99m}Tc DTPA	70±10

★ The best binding efficiency with eggs was found ^{99m}Tc99m MAA among the particulate and nonparticulate radiopharmaceuticals. This may be related to MAA binding to egg albumin proteins firmly as it becomes denatured during cooking.

Tc-99m ECD (Neurolite ®)

- Formulation

Vial A Bicisate ·2HCl (l,l-ECD·2HCl)
EDTA (Edetate disodium dihydrate)
$SnCl_2$ .. pH = 2.7 ± 0.25
Vial B Phosphate buffer pH = 7.6 ± 0.4



Cerebral retention
l.l > d.l > d.d

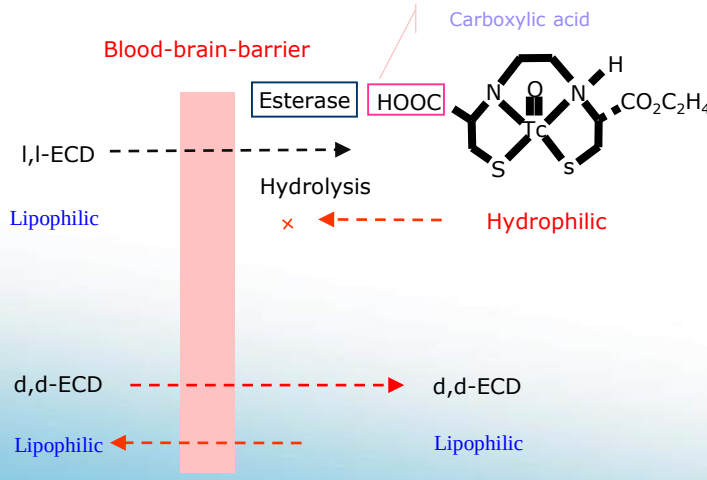
With a sterile shielded syringe, aseptically add 3.70 GBq (100 mCi) sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection, in approximately 2.0 ml, to vial B. Without withdrawing the needle, remove an equal volume of air to maintain pressure within the vial.

With a sterile syringe, rapidly inject 3.0 ml of Sodium Chloride Injection (0.9%) into vial A (the lyophilized vial) to dissolve the contents. Without withdrawing the needle, remove an equal volume of air to maintain pressure within the vial. Shake the contents of the vial for a few seconds.

With another sterile syringe, immediately (within 30 seconds) withdraw 1.0 ml of vial A and inject it into vial B.

Swirl the contents of the vial B for a few seconds and allow this mixture to stand for thirty (30) minutes at room temperature.

- Mechanism



Tc-99m ECD (Neurolite ®)

- Comparison of ^{99m}Tc HMPAO and ^{99m}Tc ECD

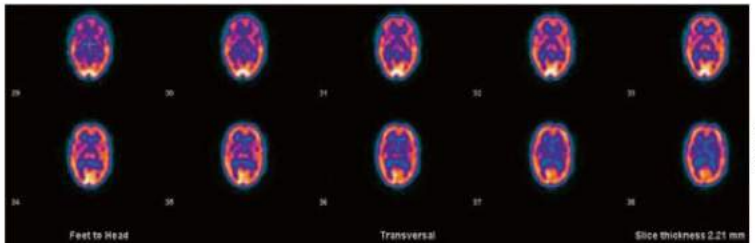
Table 4.1. Pharmacokinetics of technetium radiopharmaceuticals for brain perfusion SPECT.

Parameter	^{99m}Tc-HMPAO	^{99m}Tc-ECD
In vitro Characteristics		
Stability	30 min (>4 h with stabilizer)	>6 h
Biologic Characteristics		
Plasma protein binding	Higher extraction	Hydrophilic
First extraction (%)	hydrophilic conversion	conversion by
Retention mechanism	by interaction with glutathion	de-esterification
Brain kinetics		
	2%–3%*	4%–7%
Brain uptake (% I.D)	2 min	2 min
peak brain activity	12%–15% over 15 min	12%–14% the first hour; then
Brain washout		6%/h
	50% liver–gut	15% liver–gut
Excretion (% at 48 h pi)	40% kidneys	75% kidneys
Dosimetry		
	555–1,100 MBq	555–1,100 MBq
injection dose (MBq)	Lachrymal glands	Urinary bladder
Target organs	Gallbladder wall	Gallbladder wall
Imaging		
Recommended imaging time	Upto 4 h p.i.	Up to 2 h p.i.
Ratio of Gray matter to white matter	2–3:1	4:1

- Clinical application：

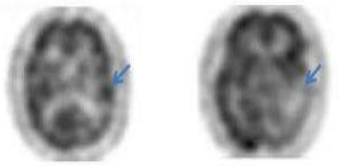
  Brain scintigraphy、acute cerebral infarction 、 inflammatory conditions in the brain、 cerebral blood flow

Distribution Patterns: Normal



Normal SPECT scan

Abnormal Distribution



SPECT ictal　　SPECT interictal

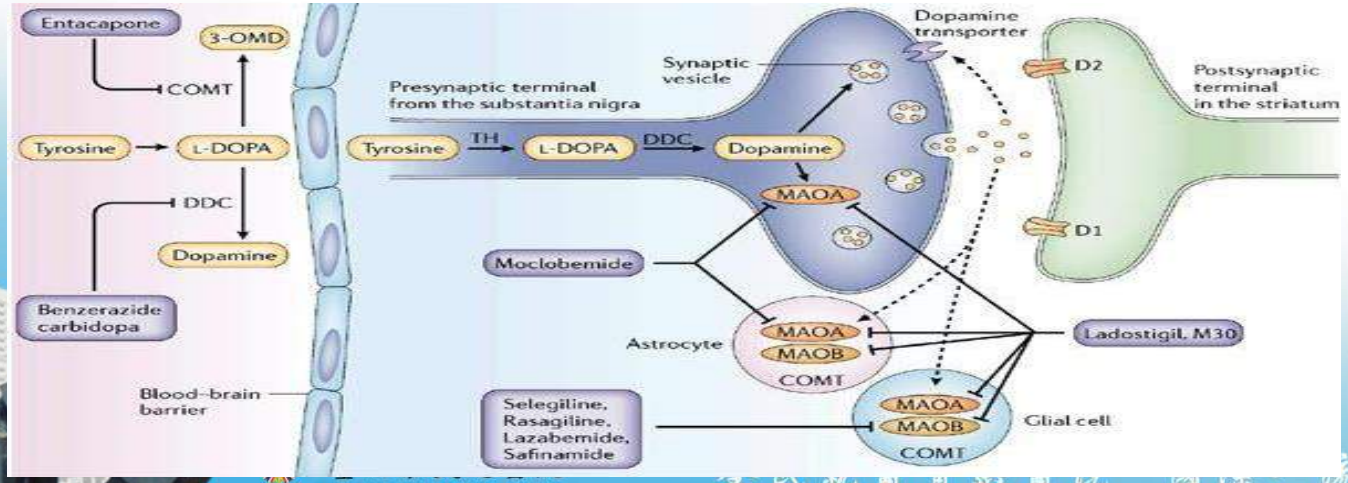
Alzheimer's disease　　Frontotemporal dementia

Handbook of Nuclear Medicine and Molecular Imaging P112

RadTool Nuclear Medicine Flash Facts P40 ~ 41

Radioligands for PET and SPECT imaging of the dopamine system

Target site		PET	SPECT
Presynaptic	Synthesis	^{18}F-FDOPA	
	Dopamine transporter	^{11}C-Cocaine	^{123}I-βCIT
		^{11}C-Methylphenidate	^{123}I-FPCIT
	Monoamine transporter	^{11}C-DTBZ	^{99m}TC-TRODAT-1
Postsynaptic	D_1 receptor	^{11}C-SCH 23390	-
	D_2 receptor	^{11}C-Raclopride	^{123}I-IBZM
		^{18}F-Fallypride	



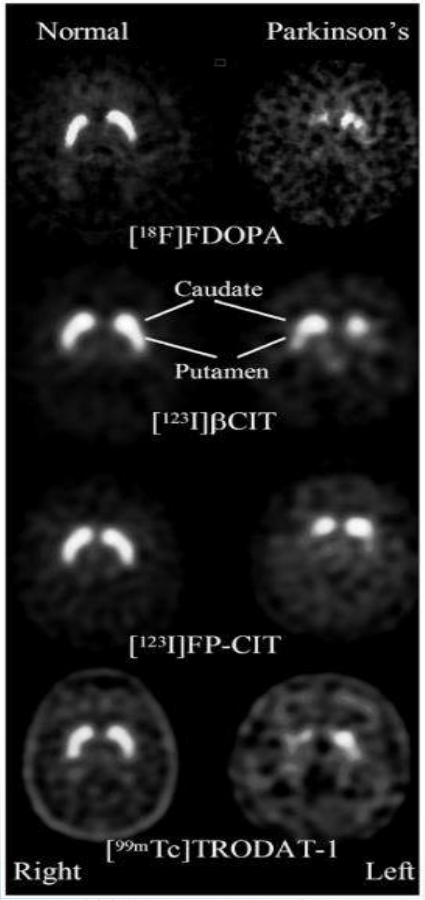
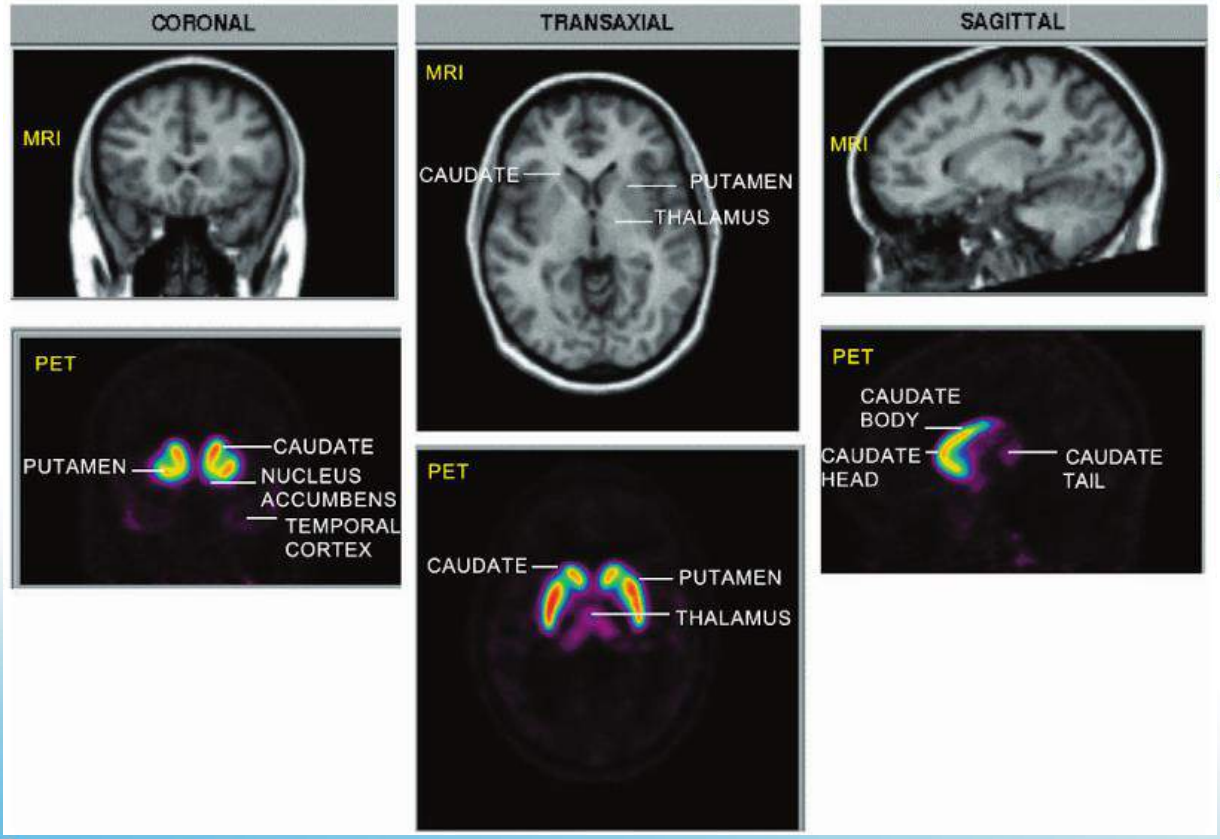
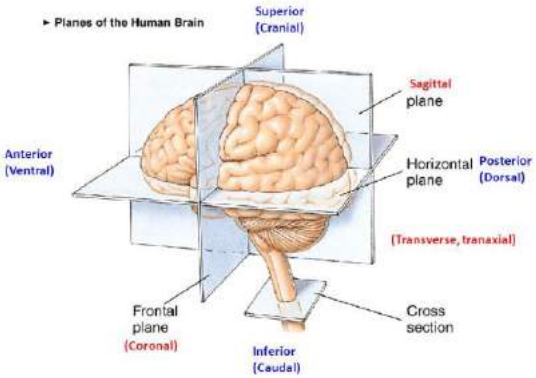


Fig. 3.7. [^{18}F]FDOPA PET images (parametric images of influx rate constant, K_i) and dopamine transporter (DAT) SPECT images using [^{123}I]β-CIT (24 h post injection), [^{123}I]FP-CIT (4 h post injection) and [^{99m}Tc]TRODAT-1 (3 h post injection) of normal controls (*left column row*) and Parkinson's disease patients (*right column*). In both columns, scans shown are from different normal individuals and Parkinson's disease patients

https://www.nature.com/articles/nrn1883/figures/1

MRI and corresponding PET image slices the human brain showing binding of ^{18}F-fallypride to dopamine D2 receptors





Emission Tomography: The Fundamentals of PET and SPECT p97

^{201}Tl-Thallium Chloride

- Description :

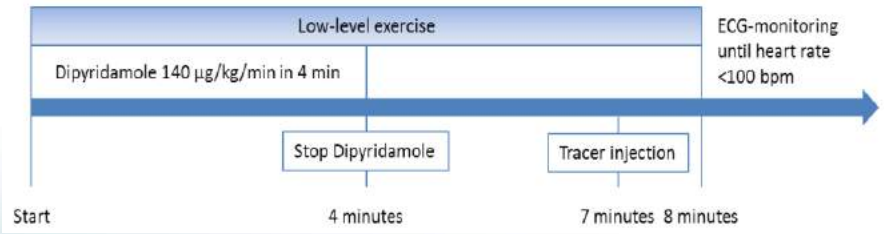
  ^{201}Tl-Thallium chloride 2mCi/ml Benzyl alcohol 9mg/ml

  Sodium chloride 9mg/ml
- PH : between 4.5 ~ 7.0
- Appearance: colorless transparent fluid
- ^{201}Tl is a cyclotron-produced potassium analog radioisotope with a half-life of 73 h.

- Types of stress tests used in myocardial perfusion imaging

Stress type		
Exercise		Bicycle stress
		Treadmill stress
Pharmacological	Vasodilation*	Adenosine
		Regadenoson
		Dipyridamole
	Sympathomimetic[5]	Dobutamine

- Timeline of Dipyridamole plus low-level exercise testing



EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT P35 / P38

^{201}Tl-Thallium Chloride

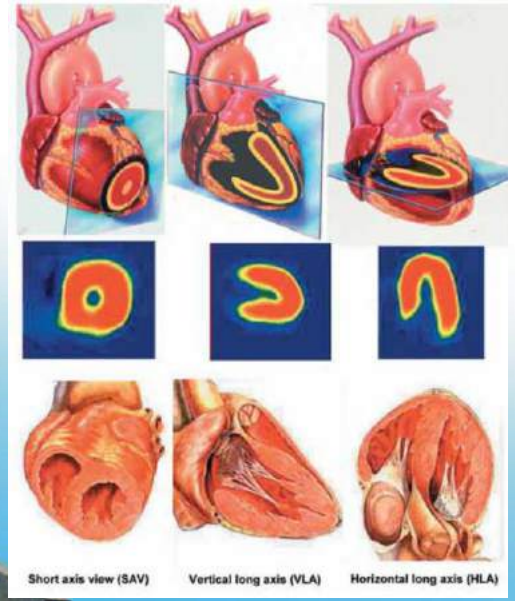
- Patient Preparation：
  - be fasting for at least 2 hours
  - Restrict intake of Beta Blockers
    - 、Calcium Channel Blockers
    - 、Xanthine derivatives (Theophylline 、Caffeine)

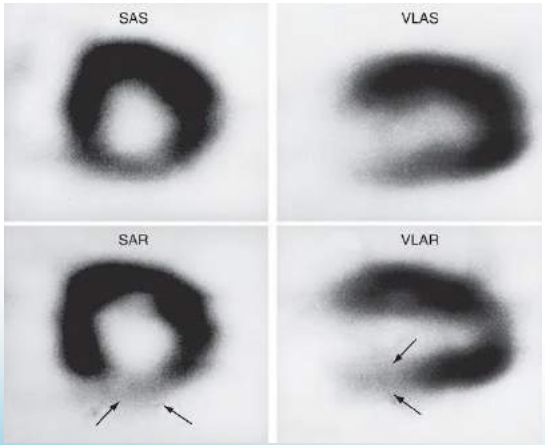
- Clinical application：

Myocardial perfusion imaging (MPI)
- Non-reversible defects (myocardial infarction)
- Reversible defects (myocardial ischemia)

Parathyroid scan (dual-isotope technique)

Cancer detection scan





Reverse Redistribution (Reverse Perfusion Defect). (Top row) Single-photon emission computed tomography myocardial perfusion stress images both in short-axis stress *(SAS)* and vertical long-axis stress *(VLAS)* projections that demonstrate slightly reduced perfusion of the inferior wall. However, the rest (redistribution) images in the bottom row show that the defect is much more obvious *(arrows)*. *SAR*, Short-axis rest; *VLAR*, vertical long-axis rest.

Essentials of Nuclear Medicine and Molecular Imaging ,p136

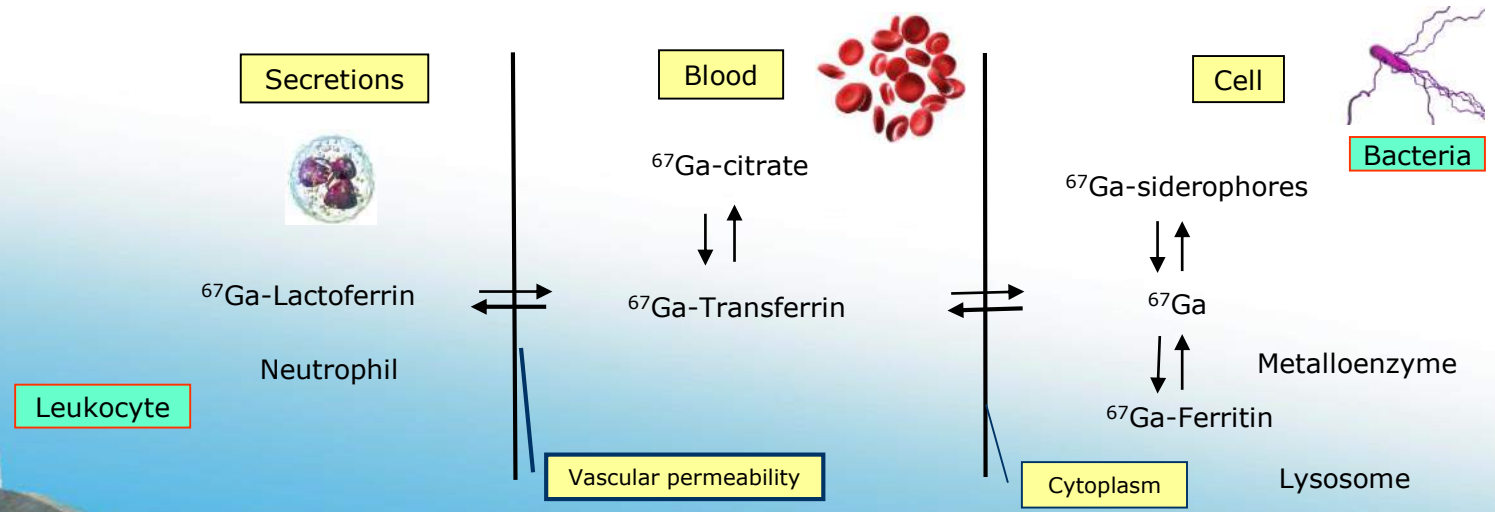
^{67}Ga- Gallium Citrate

- Description:

^{67}Ga-Citrate	2mci/ml	Sodium citrate	10mg/ml
Benzyl alcohol	45ul	Sodium chloride	Appropriate amount

- PH : between 5 ~ 8.0
- Appearance: colorless transparent fluid
- Mechanism :

Affinity : siderophore > ferritin > lactoferrin > transferrin



^{67}Ga- Gallium Citrate

- Factors altering Ga-67 biodistribution :

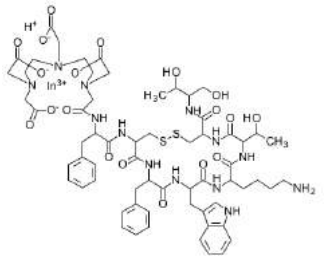
	Renal	Liver	Bone
Chemotherapy	+	-	+
Iron overload (Multiple transfusion)	+	-	+
Acute tubular necrosis (ATN)	+		
Acute renal failure (ARF)	+		
Leukemia	+		+
Lymphoma	+		
Congestive heart failure (CHF)	+		
Gadolinium contrast			+
Elevated serum aluminum			+
Liver failure		-	

+ = Increase uptake - = Decrease uptake

- Clinical application：

Soft tissue sarcomas 、
Hodgkin`s disease 、
Non-Hodgkin`s lymphoma
Hepatocellular carcinoma
Lung cancer ・・・

^{111}In-Pentreotide (OctroScan®)



- Composition:

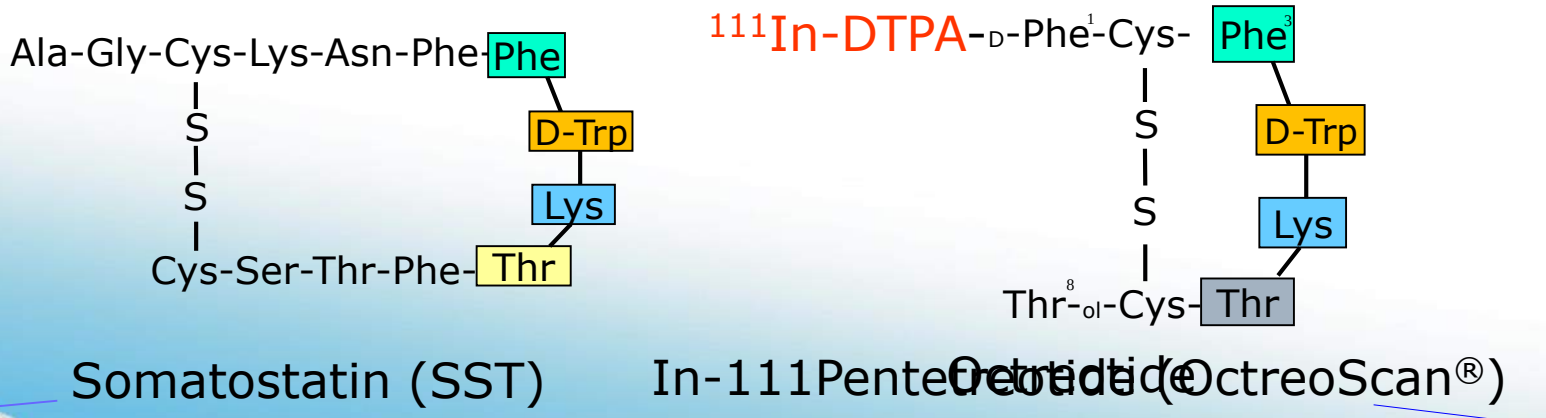
Pentetreotide kit :

Pentetreotide	10μg	Gentisic acid	2mg		
Trisodium citrate	4.9mg	Citric acid	0.37mg	Inositol	10mg

Indium In-111 chloride solution:

Indium In-111 chloride 1.1ml (3mCi /ml)

- Comparison of somatostatin analog octreotide :



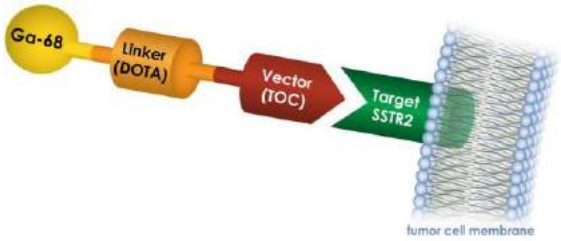
Somatostatin (SST)

14-amino acid long peptide produced in the hypothalamus ,pitutary gland ,brainstem ,GI tract ,pancreas . Inhibits release of growth hormone , insulin ,glucagon ,gastrin ,serotonin ,cacitonin..

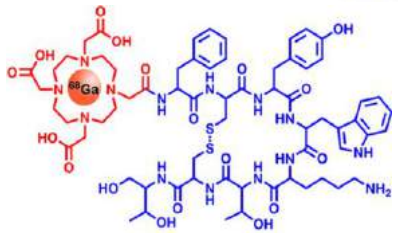
In-111Pentetreotide (OctreoScan®)

8-amino acid segment of somatostatin that maintains active binding properties ,It is resistant to enzymatic degradation in the body.

Phe =Phenylalanine



^{111}In-Pentreotide (OctroScan®)



[68 Ga]-DOTATOC : DOTA-Phe^1-Tyr^3-octreotide)

- Overview of imaging agent :

Radioligand	Receptor binding
^{111}In-DTPA-D-Phe^1-Octreotide	hSSTR 2,5(3)
^{111}In-DOTA-lanreotide	hSSTR 2~5(1)
^{111}In-DOTA-Tyr^3-Octreotide	hSSTR 2,5(3)
^{99m}Tc-depreotide (P829)	hSSTR 2,3,5
^{123}I-VIP	hSSTR 3, VIP 1,2

hSSTR=human somatostatin receptors

Tyr=Tyrosine

VIP=Vasoactive intestinal peptide

- Clinical application：
  Neuroendocrine tumors (NET)、
  Pheochromocytoma、
  Small cell carcinoma of lung 、
  Insulinoma 、Gastrinoma ..

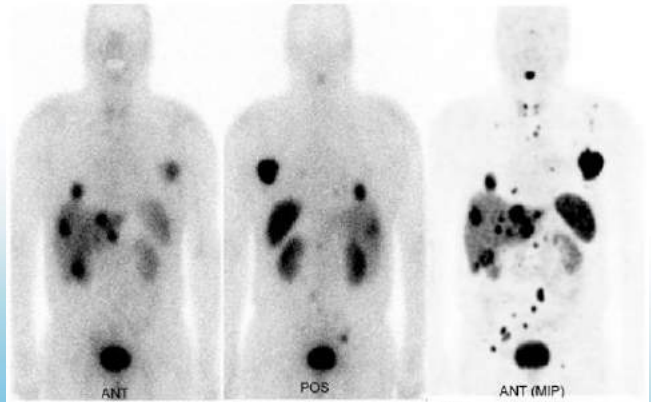


Fig. 15. Comparison of ^{111}In-DTPAOC with ^{68}Ga-DOTA-TOC in the same tumour patient

https://uihc.org/health-topics/what-theranostics

^{131}I- NP-59 (Adosterol ®)

- Composition:

^{131}I-6β-Iodomethyl-19-Norcholesterol (NP-59)	1mCi
Ethanol	0.016ml
Polysorbate 80 (Tween-80)	0.032ml
Physiological saline	appropriate amount

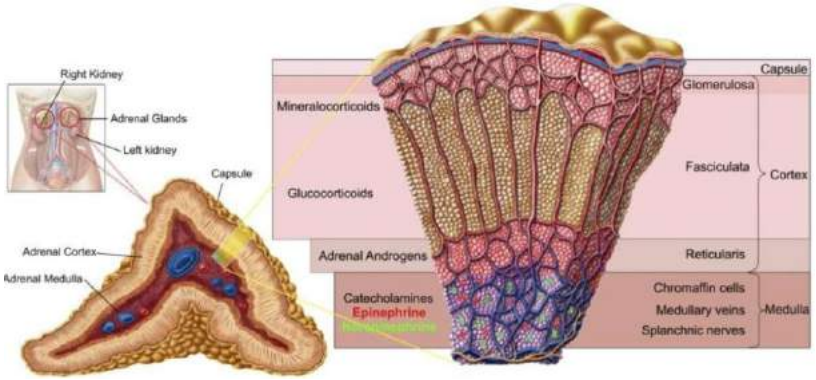
- ^{131}I-labeled NP-59 is use in Adrenocortical scan.
  - Cushing's syndrome、Conn's syndrome 、adrenal adenoma
- Radiocholesterols are dissolved in an alcoholic vehicle ontain Tween-80 and should be injected intravenously over 2~3min .

★^{131}I- MIBG (Metaiodobenzylguanidine)

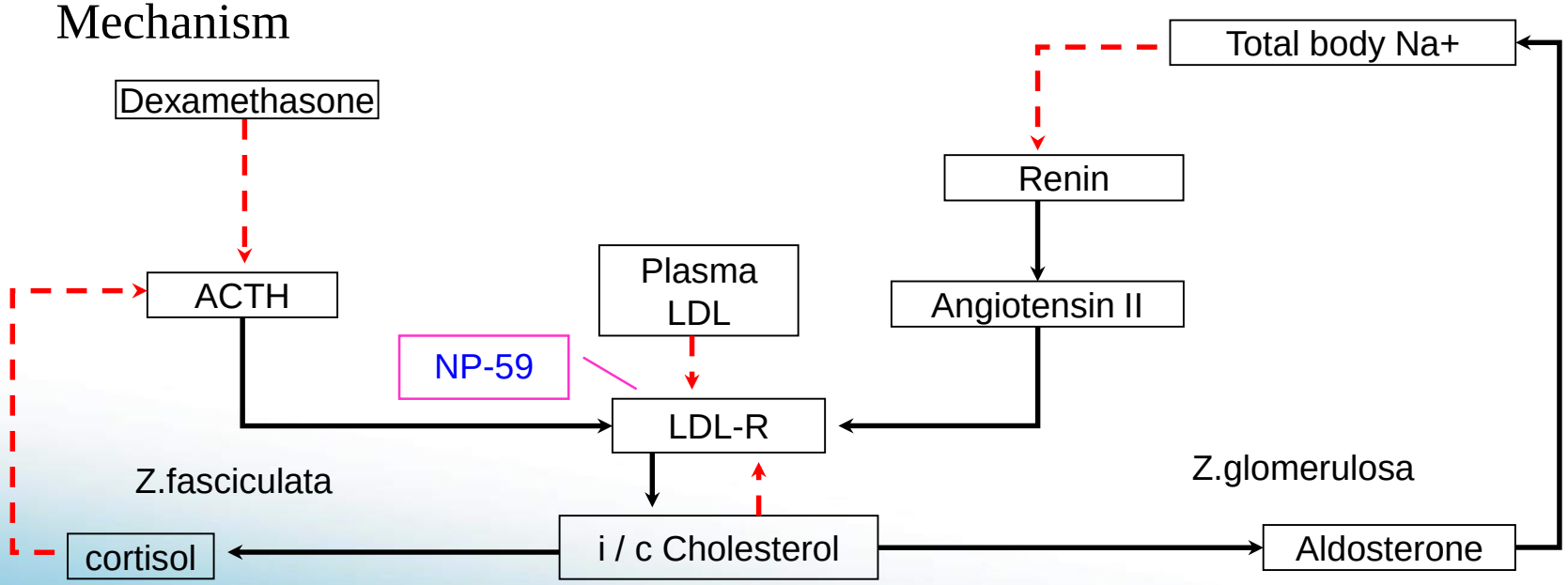
- Norepinephrine analogue .
- Adrenal medullary imaging agent.

Pheochromocytoma 、 Medullary thyroid cancer (MTC) 、 Neuroblastoma ..

^{131}I- NP-59 (Adosterol ®)



- Mechanism



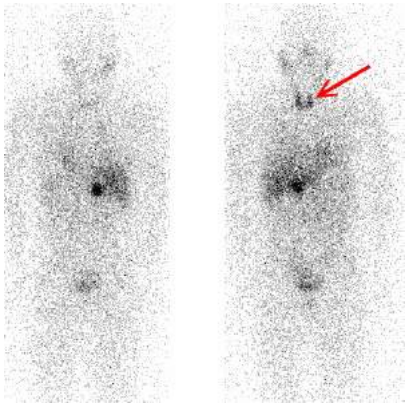
Regulation of adrenocotical intracellular cholesterol pool and hormone biosynthesis

→ = Increases

⇢ = Inhibits

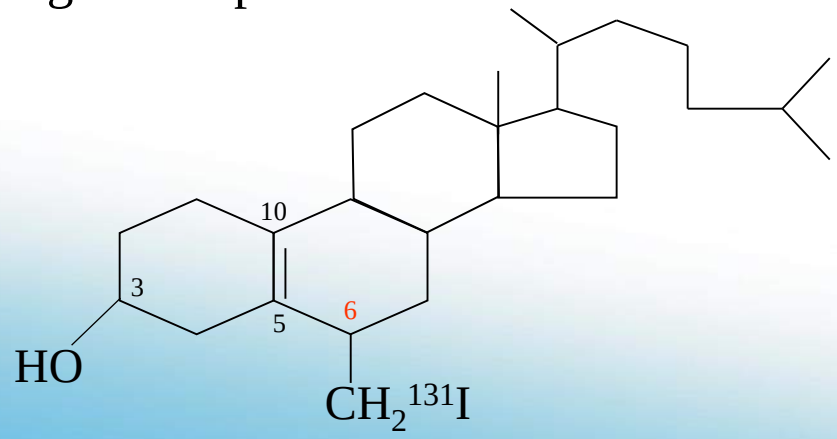
LDL-R = Low density lipoprotein receptor

^{131}I- NP-59 (Adosterol ®)



- Administer an appropriate iodine drug thyroid gland (such as Lugol` solution or SSKI).
- Dexamethasone suppression .
- At 4°C, NP-59 is stable for 2 weeks , an deiodination occurs at room or higher temperature .

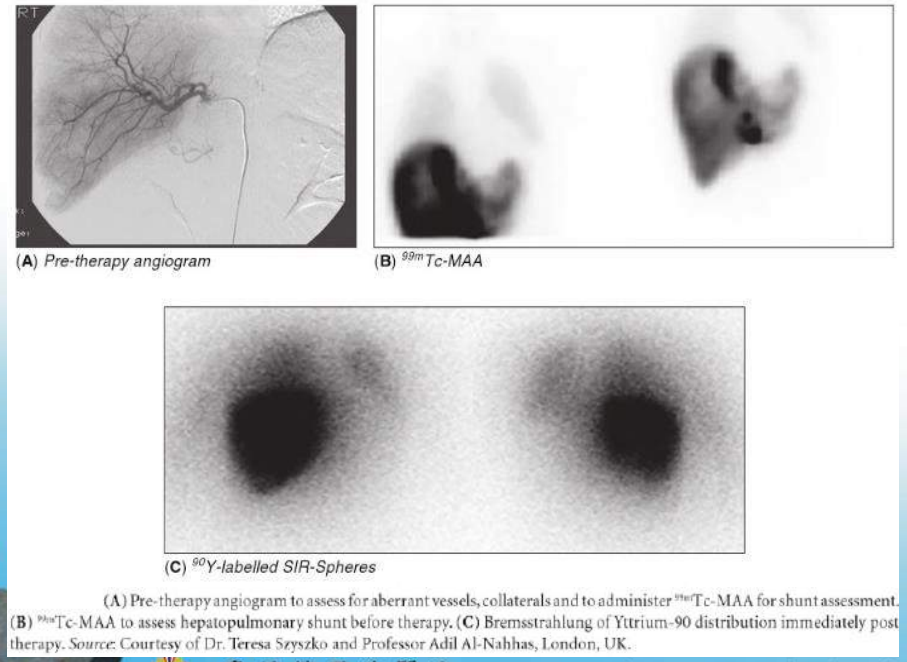
Dry ice is the solid form of carbon dioxide.
It has a temperature of -78℃ .



SSKI= Supersaturated potassium iodide

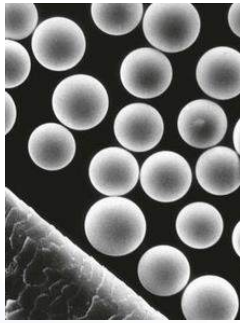
^{90}Y-Microspheres (SIR-Spheres®)

- Energy (Mean /Maximum) (MeV) : 0.94 /2.3
- Range (Mean /Maximum) (mm) : 2.5 /11
- SIR-Spheres® are intended for use on the day of calibration. (>24hr , Particle number > 30%).
- SIR-Spheres® is intended for implantation into hepatic tumours via the hepatic artery.
- For treating unresectable liver metastasis from primary colorectal cancer.



Characteristics of Microspheres

Trade name	Sir-Spheres ®	TheraSphere ®
Microsphere material	Resin	Glass
Manufacturer and location	Sirtex Medical (Singapore)	MDS Nordion (Canada)
Isotope ^{90}Y	Attached to the surface	Incorporated into the glass matrix
Diameter (μm)	20 ~ 60	20 ~ 35
Particles /activity (million/3GBq)	40 ~ 80	1.2
Specific gravity	1.6g/dl	3.6g/dl
Specific activity per microsphere	50Bq	2500Bq
Expiry (Post calibration)	24hrs	12days
Activity per commercially	Bulk dose (Can be divided)	35 dose size (3~20GBq)



Magnified view of ^{90}Y glass microspheres (TheraSphere) compared to size of a hair.

^{90}Y-Microspheres - Prescription Form

台北榮民總醫院
Taipei Veterans General Hospital

Yttrium-90
2015/10/12 Version 7.1

Prescription Form for SIRT on 2018 / 10 / 25

Minute Taker: [illegible] Date: 2018/10/17

Basic Information & Medical History

Name [illegible] (M)/ F, 55 y/o) Chart No. 42452502 Ht 175.9 cm Wt 80.5 kg
Diagnosis NET ECOG 0 BCLC ____ Child-Pugh ____ CLIP ____ Okuda ____
□EHD ____ □HBV/HCV □DM/HTN □PVT □Cirrhosis □Ascites □ ____
Treatment ☑SIRT 2018.3.19 ☑OP ×13 ☑TACE □R/T ☑L/A ☑C/T □T/T

CT & ^{99m}Tc-MAA Scan (Date: 2018 / 10 / 16)

CT vs MAA : Matched
Lung shunting 4.74 %
Signature: [illegible]

Site	Whole Liver	Right Lobe	Left Lobe	Lung	Spleen
Total Volume (cc)	1540.1	1115.1	425	5847	2845
Tumor Volume (cc)	92.3	89.3	3		

Tumor burden 6.1 % (# 210 , 4.6 cm)

Planned Injection Time: 11:30
Signature: [illegible]

Dosimetry

BSA Model: W 1.83 GBq
Partition Model:

Tx Location & Artery	R		
T-N Ratio	2.1		
Activity (GBq)	1.1		
Tumor Dose (Gy)	87.8		
Normal Liver Dose (Gy)	41.6		
Average Dose (Gy)	45.3		
Lung Dose (Gy)	1.5		

Signature: [illegible]

Prescribed Dose

Tx Location & Artery			
Activity & Time before Infusion	____mCi at ____ : ____	____mCi at ____ : ____	____mCi at ____ : ____
Infusion Time	~	~	~
Residual Activity &Time	____mCi at ____ : ____	____mCi at ____ : ____	____mCi at ____ : ____

Actual Activity (GBq)			
Actual Tumor Dose (Gy)			
Actual Normal Liver Dose (Gy)			
Actual Average Dose (Gy)			
Actual Lung Dose (Gy)			

Signature: ____

台北榮民總醫院
Taipei Veterans General Hospital

Yttrium-90
2015/10/12 Version 7.1

Glass

Prescription Form for SIRT on 2018 / 11 / 1

Basic Information & Medical History

Minute Taker: [illegible] Date: 2018/10/24

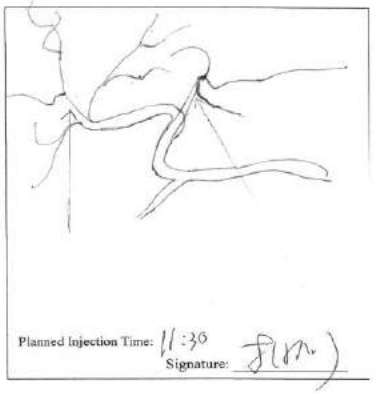
Name [illegible] (M)/ F, 82 y/o) Chart No. 31598397 Ht 158 cm Wt 73.2 kg
Diagnosis HCC ECOG 0 BCLC C Child-Pugh A5 CLIP 1 Okuda I
□EHD ____ ☑HBV/HCV ☑DM/HTN ☑PVT Vp4 □Cirrhosis □Ascites □ ____
Treatment □SIRT ____ □OP □TACE □R/T □L/A □C/T □T/T

CT & ^{99m}Tc-MAA Scan (Date: 2018 / 10 / 23)

CT vs MAA : Matched
Lung shunting 6 %
Signature: [illegible]

Site	Whole Liver	Right Lobe	Left Lobe	Lung	Spleen
Total Volume (cc)	2081	1382.8	698.2	410.7	583.7
Tumor Volume (cc)	assume 60				

Tumor burden 2.9 % (# 1 , 4.3 cm)



Planned Injection Time: 11:30
Signature: [illegible]

Dosimetry

BSA Model: W 1.58 GBq
Partition Model: only 5.5 4

Tx Location & Artery	L	R	
T-N Ratio	1	1	
Activity (GBq)	2.28	1.68	
Tumor Dose (Gy)	146	136	
Normal Liver Dose (Gy)	146	136	
Average Dose (Gy)	146	136	
Lung Dose (Gy)	6.7	5	

Signature: [illegible]

Prescribed Dose

Tx Location & Artery			
Activity & Time before Infusion	____mCi at ____ : ____	____mCi at ____ : ____	____mCi at ____ : ____
Infusion Time	~	~	~
Residual Activity &Time	____mCi at ____ : ____	____mCi at ____ : ____	____mCi at ____ : ____

Actual Activity (GBq)			
Actual Tumor Dose (Gy)			
Actual Normal Liver Dose (Gy)			
Actual Average Dose (Gy)			
Actual Lung Dose (Gy)			

Signature: ____

^{90}Y-Microspheres - Administration set

Sir-Spheres ®

TheraSpheres ®

^{90}Y-Ibritumomab tiuxetan (Zevalin ®)

- ZEVALIN® is a CD20-directed radiotherapeutic antibody administered as part of the ZEVALIN therapeutic regimen indicated for the treatment of patients with:
  - Relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL).
  - Previously untreated follicular NHL who achieve a partial or complete response to first - line chemotherapy.
- Rituximab is administered prior to Zevalin® for both step to clear most normal B cells and thus reduce the toxicity of the Zevalin® .

◆ The entire treatment regimen can be completed in 7–9 days
RRZ: the ZEVALIN treatment regimen simplified

Only administer rituximab/ZEVALIN in facilities where immediate access to resuscitative measures is available.

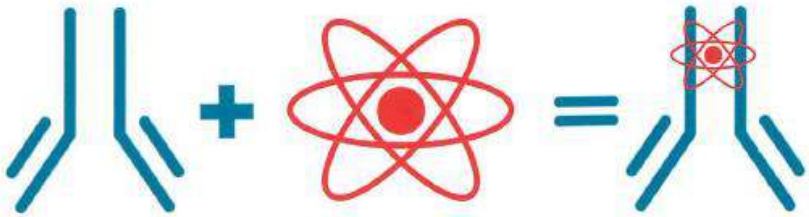
◆ Important Dosing and Administration Information
- Premedicate with acetaminophen 650 mg and diphenhydramine 50 mg orally prior to rituximab infusion
- Intravenous injection of ZEVALIN over 10 minutes as follows:
  - *0.4 mCi/kg (14.8 MBq per kg) for patients with normal platelet count
  - *0.3 mCi/kg (11.1 MBq per kg) in relapsed or refractory patients with platelet count of ≥100,000 – ≤149,000 cells/mm3
  - *The maximum dose of Y-90 ZEVALIN is 32.0 mCi (1184 MBq)

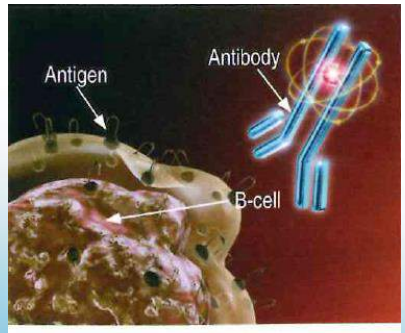
https://www.nature.com/articles/ncpneuro0901/figures/2

ZEVALIN
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

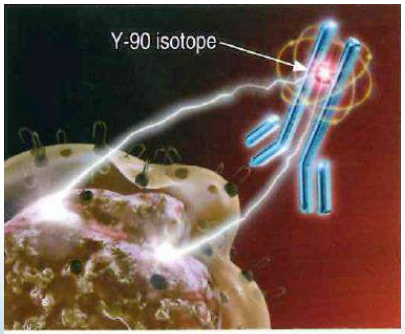
What is Y-90 Zevalin ？

- **Antibody**
  Ibritumomab is a monoclonal antibody that targets the CD20 antigen found on >90% of B-cells
- **Chelator**
  The chelate tiuxetan, which tightly binds Yttrium-90, is covalently linked to ibritumomab
- **Radioisotope**
  Yttrium-90 is the high-energy beta emitter in ZEVALIN

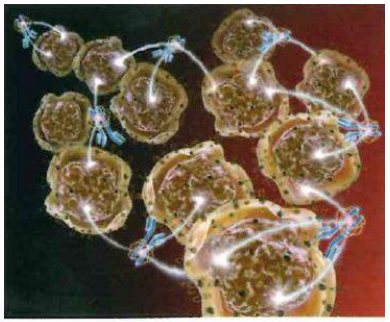




Monoclonal antibody targets the CD20 antigen found on >90% of B-cells



Y-90 isotope attacks surrounding B-cells with high energy beta radiation



Y-90 beta emissions induce cellular damage in target and neighboring cells via free radicals

^{90}Y-Ibritumomab tiuxetan (Zevalin ®)

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

Directions for radio-labeling of Zevalin with yttrium-90 :

Step 1 : Transfer sodium acetate solution to the reaction vial

The volume of sodium acetate solution added is equivalent to 1.2 times the volume of yttrium-90 chloride to be transferred in step 2。

Step 2 : Transfer yttrium-90 chloride to the reaction vial

Aseptically transfer 40mCi of yttrium-90 chloride with a 1 ml sterile syringe to the reaction vial containing the sodium acetate solution transferred in step 1。

Step 3 : Transfer ibritumomab tiuxetan solution to the reaction vial

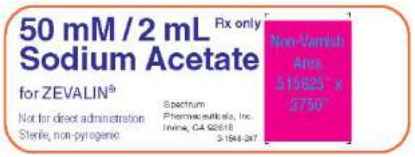
Add 1.3 ml ibritumomab tiuxetan solution to the reaction vial Mix completely by coating the entire inner surface of the reaction vial。

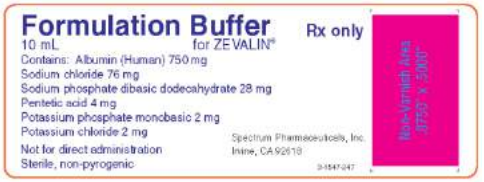
Incubate the Yttrium-90 chloride/acetate/ibritumomab tiuxetan solution at room temperature for five minutes

Step 4 : Add the formulation buffer to the reaction vial

Immrdiately add the formulation buffer to quench the labeling。

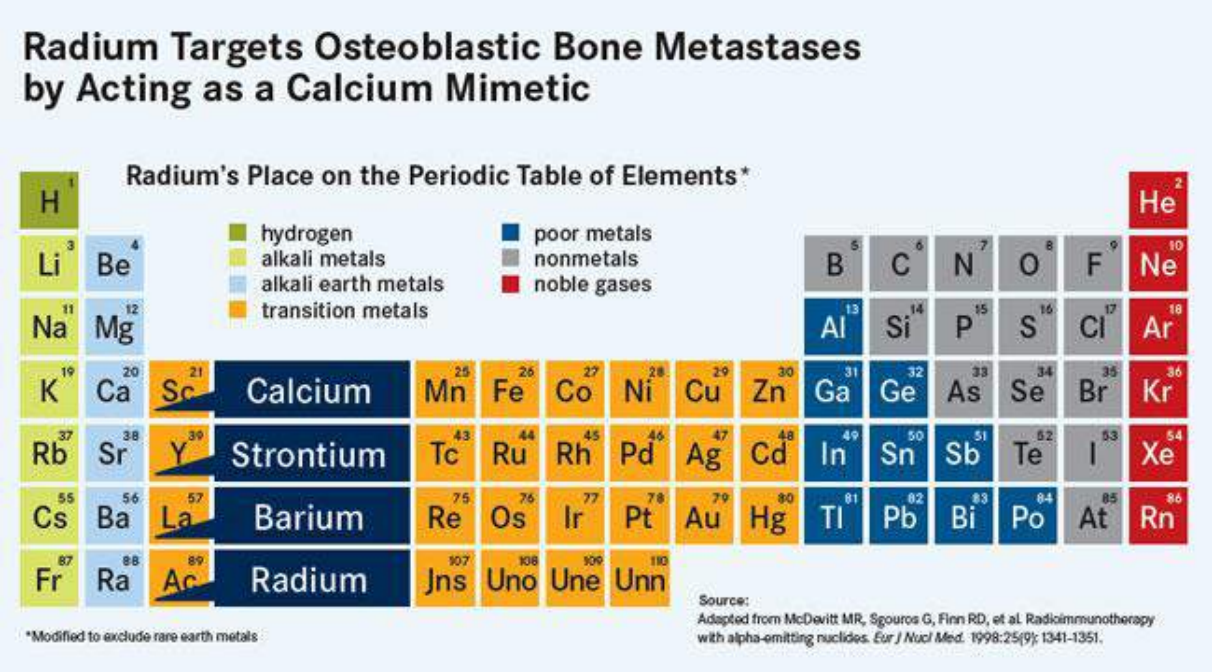
(FB volume = 10ml - the volumes of $^{90}YCl_3$ + acetate buffer + antibody)

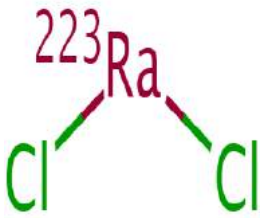


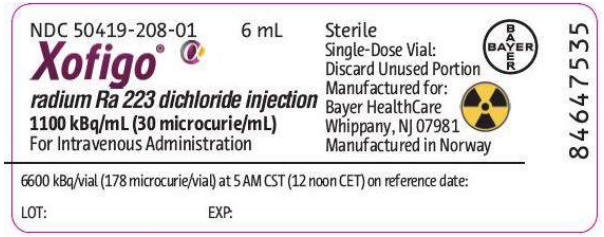


^{223}Ra-Dichloride (Xofigo®)

- Radium belongs to the same group of elements as Calcium.
- Radium-223 is a calcium mimetic that binds to newly formed bone stroma,
- Radium-223 mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover (ie, bone metastases)

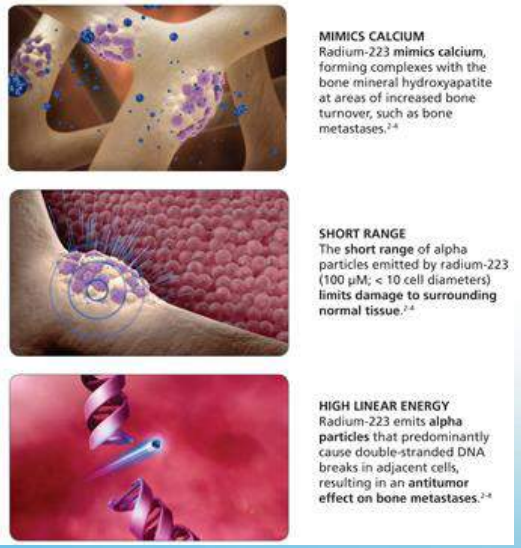






^{223}Ra-Dichloride (Xofigo®)

- Xofigo® is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease.
- $^{223}RaCl_2$ emits high-energy ionizing α- particle which cause lethal, double-strand DNA breaks in adjacent tumor cells in the bone.



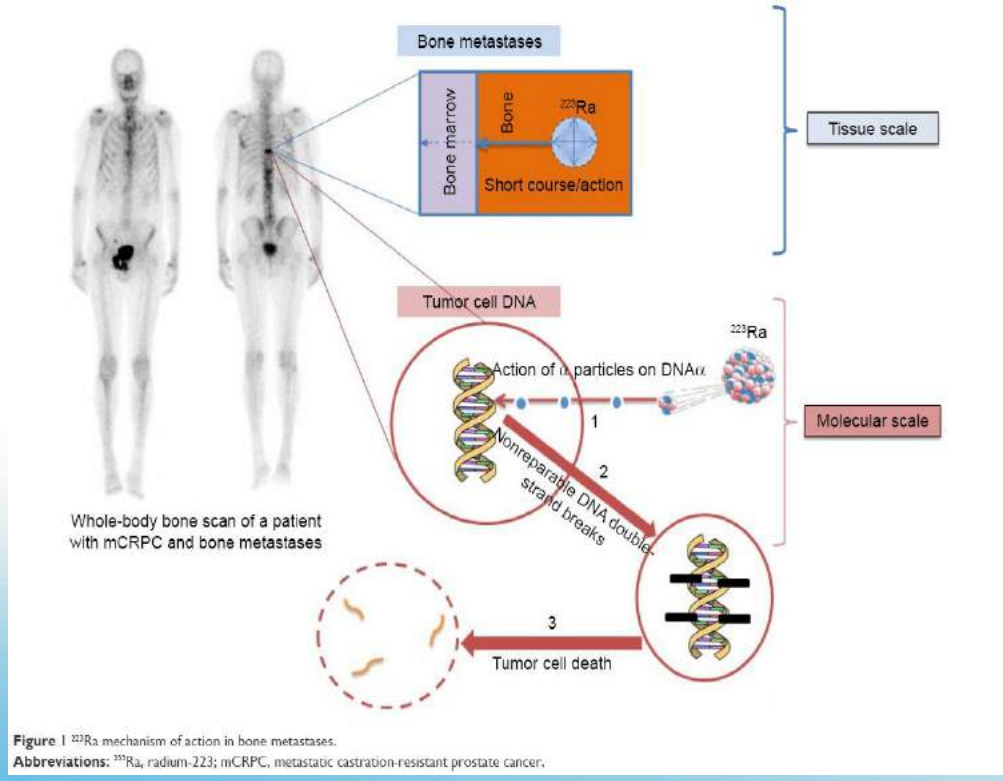
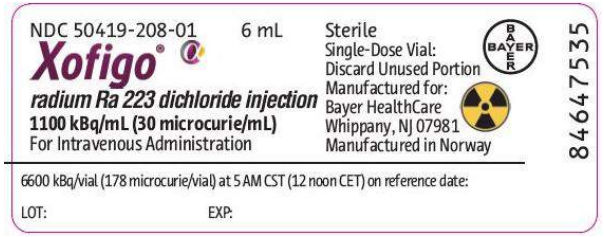


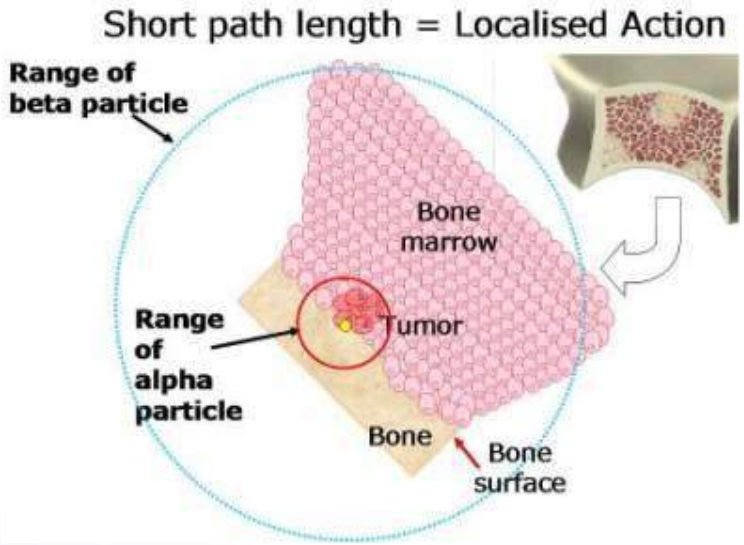
Figure 1 ^{223}Ra mechanism of action in bone metastases.
Abbreviations: ^{223}Ra, radium-223; mCRPC, metastatic castration-resistant prostate cancer.



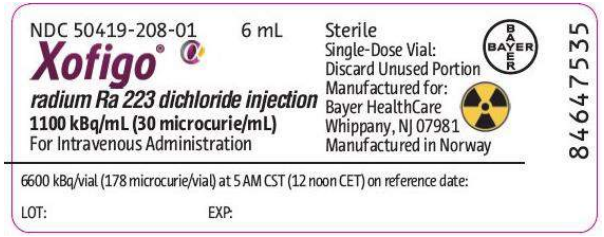
Why Alpha?

- α-particles have a high energy, but short path length - which minimizes damage to healthy tissue surrounding the cancer cells
- In contrast, ß-particles - used in bone pain palliation agents (e.g. Sr-89 Metastron, Sm-153 Quadramet) – produce low-energy radiation and a longer track length

	α	β
Relative particle mass	7000	1
Initial energy (MeV)	3–8	0.01–2.5
Range in tissue (µm)	40–90	50–5000
LET (KeV/µm)	60–230	0.015–0.4
Charge	+2	–1
Ion pairs/µm	2000–7000	5–20
DNA hits to kill cell	1–5	100–1000
Relative biological effectiveness	20	1

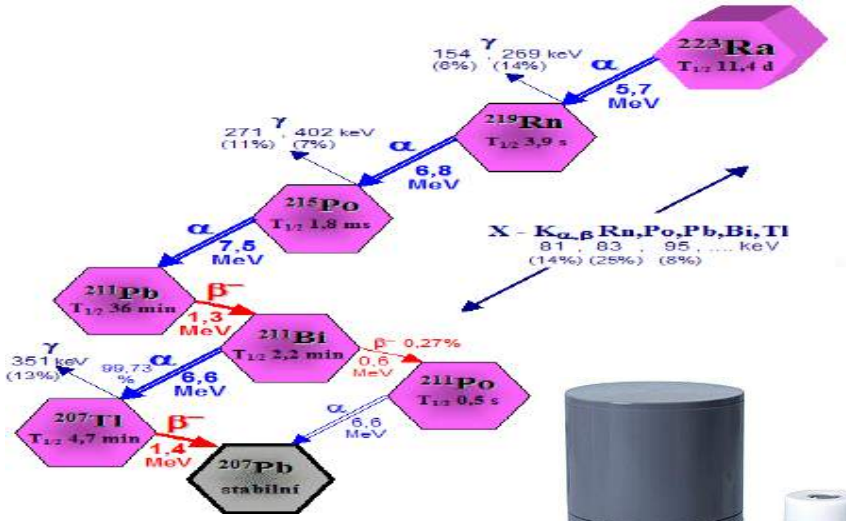


^{223}Ra-Dichloride (Xofigo®)



- Recommended Dosage :
  55 kBq (1.48 μCi) / kg body weight, given at 4-week intervals for 6 injections
- Radium-223 emits mainly α-particles
- Tumor-to-marrow ration : 30 : 1
- T1/2 = 11.43 days
- Of the total decay energy
  95.3 % emitted as α-particles
  3.6 % emitted as β-particles
  1.1 % emitted as γ- or X-rays

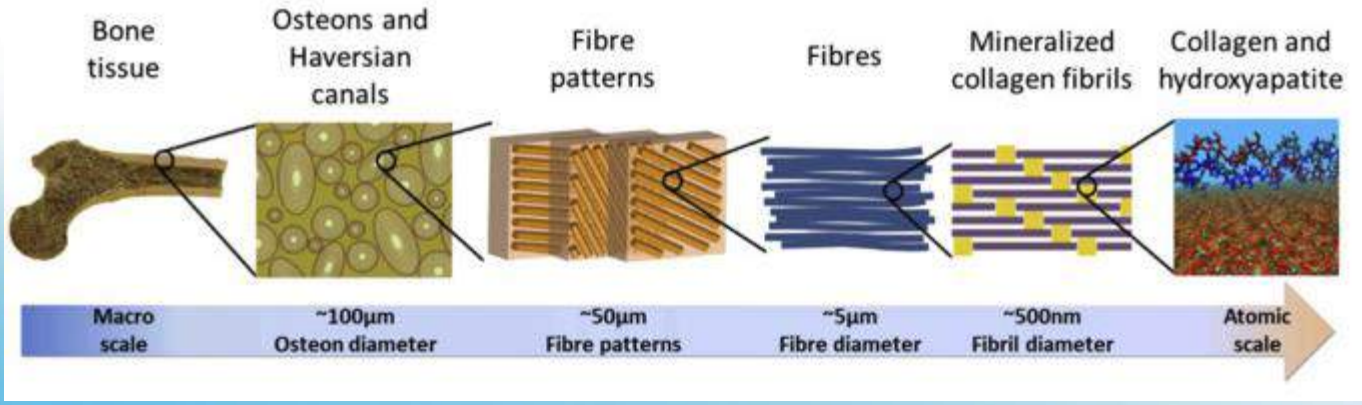
Hematologic	1`st	2`nd ~ 6`th
Absolute Neutrophil Count (ANC)	≥1,500/ul	≥1,000 /ul
Platelet count	≥100,000 /ul	≥50,000 /ul
Hemoglobin	≥10 g/dl	



Radium-223 decay chain[1]

Strontium-89 Chloride (Metastron™)

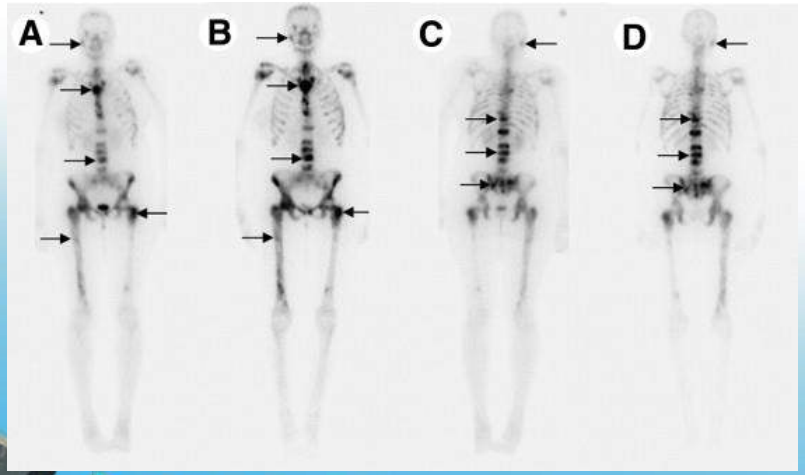
- Strontium-89 belongs to the same group of elements as Calcium.
- Strontium-89 mimics calcium, and is incorporated into hydroxyapatite in the bone after intravenous injection.
- Metastron is indicated for the relief of bone pain in patients with painful skeletal metastases.
- PRECAUTION ：Platelet counts below 60,000 and white cell counts below 2,400.
- Tumor-to-marrow ration： 10 : 1



Strontium-89 Chloride (Metastron™)

Comparison Between Bone Seeking Radiopharmaceuticals

Radiopharmaceutical	Standard Dose (SI)	Half-Life (d)	Beta Energy MeV (Maximum)	Gama Energy keV (%)	Maximum Penetration in Tissue (Average)	Remarks
P-32 phosphate	5-10 mCi (185-370 MBq)	14.3	1.71	None	8 mm (3 mm)	FDA approved, but rarely used nowadays.
Sr-89 chloride	4 mCi (148 MBq)	50.5	1.46	910 (0.01%)	6 mm (2.4 mm)	FDA approved longest half-life.
Sm-153 lexidronam	1 mCi /kg (37 MBq /kg)	1.9	0.81	103 (28%)	2.5 mm (0.6 mm)	Most common agent used in the United States.
Re-186 HEDP	35 mCi (1295 MBq)	3.8	1.07	137 (9%)	4.5 mm (1.1 mm)	Approved in Europe.
Re-188 HEDP	30-118 mCi (1.1-4.4 GBq)	0.7	2.12	155 (15%)	10.4 mm (3.1 mm)	Experimental, produced from a ^{188}W/^{188}Re generator



Expected targeting of osteoblastic metastases by Sm-153-ethylenediaminetetramethylene phosphonic acid scintigraphy. Anterior and posterior whole body bone scan images of a patient with metastatic prostate cancer demonstrating several osteoblastic lesions in the axial and appendicular skeleton (arrows). Images (A) and (C) were acquired 4 h after injection of Tc-99m-MDP whereas images (B) and (D) were acquired 2 h after a therapeutic dose (70 mCi) of Sm-153- ethylenediaminetetramethylene phosphonic acid. There is perfect match of the areas of osteoblastic metastases between the whole body scans.

Systemic Metabolic Radiopharmaceutical Therapy in the Treatment of Metastatic Bone Pain • Seminars in Nuclear Medicine_, Volume 40, Issue 2 March 2010, p 89-104

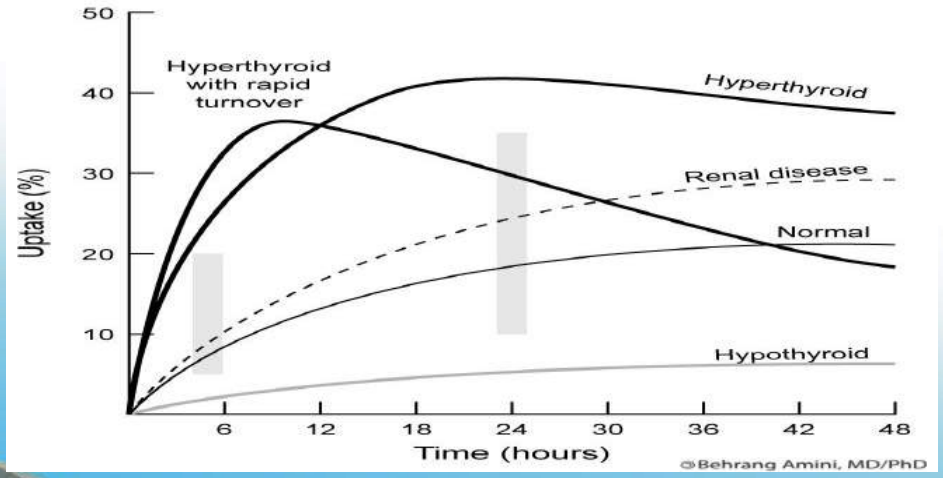
^{131}I- Sodium Iodide

- ^{131}I sodium iodide is available as a stabilized aqueous solution or solid capsule form for oral administration
- Radioiodine therapy is a nuclear medicine treatment for an overactive thyroid a condition called hyperthyroidism (Graves' disease、…) , and also may be used to treat thyroid cancer (Papillary and follicular thyroid carcinoma ..).

Thyroid Scan : Radionuclides			
Radionuclides	I-123	I-131	Tc-99m Pertechnetate
Decay	Electron	Beta- minus decay	Isomeric transition
T ½	13hrs.	8days	6hrs.
Energy kev	159	364	140
Radiation emitted	γ	γ & β	γ
Localization by	Active transport : Trapping & Organification		Active transport : Trapping
Administration	Oral	Oral	IV
Dose	100 ~ 400 μCi	50 ~ 100 μCi	3mCi

^{131}I- Sodium Iodide
- Thyroid radioiodine uptake curves

- Thyroid uptake may be quantified at 4-6 hours and at 24 hours. The gray bars define the rough normal ranges at 4-6 hours (5%-20%) and 24 hours (10%-35%).



http://roentgenrayreader.blogspot.com/2010/07/thyroid-radioiodide-uptake-raiu-curves.html

http://www.biodex.com/nuclear-medicine/products/atomlab-960-thyroid-uptake-system

Drug ,Food ,Radiographic Contrast Agents ,and Therapies that Decrease or Increases the %RAIU

Drug and Chemical Substances that Decrease 24hr Thyroid Uptake			
Substance	Avg . Duration of Effect	Substance	Avg . Duration of Effect
Iodide-Containing Drug		X-ray Contrast Media	
Lugol`s Solution	1 - 4 weeks	Hypaque Sodium	1 - 2 weeks
Vitamin –mineral products		Lipiodol , Ethiodol	1 year or more
Isopropamide iodide		Bracco	3months
Amiodarone , benziodarone		Nycomed	2months
Antithyroid Drugs		Thyroid Medication	
Methimazole , Propylthiouracil	2 - 8 days	Thyroid hormone , Thyroxine , Liothyronine	1 - 2 weeks

Drug and Chemical Substances that incresed 24hr Thyroid Uptake
Iodine Defiviency
Pregnancy
Rebound after therapy withdrawal (Thyroid hormone 、Antithyroid drug)
lithium

^{18}F-FDG (Fluorodeoxyglucose)

- Glucose analogue
- ^{18}F-FDG enter the cells using the same pathway as glucose (Glucose transporter (GLUT)) but is not used in glycolysis and metabolically trapped inside the cell after phosphorylation.
- Clinical application：

  Evaluating the extent of disease in known malignancies (staging/restaging)、Breast cancer 、 Colorectal cancer、 Melanoma、Heard and neck cancer 、 Lung cancer 、 Epilepsy、Alzheimer disease 、

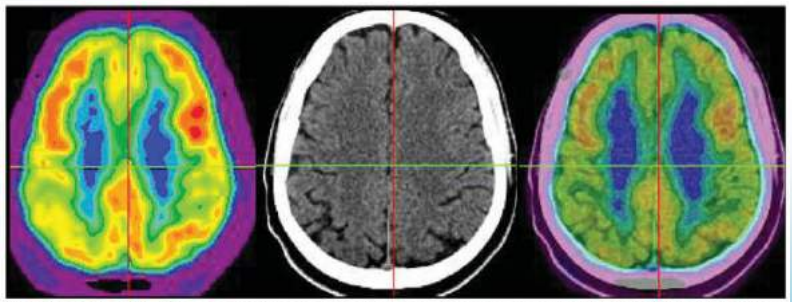
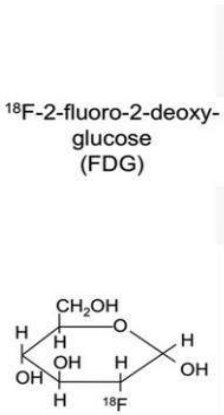
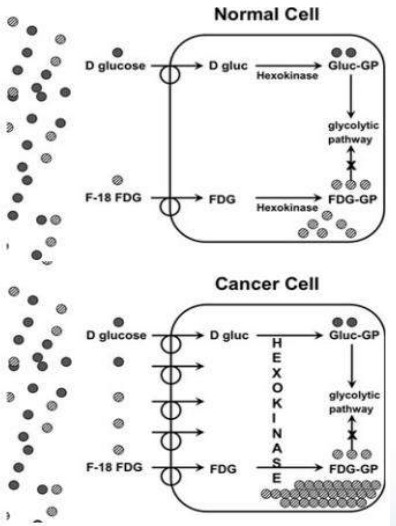


Fig. 3.2. The value of PET/CT in the evaluation of Alzheimer's disease – transverse plane FDG-PET (*left*), CT (*middle*) and fused PET/CT (*right*) images. Study reveals evidence of bilateral posterior parietal hypometabolism without evidence of significant cortical atrophy on CT

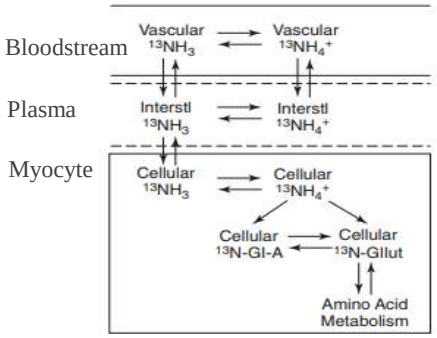
Clinical Nuclear Medicine,p78





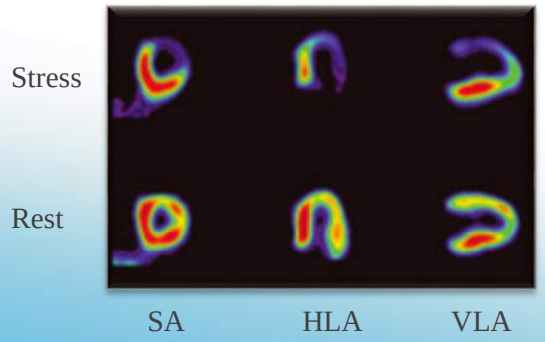
Physiologic biodistribution of tracer. The Brain 、salivary glands、Thyroid 、Myocardium 、 liver-spleen、 kidneys 、 bladder show a major uptake ^{18}F-FDG

^{13}N-Ammonia



- It`s 9.96-minute half-life requires an on-site cyclotron ^{16}O (p, α) ^{13}N and synthesis.
- In the bloodstream, ^{13}N-Ammonia consists of neutral NH_3 in equilibrium with its charged ammonium (NH_4) ion . The neutral NH_3 molecule readily diffuses across plasma and cell membranes, Inside the myocyte, it re-equilibrates with its ammonium form, which is trapped in glutamine via the enzyme glutamine synthase.
- Clinical application：

  Evaluation of myocardial perfusion in patients with suspected or existing coronary artery disease



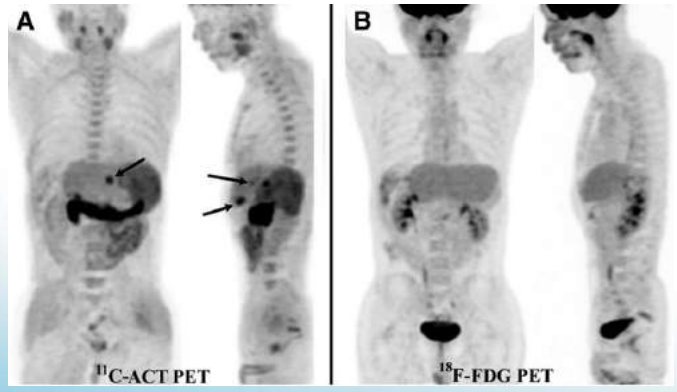
^{13} N-Ammonia PET images demonstrating anterior and lateral defects during pharmacological stress and significant improvement at rest, consistent with ischemia.

Common Cardiac PET Tracers			
Tracer	Half-Life	Machaism	Production Method
N-13 Ammonia	9.8min	Perfusion	Cyclotron
Rb-82	75sec	Perfusion	Generator
O-15 H_2O	2min	Perfusion	Cyclotron
F-18FDG	109min	Glucose metabolism	Cyclotron

^{11}C-Acetate

- It`s 20-minute half-life requires an on-site cyclotron ^{14}N (p, α) ^{11}C and synthesis.
- The main mechanism for in vivo retention is conversion of acetate by acetyl-CoA synthetase in either the cytosol and/or mitochondria to acetyl-CoA. Acetyl-CoA is then converted by fatty acid synthetase into fatty acids and incorporated into the intracellular phosphatidylcholine membrane microdomains (dominant pathway in cancer cells) or alternatively oxidized through the tricarboxylic acid cycle in mitochondria to carbon dioxide and water (dominant pathway in normal myocardium)
- Clinical application：

  Prostate cancer 、 HCC、 renal cell carcinoma 、 bladder carcinoma .

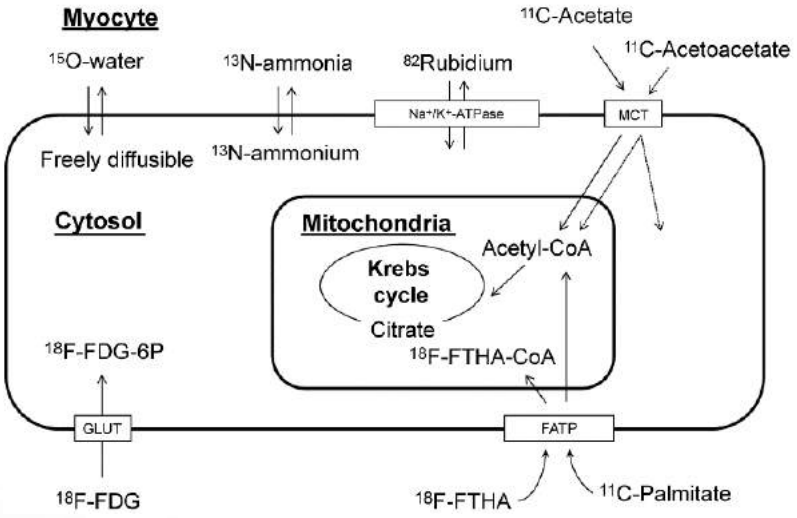


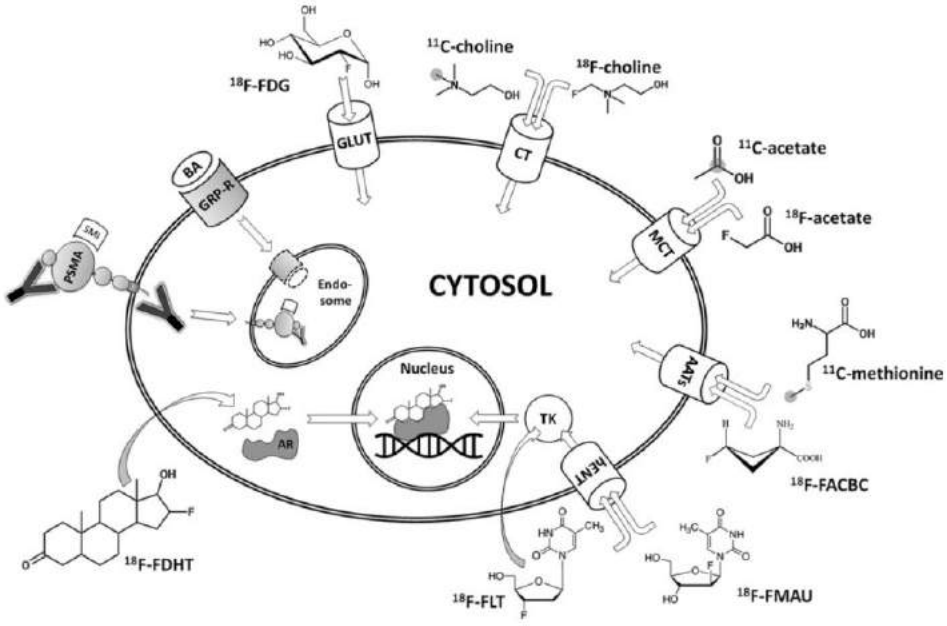
. Maximum-intensity-projection PET images of typical patient who had HCC and met Milan criteria. Three hypermetabolic liver lesions (arrows), each smaller than 3 cm, in left lobe (after right hepatectomy) were avid for 11C-ACT (A) but not 18F-FDG (B). There was no extrahepatic metastasis

Physiologic biodistribution of tracer. The salivary glands、liver、spleen、pancreas show a major uptake ^{11}C-Acetate

Cheung et al. J Nucl Med 2013;54:192-200

Diagram of an overview of molecular imaging strategies currently applied for Myocardial blood flow / Prostate cancer



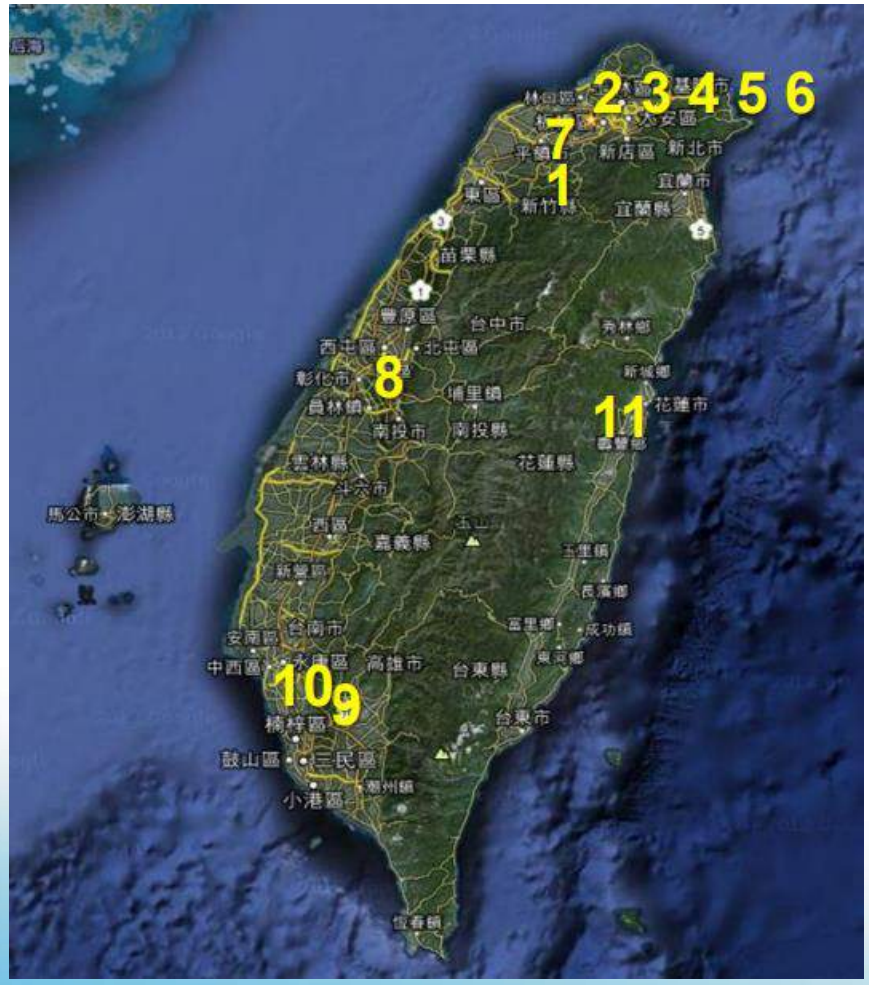


AATs = amino acid transporters, AR = androgen receptor, BA = bombesin analog, CT = choline transporter, 18F-FACBC = anti-fluorine 18 (18F)-1-amino-3-fluorocyclobutane-1-carboxylic acid,, 18F-FDHT = 18F-16b-fluoro-5a-dihydrotestosterone, 18F-FLT = 18Ffluorothymidine, 18F-FMAU = 18F-fluoro-methyl-arabinofuranosyl-uracil, GRP-R = gastrin-releasing peptide receptor, hENT = human equilibrative nucleoside transporter, PSMA = prostate-specific membrane antigen, SMI = small molecule inhibitor, TK = thymidine kinase, Y = antibody, Glucose transporters (GLUT), 18-fluorodeoxyglucose-6-phosphate (^{18}F-FDG-6-P), Monocarboxylate transporter (MCT), 14(R,S)-Fluoro-6-Thia-Heptadecanoic Acid (FTHA), Fatty acid transport protein (FATP).

Croteau et al., J Clin Toxicol 2014, 4:5
https://pubs.rsna.org/doi/pdf/10.1148/rg.2016150059

目前臺灣生產正子放射同位素藥品機構

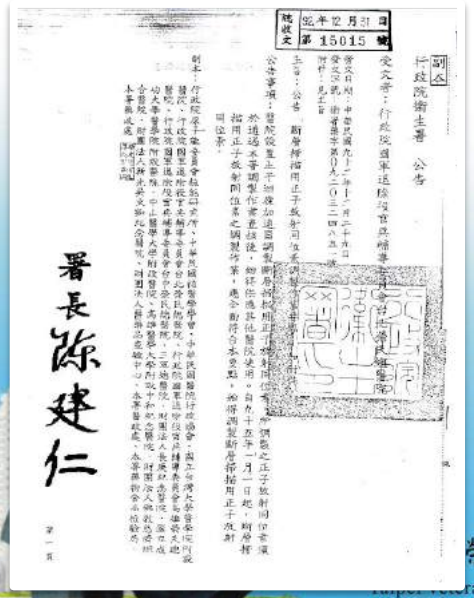
- 1. 核能研究所 - 藥廠
- 2. 士宣生技(股)公司 - 藥廠
- 3. 臺北榮民總醫院
- 4. 新光吳火獅紀念醫院
- 5. 國立臺灣大學醫學院附設醫院
- 6. 三軍總醫院
- 7. 長庚紀念醫院林口分院
- 8. 中山醫學大學附設醫院
- 9. 義守大學附設醫院
- 10.阮綜合醫院
- 11.佛教慈濟醫學中心

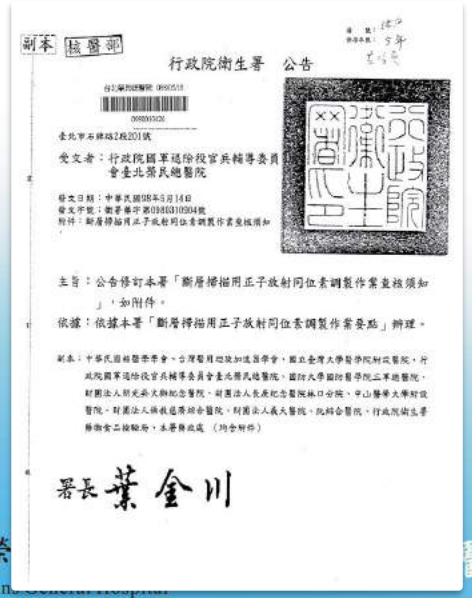


PET Radiopharmaceuticals	
Nuclide	Half - life (min)
C-11	20
N-13	10
O-15	2
F-18	110
Ga-68	68

醫院調製正子放射同位素藥品法規依據

- 92年12月29日衛署藥字第0920324851號公告 「斷層掃描用正子放射同位素調製作業要點」
- 98年5月14日衛署藥字第0980310904號公告修訂「斷層掃描用正子放射同位素調製作業查核頇知」
- 104年9月4 日FDA 藥字第1041404179 號 公告修訂「斷層掃描用正子放射同位素調製作業要點
- 108年4月2 日FDA 藥字第1071410139 號 公告訂定「斷層掃描用正子放射同位素優良調製作業指引

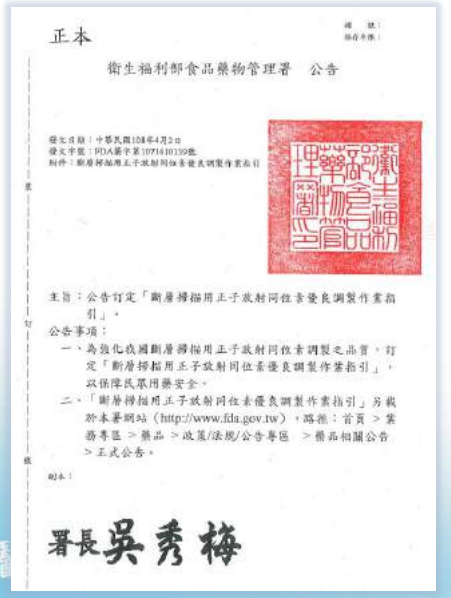

署長陳建仁


行政院衛生署 公告

署長葉金川


衛生福利部食品藥物管理署 公告

署長姜郁美


正本

衛生福利部食品藥物管理署 公告

署長吳秀梅

國內醫院已核備可調製正子放射同位素藥物

醫院	已核備調製正子掃描造影藥物
臺北榮民總醫院	F-18-FDG、C-11-Sodium acetate、N-13-Ammonia、F-18-Sodium fluoride
新光吳火獅紀念醫院	F-18-FDG
國立臺灣大學醫學院附設醫院	F-18-FDG、F-18-Sodium fluoride、F-18-FDOPA
三軍總醫院	F-18 FDG、F-18-Sodium fluoride
長庚紀念醫院林口	F-18 FDG、F-18-Sodium fluoride、F-18 FLT、C-11 Sodium acetate
中山醫學大學附設醫院	F-18 FDG、F-18-Sodium fluoride、F-18 FLT
義守大學附設	F-18 FDG、F-18-Sodium fluoride
阮綜合醫院	F-18 FDG、F-18-Sodium fluoride、C-11 Sodium acetate
佛教慈濟醫學中心	F-18 FDG、F-18-Sodium fluoride、F-18 FDOPA

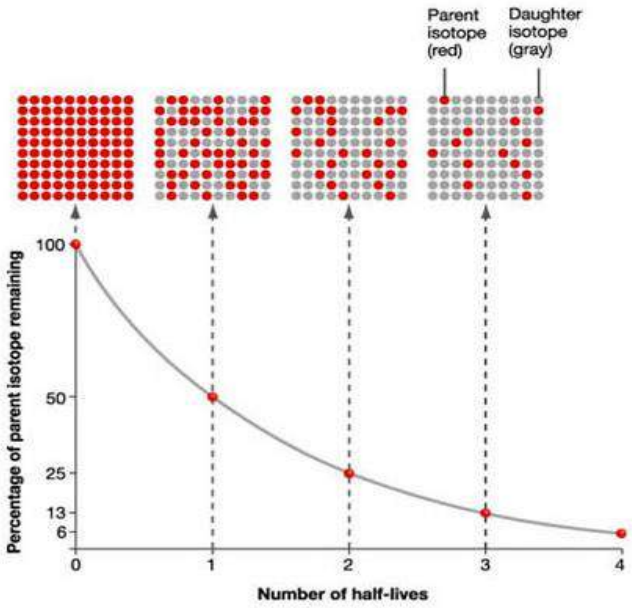
Practice of Nuclear Pharmacy

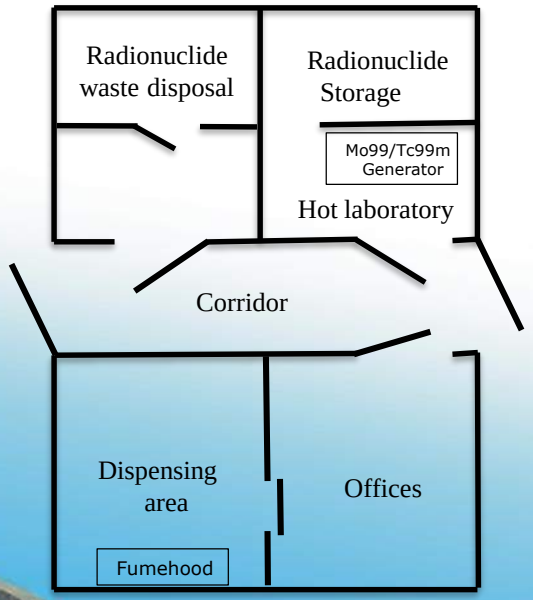
- Procurement and Storage
- Preparation
- Quality assurance
- Dispensing
- Distribution
- Health and Safety
- Provision of Information and Consultation
- Monitoring patient outcome
- Regulatory process

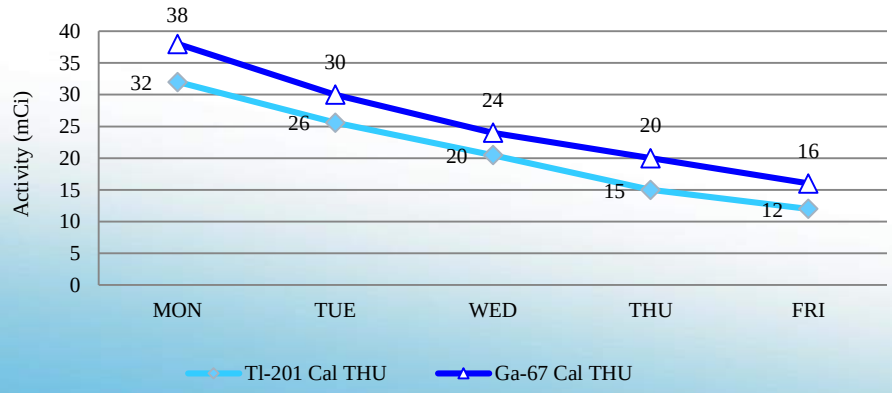
Type of Nuclear Pharmacies
Institutional nuclear pharmacy
Commercial centralized nuclear pharmacy

Practice of Nuclear Pharmacy - Procurement and Storage

- Radioactivity & nonradioactivity drug
- Radioactive Decay and half-life
- Calibration time
- Restricted area







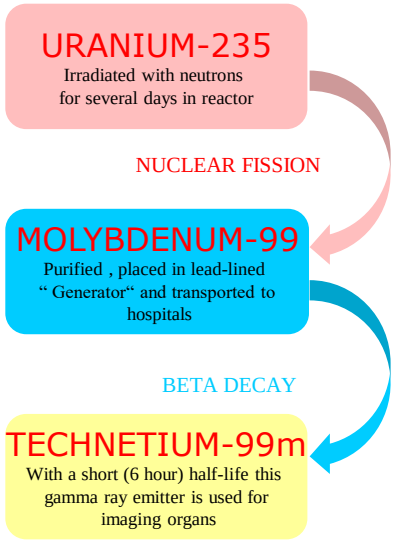
Practice of Nuclear Pharmacy – Preparation

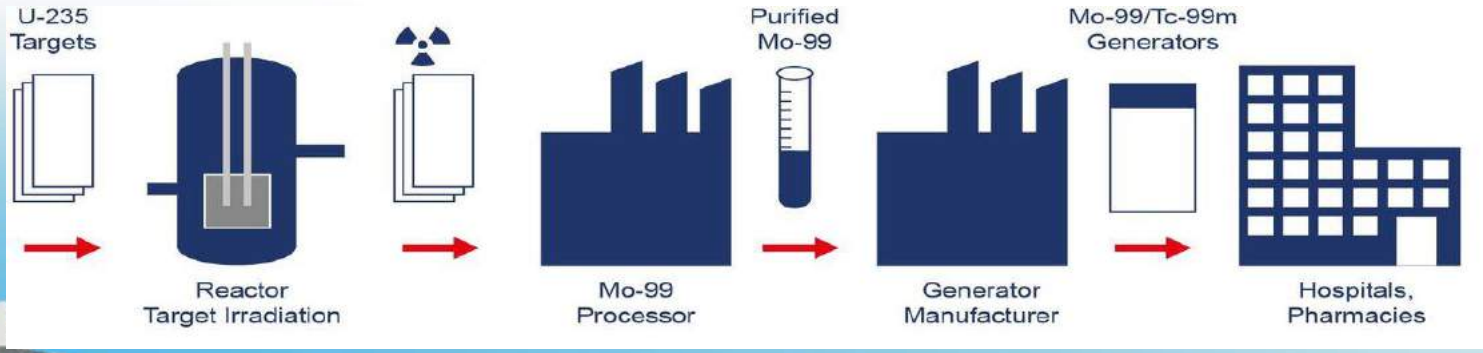
	Examples
Ready-to-use prepared product	^{133}Xe gas , ^{131}I-Hippuran ^{67}Ga-citrate , ^{201}Tl-chloride , $^{99m}TcO_4$ $^{223}Ra\text{-}Cl_2$
Instant ^{99m}Tc kit	DTPA , MDP , DISIDA , MAA PYP , HMPAO, Phytate ….
^{99m}Tc kits requiring heating	Sestamibi , MAG_3 , Sulfur colloid
Products requiring significant manipulation	^{99m}Tc-Trodat-1 , ^{99m}Tc-ECD ^{131}I-NP59 , ^{111}In-pentetreotide, ^{99m}Tc-RBC , ^{223}Ra-Dichloride (Xofigo®) ^{90}Y-Resin Microspheres (SIR-Spheres®) ^{90}Y-Glass Microspheres (Thera-Spheres®) ^{18}FDG , $^{13}NH_3$, ^{11}C-sodium acetate…

Practice of Nuclear Pharmacy –

Preparation - Mo-99/Tc-99m generator systems

- The Current Mo-99 Supply Chain consists of :
  - Uranium Target manufactures
  - Nuclear research reactors for target irradiation
  - Processing facilities to dissolve the irradiated target and extract Mo-99
  - Mo-99 / Tc-99m generators manufacturers
  - Radiopharmacies to elute Tc-99m from the Generator and prepare radiopharmaceutical doses to be injected to the patient for diagnosis





Practice of Nuclear Pharmacy – Preparation - Mo-99/Tc-99m generator systems

Current Status of Mo-99 Supply

Reactors	Countries	Targets	Operating weeks / year	Irradiation capacities / week [6-day Ci]	Irradiation capacities / year [6-day Ci]	End of operation
BR2	Belgium	HEU	21	7 800	163 800	> 2026
HFR	The Netherlands	HEU	39	6 200	241 800	2024
(NRU)	***(Canada)***	***(HEU)***	***(40)***	***(4 680)***	***(187 200)***	***(Nov 2016)***
SAFARI	South Africa	HEU/LEU	44	3 000	130 700	2030
LVR-15	Czech Republic	HEU	30	3 000	90 000	2028
MARIA	Poland	HEU	36	2 700	95 000	2030
OPAL	Australia	LEU	43	2 150	92 450	2055
RA-3	Argentina	LEU	46	400	18 400	2027

Irradiators	Countries	Targets	Operating weeks / year	Irradiation capacities / week [6-day Ci]	Irradiation capacities / year [6-day Ci]	Full production
RIAR	Russia	HEU	50	1 000	50 000	2015
KARPOV	Russia	HEU	48	350	16 800	2015
MURR	NorthStar USA	Mo-98 natural	52	750	39 000	2017
MURR	NorthStar USA	Mo-98 enriched	52	2 250	117 000	2018
NORTHSTAR	USA	Mo-100 LINAC	52	3 000	156 000	2018
FRM-II	Germany	LEU	32	2 100	67 200	2019
MURR/GA	USA	LEU	52	4200	218 000	2019
SHINE	USA	LEU solution	50	4 000	200 000	2020
KJRR	Korea	LEU	43	400	17 200	2020
RA-10	Argentina	LEU	48	2 500	120 000	2020
CARR	China	LEU	34	1 000	34 000	2021
RMB	Brazil	LEU	41	1 000	41 400	2021
JHR	France	LEU	32	4 800	153 000	2021


Nuclear Research Centre's Belgian Reactor 2 (BR2)


High Flux Reactor (HFR)


SAFARI-1 Reactor


LVR-15 REZ Reactor


Maria Research Reactor

Practice of Nuclear Pharmacy –

Preparation - Mo-99/Tc-99m generator systems

Interruptions of Mo-99 Supply (2009-2018)

Year(s)	Reactor or Processing Facility	Duration of Facility Shutdown	Planned or Unplanned Shutdown	Reason for Shutdown
2008-2009	HFR (Netherlands)	6 months	unplanned	Gas bubbles detected in the main cooling system
2009-2010	NRU (Canada)	14 months	unplanned	Reactor vessel welding repairs
2010	HFR	6 months	unplanned	Repair of a primary cooling pipework
2012-2013	HFR	8 months	unplanned	Repair of a primary cooling pipework
2013-2014	HFR	6 months	unplanned	Issue with control rod
2013-2014	NTP (South Africa)	2 months	unplanned	Positive pressure in a hot cell caused a leak of noble gases
2013-2014	SAFARI-1 (South Africa)	2 months	unplanned	NTP processing facilities shutdown
2013-2014	Mallinckrodt (Netherlands)	6 months	unplanned	HFR unplanned outage
2015	HFR	1 reactor cycle	unplanned	Maintenance
2015-June 2016	BR-2 (Belgium)	16 months	planned	Major refurbishment

SNMMI Value Initiative
SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

ALERT: Significant Shortages of Mo-99 Expected in November

October 31, 2018

A significant shortage of Mo-99 is expected for the first half of November.

The NTP facility in South Africa, which has experienced problems since late last year, has not yet been able to return to service.

The NTP shutdown coincides with a planned 11-day shutdown of the OPAL reactor in Australia that began October 29, so significant shortages of Mo-99 are anticipated starting in early November.

With significant shortages anticipated, it is essential that users contact their generator/nuclear pharmacy providers for advice about their local situation.

The Association of Imaging Producers & Equipment Suppliers (AIPES) Emergency Response Team is closely following the situation. The group issued an update on October 30, and SNMMI will post updates as they become available.

MEMBERS: If your institution is experiencing a generator shortage, please consider posting this information on SNMMI Connect so that SNMMI leadership can use this information in future discussions with the U.S. Department of Energy about expanding domestic production of Mo-99.

NRG

High Flux Reactor back in operation

Update Wednesday 31th of October 2018

Last week on Thursday 0.9 cubic metres of water with radioactive contamination (including tritium) was released into the basement of the pump building next to the High Flux Reactor, and has run into the ground beneath the building. The reactor was shut down and the regulator ANVS informed. It concerned a malfunctioning valve used to close off pipe work in the pump building. NRG immediately repaired the leak in the pipework, took the valve out of service, and took measures to prevent reoccurrence. Subsequent measures have been agreed with the regulator, including a plan for ground remediation. The investigation into the events leading up to the incident has begun, but is not yet completed.

NRG has provided further clarification on the measures already taken this morning, and on this basis the regulator has judged that the reactor can be safely restarted. This afternoon NRG has restarted the reactor following normal protocol. Employees have been informed about the actual status. Nearby residents will also receive further information from us about what the leakage means for the nearby residents.

Because the reactors of four of the six large producers of medical isotopes worldwide are currently out of operation, a global shortage of these products threatens. Cancer patients, and also for instance people with a thyroid disorder, are dependent on the isotopes that are made in Petten for their treatment. Now the reactor has been restarted, the first deliveries of molybdenum can be expected in a week. In a week and a half we expect to be back at normal production levels.

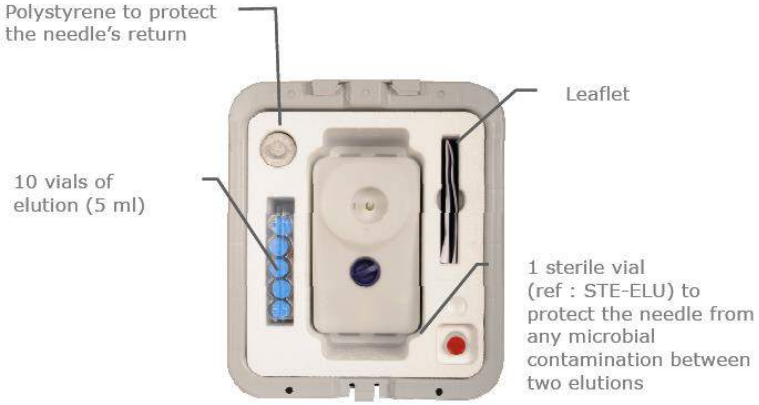
Practice of Nuclear Pharmacy –

Preparation - Mo-99/Tc-99m generator systems

TEKCIS®
2-50 GBq radionuclide generator

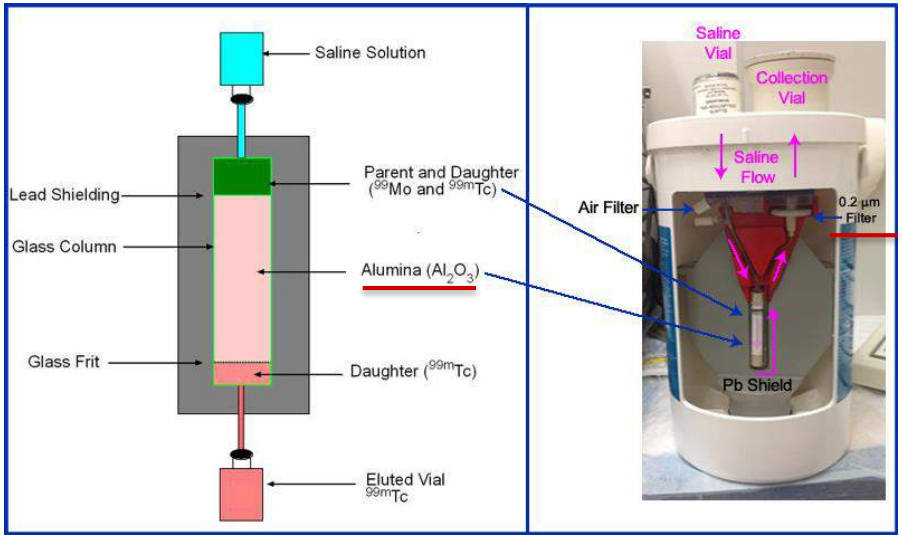
Elution solution : aqueous sterile and pyrogen free 0.9 % sodium chloride and 0.005% sodium nitrate solution.

Availability and Calibration	on Monday calibrated Saturday 12 a.m. on Tuesday calibrated Saturday or Wednesday (following week) 12 a.m. on Wednesday calibrated Wednesday (following week) 12 a.m. on Thursday calibrated Wednesday 12 a.m. on Friday calibrated Wednesday or Saturday (following week) 12 a.m.
Ordering deadline	3 days before the shipment day, before 11 a.m.
Expiry	20 days after the manufacturing date
Elution volume	5, 10 or 15 mL
Radiochemical purity	≥ 95 %
Radionuclidic purity	^{99}Mo ≤ 0.1 %, ^{131}I ≤ 5.10^{-3} %, ^{103}Ru ≤ 5.10^{-3} %, ^{89}Sr ≤ 6.10^{-5} %, ^{90}Sr ≤ 6.10^{-6} %, α ≤ 1.10^{-7} %, other γ ≤ 0.01 % at the date indicated on the label
pH	4.0-8.0
Storage	- Generator : 20 days. Not above 25°C. - Sodium (^{99m}Tc) pertechnetate solution : store at 2-8°C and use within 10 hours after elution.
Precalibred quantities	2 - 4 - 6 - 8 - 10 - 12 - 16 - 20 GBq
Indications	1. Reagent for labelling various kits to be used with ^{99m}Tc 2. Administered intravenously the eluate might be used in : • Thyroid scintigraphy • Salivary gland scintigraphy • Localization of ectopic gastric mucosa • Cerebral scintigraphy 3. In conjunction with a reducing agent for labelling red blood cells for : • Cardiac and vascular scintigraphy • Diagnosis and localisation of occult gastrointestinal bleeding 4. Administered by instillation into the eye for : • Lacrymal duct scintigraphy



Practice of Nuclear Pharmacy –

Preparation - Mo-99/Tc-99m generator systems



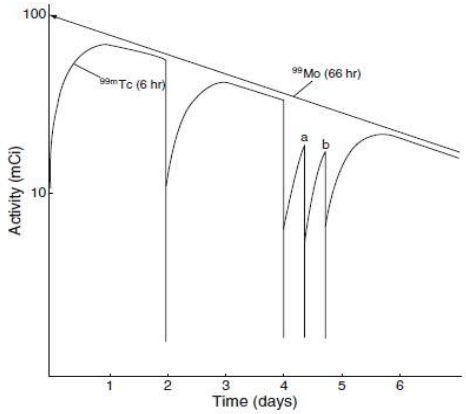


FIGURE 5.2. Typical decay growth relationship of ^{99}Mo and ^{99m}Tc activities in a Moly generator. On day 2, ^{99m}Tc activity is eluted with saline and then starts growing after elution. The yield of ^{99m}Tc is approximately 80 90%. It takes approximately 24 h to reach maximum activity of ^{99m}Tc after elution. Positions *a* and *b* indicate elutions of ^{99m}Tc activity at 8 and 17 h after elution on day 4.

Sunday Manufactured

Expected mCi of Tc 99m at 2:00 a.m. EST

Gen Size	1 day Post Cal	2 day Post Cal	3 day Post Cal	4 day Post Cal	5 day Post Cal	6 day Post Cal	7 day Post Cal	8 day Post Cal	9 day Post Cal	10 day Post Cal	11 day Post Cal	12 day Post Cal	13 day Post Cal	14 day Post Cal
1000	701	573	447	348	270	210	163	127	98	76	59	46	36	28
2000	1403	1146	894	695	540	420	326	253	197	153	119	92	72	56
2500	1754	1433	1118	869	675	525	408	317	246	191	149	115	90	70
3000	2104	1720	1341	1043	810	629	489	380	295	229	178	139	108	84

3:00 PM (15:00) Taiwan Time = 2:00 AM (2:00) EST

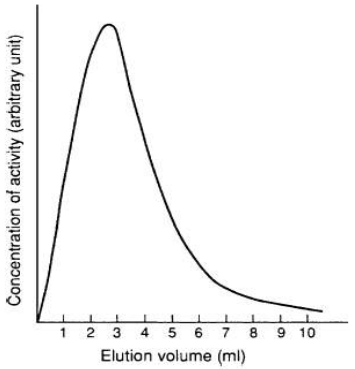


FIGURE 5.4. Elution profile of the ^{99m}Tc activity expressed as concentration of radio activity versus eluate volume. The profile may be broader or narrower depending on the type of generator. For generators using fission produced ^{99}Mo, the eluate volume is about 2 3 ml due to the smaller alumina column.

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http://www.people.vcu.edu/~mhcrosthwait/clrs461/Radionuclide%20Production2.html

Practice of Nuclear Pharmacy – Preparation - Mo-99/Tc-99m generator systems

- $(NH_4)_2{}^{99}MoO_4$
  Ammonium molybdate

- $^{99}MoO_4^{-2}$ → $^{99m}TcO_4^{-1}$

- $Na^{99m}TcO_4$
  Sodium Pertechnetate

A **technetium-99m generator**, or colloquially a **technetium cow** or **moly cow.**

Elution or " milking " of the generator is carried out under aseptic conditions.

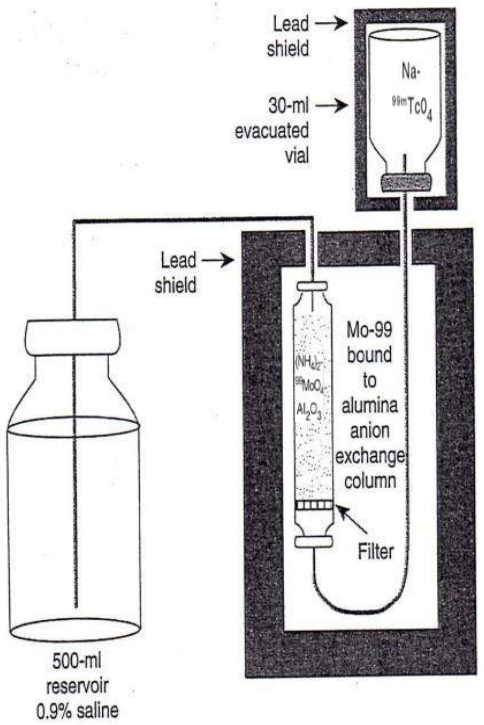

Figure 1-3 "Wet" radionuclide generator system.

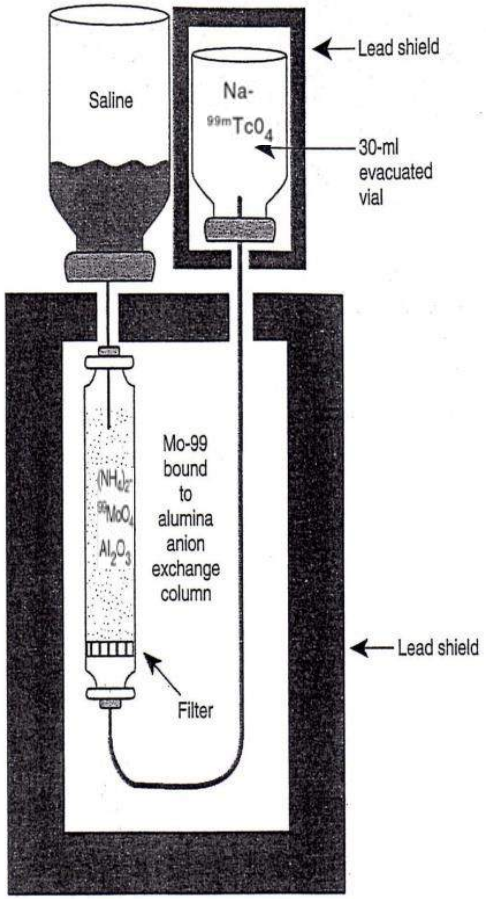

Figure 1-4 "Dry" radionuclide generator system.

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Practice of Nuclear Pharmacy –

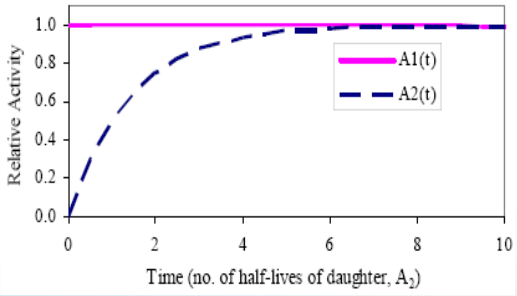
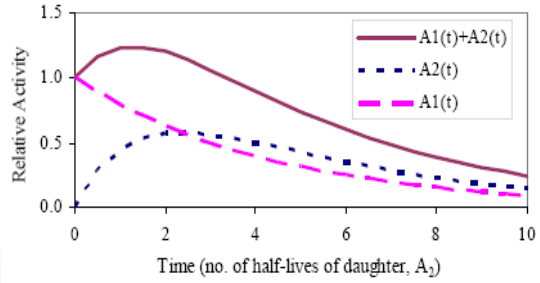
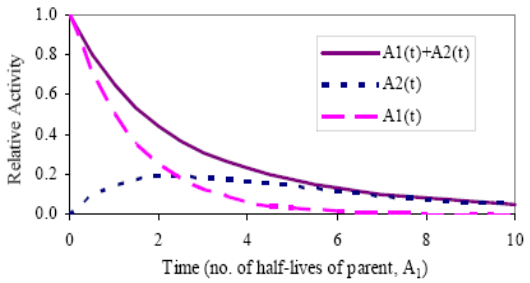
Preparation - Mo-99/Tc-99m generator systems

Radionuclides	Parent(Mo-99)	Daughter(Tc-99m)
Half-life	66hr	6hr
Mode of decay	β^-	Isomeric transition
Daughter products	Tc-99m ,Tc-99	Tc-99
Principal photon energies	740keV ,780keV	140keV(89%)

Generator function	
Composition of ion exchange column	Al_2O_3
Eluant	Normal saline
Time from elution to maximum daughter yield	23hr

Practice of Nuclear Pharmacy –

Preparation - Mo-99/Tc-99m generator systems

永久平衡 (Secular equilibrium)	暫態平衡 (Transient equilibrium)	不平衡 (No equilibrium)
母核 $T_{1/2}$>>子核$T_{1/2}$ 100倍以上	母核 $T_{1/2}$>子核$T_{1/2}$ 10-100倍	母核 $T_{1/2}$<子核$T_{1/2}$
		
達平衡時放射活度： $A_2 \fallingdotseq A_1$	$A_2 = \frac{\lambda_2}{\lambda_2 - \lambda_1} A_1$	
$^{68}Ge \xrightarrow{\beta^-} {}^{68}Ga$ $T_{1/2}=275d$ $T_{1/2}=68\,min$	$^{99}Mo \xrightarrow{\beta^-} {}^{99m}Tc$ $T_{1/2}=67h$ $T_{1/2}=6h$	$^{218}Po \xrightarrow{\alpha} {}^{214}Pb$ $T_{1/2}=3\,min$ $T_{1/2}=27\,min$

Practice of Nuclear Pharmacy –

Preparation - $^{68}Ge/^{68}Ga$ generators

Examples of commercial $^{68}Ge/^{68}Ga$ generators.

	Eckert & Ziegler Cyclotron Co. Ltd.	Eckert & Ziegler IGG100 and IGG101 GMP; Pharm. Grade	I.D.B. Holland B.V.	Isotope Technologies Garching
				
Column matrix	TiO_2	TiO_2	SnO_2	SiO_2/organic
Eluent	0.1 M HCl	0.1 M HCl	0.6 M HCl	0.05 M HCl
^{68}Ge breakthrough	<0.005%	<0.001%	~0.001%	<0.005%
Eluate volume	5 mL	5 mL	6 mL	4 mL
Chemical impurity	Ga: <1 μg/mCl Ni < 1μg/mCl	Fe: <10 μg/GBq Zn: <10 μg/GBq	<10 ppm (Ga, Ge, Zn, Ti, Sn, Fe, Al, Cu)	Only Zn from decay
Weight	11.7 kg	10 kg 14 kg	26 kg	16 kg

Preparation (^{99m}Tc)	Manufacturing (^{68}Ga)
1. Generator elution into **product** vial with API	1. Generator elution into **reaction** vial
2. Labelling in the **product** vial	2. Labelling in the reaction vial
	3. **Purification** of the product
3. Formulation	4. Formulation
	5. **Sterile filtration**
	6. **Quality control**
	7. Dispensing
4. Release	8. Release

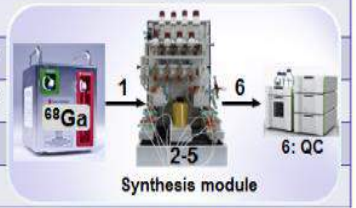


Table 2 – ^{99m}Tc tracers with their ^{68}Ga analogs.

Diagnostics	^{99m}Tc	^{68}Ga
Peptide receptors	^{99m}Tc-HYNIC-peptide	^{68}Ga-DOTA-peptide
Bone metastases	^{99m}Tc-MDP	^{68}Ga-phosphonates
Renal function	^{99m}Tc-DTPA/MAG3/DMSA	^{68}Ga-EDTA
Cardiac function	^{99m}Tc-RBC/MIBI	^{68}Ga-BAPEN
Lung function	^{99m}Tc-MAA	^{68}Ga-MAA
Hepatobiliary	^{99m}Tc-IDA	^{68}Ga-IDA
Infection	^{99m}Tc-WBC	^{68}Ga-citrate
Brain imaging (perfusion)	^{99m}Tc-ECD	^{68}Ga-ECD

Table 3 – ^{68}Ga analogs to commonly used ^{18}F and ^{11}C PET tracers.

Diagnostics	$^{18}F/^{11}C$	^{68}Ga
Angiogenesis	^{18}F-galacto-RGD	[^{68}Ga]DOTA-RGD, ^{68}Ga-VEGF
General cancer imaging	^{18}FDG	^{68}Ga-CXCR4 biomarker, ^{68}Ga-uPAR biomarker, ^{68}Ga-SCN-NOTA-BZA
Hypoxia	^{18}F-nitroimidazloes (FAZA, FMISO, FETNIM)	^{68}Ga-DOTA-imidazoles
Proliferation	^{18}FLT	^{68}Ga-DO3A-thymidine
Glioma	^{18}FET, ^{11}C-methionine	^{68}Ga-glutamine, ^{68}Ga-DO3A-alanine, ^{68}Ga-DO2A-tyrosine,
Prostate cancer	^{18}FDG, ^{11}C-acetate, ^{18}F-choline, ^{11}C-choline	^{68}Ga-DOTA-PSMA

Peptide analogs : TOC (Tyr3-OC), TATE (Tyr3-Thr8-OC) and NOC (Nal3-OC)
PSMA : prostate specific membrane antigen

Practice of Nuclear Pharmacy –

Preparation - Mo-99/Tc-99m generator systems

Elution Cell

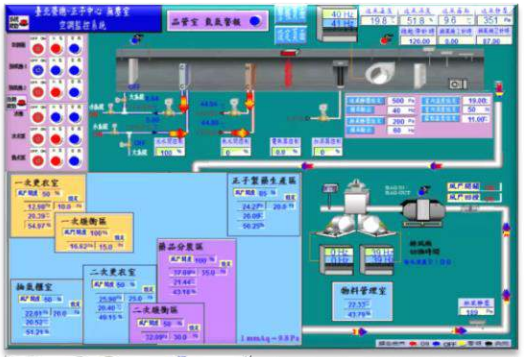
Practice of Nuclear Pharmacy – Quality Assurance

Quality Assurance			
Product Design	Good Manufacturing Practice	Quality Control	Process Development

- Personnel resources
- Facilities and equipment
- Quality Control （Ex：Physicochemical Tests、Biological Tests)
- Production and process controls
- Finish drug product controls and acceptance criteria
- Records

No.	QC Tests	Acceptance Criteria
1	Appearance	Clear, colorless or slightly yellow
2	pH	5.0 – 8.0
3	Radionuclidic Identity	Half-life: 105 – 115 min
4	Radiochemical Purity	> 95% (Radio-TLC)
5	Kryptofix 2.2.2	< 50 μg/mL
6	Residual Solvents	< 0.04% acetonitrile < 0.5% alcohol < 0.5% ether
7	Bacterial Endotoxins	175 EU/V
8	Sterility	Meet the Test
9	Membrane Filter Integrity	>50 psi
10	Radionuclidic Purity	>99.5% (511, 1022 keV)
11	Specific Radioactivity	No carrier added

^{18}FDG Quality Control



Practice of Nuclear Pharmacy – Dispensing

- Radioactive material
- USP 〈797〉 Pharmaceutical compounding – sterile preparations
  low-Risk level CSPs / ISO Class 5
  Mo-99/Tc-99m Generator / ISO Class 8
- As Low As Reasonably Achievable (ALARA)
- Basic storage and shielding equipment (ex：lead、Tungsten)

Risk Level of Common Drugs Used in Nuclear Medicine	
Imaging Agent	Microbial Risk Level
Tc-99m、Tl-201、Ga-67、Y-90	Low
Radiolabeled blood cell	High
Mo-99 / Tc-99m Generator	Immediate- use
Interventional drug (ex：Persantine 、Lasix)	Low

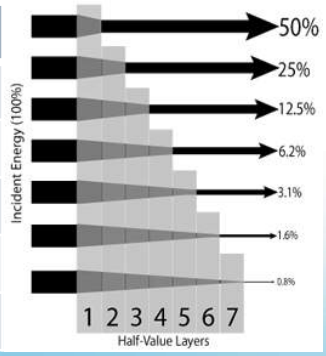
ISO 14644-1 Cleanroom Standards			
Class	Maximum particles /m³		FED STD209 equivalent
	≧0.5um	≧5um	
5	3,520	29	Class 100
6	35,200	293	Class 1000
7	352,000	2,930	Class 10000
8	3,520,000	29,300	Class 100000

Compounded Sterile Preparations = CSPs

Practice of Nuclear Pharmacy – Dispensing

- Basic storage and shielding equipment for radioactive material
  - Lead-lined storage cabinets
    - a. Radiopharmaceuticals
    - b. Radioactive sources
    - c. Radioactive waste
  - Lead L-block shields
  - Lead bricks
  - Lead /Tungsten vial and syringe shields
  - Lead foil or sheeting of various thickness

Radionuclide	Half Value Layer (HVL) cm			
	Lead	Iron	Al	Concrete
Mo-99	0.49	1.11	3.16	3.54
Tc-99m	0.07	1.13	2.68	1.27
I-131	0.25	0.93	2.67	3.02
F-18	0.41	1.1	3.0	3.32

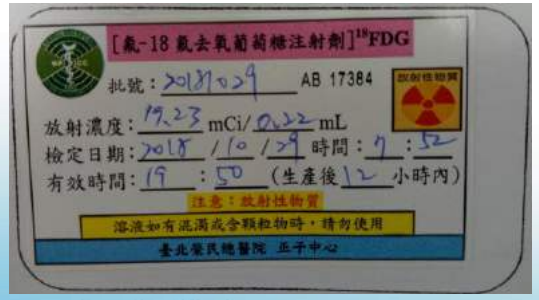


Practice of Nuclear Pharmacy – Dispensing

- USP 〈823〉▲POSITRON EMISSION TOMOGRAPHY DRUGS FOR COMPOUNDING, INVESTIGATIONAL, AND RESEARCH

> Radiopharmaceuticals administered for positron emission tomography (PET) procedures typically incorporate radionuclides that possess very short physical half-lives, $T_{½}$ (e.g., $T_{½}$ of ^{18}F = 109.7 minutes, of ^{11}C = 20.4 minutes, of ^{13}N = 9.96 minutes, and of ^{15}O = 2.03 minutes). As a result, these radionuclides are usually produced using particle acceleration techniques (e.g., cyclotron) at or within close proximity to the site where the PET procedure will be conducted

- QUALITY ASSURANCE
- CONTROL OF COMPONENTS, MATERIALS, AND SUPPLIES
- STABILITY (^{18}FDG / 12hr、^{11}C Sodium Acetate /2hr 、13N-Ammonia /15min)
- CONTROLS AND ACCEPTANCE CRITERIA FOR FINISHED PET DRUG PRODUCTS
- LABELING



Practice of Nuclear Pharmacy – Dispensing

Practice of Nuclear Pharmacy - Distribution

- 放射性物質安全運送規則
  - 第一章 總則
  - 第二章 放射性物質、包裝及包件
  - 第三章 交運、運送及貯存之管制
  - 第四章 核准作業規定
  - 第五章 附則

附表十五 聯合國九類危險物分類表

第一類	爆炸品
	1.1 項 具有巨大爆炸危險性的物件和物質
	1.2 項 具有射出危險性但不具巨大爆炸危險性的物件和物質
	1.3 項 具有起火危險性、低爆炸性且/或低射出危險性但不具巨大爆炸危險性的物件和物質
	1.4 項 不具顯著危險性的物件和物質
	1.5 項 具有巨大爆炸危險性但敏感度很低的物件和物質
	1.6 項 具有巨大爆炸危險性但敏感度極低的物件和物質
第二類	氣體
	2.1 項 可燃氣體
	2.2 項 非可燃氣體：非毒性氣體
	2.3 項 毒性氣體
第三類	可燃液體
第四類	可燃固體；易於自燃物質；遇水釋出可燃氣體物質
	4.1 項 可燃固體
	4.2 項 易於自燃物質
	4.3 項 遇水釋出可燃氣體物質
第五類	氧化劑和有機過氧化物
	5.1 項 氧化劑
	5.2 項 有機過氧化物
第六類	毒性和傳染性物質
	6.1 項 毒性物質
	6.2 項 傳染性物質
第七類	放射性物質
第八類	腐蝕性物質
第九類	其他危險性物質

附表六 包件及外包裝之分類

狀況		類別
運送指數(TI)	外表面任一點之最大輻射強度	
0	在每小時0.005毫西弗以下	Ⅰ－白
0＜TI≦1	大於每小時0.005毫西弗 但在每小時0.5毫西弗以下	Ⅱ－黃
0＜TI≦10	大於每小時0.5毫西弗 但在每小時2.0毫西弗以下	Ⅲ－黃
10＜TI	大於每小時2.0毫西弗 但在每小時10毫西弗以下	Ⅲ－黃 並為專用

行政院原子能委員會
貨品進口同意書

共 3 頁，第 1 頁

(一)申辦資料	同意書管審核准文號 (Certificate No.)	AE107011012882 □一證一用 ■一證多用
	核准日期 (Issue Date)	中華民國107年09月03日（2018.09.03）
	有效日期 (Expiration Date)	中華民國108年03月02日（2019.03.02）
	文件類別 (Document Type)	2.貨品進口同意書申請書（放射性物質）
	貨物(貨品)類別 (Goods Type)	06.非密封放射性物質
(二)申請人	申請人名稱 (Applicant)	臺北榮民總醫院
	統一編號 (Unified Business No.)	29909905
	地址 (Business Address)	台北市北投區石牌路二段201號
	聯絡人 (Contact Person)	李玉鵬技師
	電話 (Telephone No.)	02-28757270轉222
	電子郵件 (E-mail Address)	rapo2007@vghtpe.gov.tw
(三)申辦代理人	代理人名稱 (Agent)	台灣拜耳股份有限公司 BAYER TAIWAN COMPANY LTD.
	統一編號 (Unified Business No.)	23167184
	地址 (Business Address)	臺北市信義區信義路5段7號58至54樓
	聯絡人 (Contact Person)	施惠芬
	電話 (Telephone No.)	(02)27079090
	電子郵件 (E-mail Address)	finn@gastw.com.tw
	註：申辦代理人即進出口報單之納稅義務人識別碼(或貨物輸出人)。	

【申請人注意事項】
本文件正本資料儲存於本會電腦主機，可上網查證，請至原能會首頁(http://www.aec.gov.tw)點選「線上服務」之「進出口管審及輻射防護管制線上申請」之「進出口管審線上申

製發日期時間：中華民國107年10月22日12時5分50秒（2018.10.22 / 12:5.50）
本案貨到貨品分類號列(C.C.C. Code)，由海關依報會認定。

文件真偽驗證網址:https://aecie.aec.gov.tw 驗證碼:893702AE107011012882

Practice of Nuclear Pharmacy – Health and Safety

- 游離輻射防護安全標準

第 一 條 本標準依游離輻射防護法第五條規定訂定之。

第 七 條 輻射工作人員職業曝露之劑量限度，依下列規定：

一、每連續五年週期之有效劑量不得超過一百毫西弗，
且任何單一年內之 有效劑量不得超過五十毫西弗。

二、眼球水晶體之等價劑量於一年內不得超過一百五十毫西弗。

三、皮膚或四肢之等價劑量於一年內不得超過五百毫西弗。

第 十二條 輻射作業造成一般人之年劑量限度，依下列規定：

一、有效劑量不得超過一毫西弗。

二、眼球水晶體之等價劑量不得超過十五毫西弗。

三、皮膚之等價劑量不得超過五十毫西弗。

- As Low As Reasonably Achievable (ALARA)合理抑低

★ 病患注射Tc-99m 20mCi骨骼掃描，注射後3小時距離病患30cm劑量率為0.0000695mSv/min ,如工作人員接觸病患30分鐘計算, 一年要接觸479個骨骼掃描病患(連續30min暴露) ,才能到達一般人年劑量限值。

財團法人中華民國輻射防護協會

人員體外輻射劑量測試報告

委託單位：248-C 台北榮民總醫院核醫部

本期測量期間：108年09月01日 至 108年09月30日　　背景佩章讀值：正常

身份證字號	姓名	劑量計種類	本期個人等效劑量(毫西弗) Hp(10)	Hp(0.07)	年累積個人等效劑量(毫西弗) Hp(10)	Hp(0.07)	5年週期Hp(10)劑量(毫西弗)	備註
A10260****	朱力行	A	B	B	B	B	0.74	
A12896****	丁建鑫	A	B	B	0.13	0.13	0.13	
A12896****	丁建鑫	左F		B		B		
A12896****	丁建鑫	右F		B		B		
A17012****	姜振豪	A	0.08	0.08	0.80	0.80	1.76	
A20319****	張台英	A	B	B	B	B	B	
A22111****	黃佳文	A	0.15	0.11	1.16	0.96	3.08	
A22459****	張嘉容	A	0.11	0.09	0.91	0.82	1.68	
B10107****	張承培	A	B	B	B	B	B	
C24800****	測試片一	A	B	B	B	B	B	
D12018****	陳至豪	A	0.08	0.05	1.19	1.02	2.58	
E12209****	張文讀	A	B	B	B	B	B	
E12209****	張文讀	左F		B		11.39		
E12209****	張文讀	右F		B		18.51		
E22009****	蔡汶樺	A	B	B	B	B	0.16	
E22009****	蔡汶樺	左F		0.11		1.29		
E22009****	蔡汶樺	右F		0.10		1.22		
F10430****	黃延城	A	0.22	0.16	1.43	1.20	3.33	
F12023****	陳志華	A	B	B	B	B	0.06	
F22642****	張嘉慧	A	0.10	0.09	0.59	0.52	1.65	
F22856****	陳芳仕	A	0.12	0.10	1.17	0.99	1.95	
G12109****	林智偉	A	0.13	0.13	0.72	0.63	1.40	
G12206****	陳奕倫	A	0.24	0.19	1.38	1.17	2.28	
G22007****	林啟芬	A	B	B	B	B	B	
H12147****	魏文祺	A	B	B	0.38	0.32	0.75	
H22072****	劉珍娜	A	B	B	B	B	B	
H22315****	楊宛甄	A	B	B	B	B	B	
J12016****	徐景龍	A	0.06	0.06	0.23	0.21	0.53	
J22034****	林筱玲	A	0.12	0.11	1.23	1.10	2.20	
K10108****	黃文盛	A	B	B	B	B	B	
K12185****	李建順	A	0.08	0.07	0.58	0.53	0.83	
K22004****	江瑞華	A	B	B	B	B	B	
L12229****	吳元鐘	A	B	B	B	B	0.05	
L12229****	吳元鐘	左F		2.28		17.08		
L12229****	吳元鐘	右F		2.17		18.05		

<<註：指環劑量計(F)的量測結果，不在TAF的認證範圍內>>

報告編號：10809248C（第1頁/共2頁）

報告簽署人：人員劑量計測試實驗室負責人 簡文彬　核醫部專任技術師 周榮鴻 10/31　核醫部專任主任 張承培 10/31

依「游離輻射防護法」及相關法規之規定，雇主應將人員劑量監測結果(本報告)保存並告知當事人。

第一聯紫色：佩章使用單位存查

第二聯藍色：本協會存查

熱發光劑量計(TLD)的基本原理

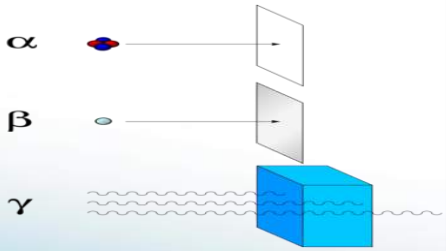
熱發光劑量計（ThermoLuminescence Dosimeter，簡稱TLD），主要材料為熱發光晶體（如氟化鋰），經輻射照射後，晶體的能階將輻射部分能量保存下來，晶體經加熱後放出磷光，再將發光量換算成輻射劑量。

Practice of Nuclear Pharmacy – Health and Safety

Radiation Countermeasures for Treatment of Internal Contamination		
Medical countermeasure	Administered for	Mechanism of action
Prussian blue, insoluble	Cesium (Cs-137) Thallium(Tl-201) Ruthenium(Rb-106)	on exchange; inhibits enterohepatic recirculation in GI tract
DTPA (calcium & zinc)	Americium(Am-241) Californium (Cf-252) Cobalt (Co-60) Curium (Cm244) Plutonium (Pu-238 and Pu-239) Yttrium (Y-90)	Chelating agent
Potassium iodide (KI)	Iodine (I -131)	Blocking agent

Practice of Nuclear Pharmacy –
Provision of Drug Information and Consultation

- Biologic effects of radiation.
- Radiation physics and protection.
- Radiopharmaceutical chemistry ,compounding ,QA ,and products.
- Diagnostic and therapeutic application of radiopharmaceuticals.
- Ancillary medication used to enhance radiopharmaceutical procedures.



Product Name	碘化鈉【^{131}I】膠囊	Manufactured Date	2018/10/01
Batch No.	I131-20181001-02	Expiration Date	3 weeks until 2018/10/21
Order No.	8251~8274		

Test Items	Specifications	Results
崩散度	≤ 20 min	<20 min
單位劑量均一度	放射活度平均值之±3.5%以內	Pass
外觀及內容物性狀	膠囊無軟化潮解，顏色無異常 膠囊上下蓋應實緊閉	Pass
	白色粉末	Pass
放射活度含量	標誌量之 90.0~110.0% 標誌量(封單)：0.3mCi@2018/10/01 08:00	0.298 mCi/capsule @校正時間：2018/10/01 08:00 標誌量之 98.0 %
放射核種純度及鑑別	364 keV±10%	361.7keV
	Purity ≥ 95%	100%
放射化學純度及鑑別	STD R_f	0.986
	R_f：STD R_f ±5%	0.963
	Purity ≥ 95%	98.22%
微生物限量*	總生菌數：≤1000 CFU/g	
	總真菌數：≤100 CFU/g	
	大腸桿菌：Negative	
Release Date	*Prepared by*	*Pharmacist*
2018/10/01		

*每年執行一批微生物限量檢驗(2018/09/07 完成)

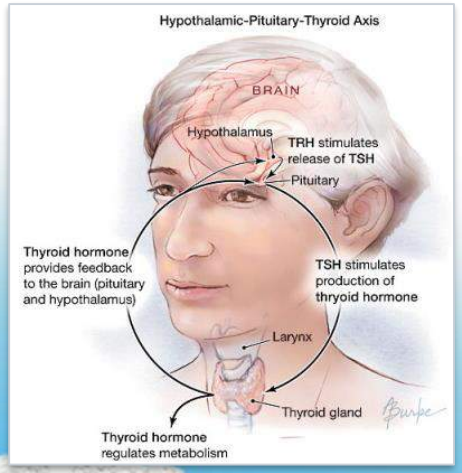
Table 18.3 CONCURRENT ADMINISTERED DRUGS KNOWN TO INTERFERE WITH TUMOR AND ABSCESS LOCALIZATION SCINTIGRAPHY

INTERFERING DRUG	EFFECT ON IMAGE
Phenytoin	Localization of RP in mediastinum, pulmonary hilar structures (patients without clinical evidence of lymphadenopathy)
Amiodarone, bleomycin, busulfan, nitrofurantoin, bacille Calmette-Guérin, chemotherapy, lymphangiographic contrast media, addictive drugs of abuse	Diffuse pulmonary localization (sometimes local pulmonary uptake)
Metoclopramide, reserpine, phenothiazines, oral contraceptives, diethylstilbestrol	Localization of RP in breast
Methotrexate, cisplatin, gallium nitrate, mechlorethamine HCl, vincristine, various chemotherapeutic agents, iron	Increased skeletal uptake Increased renal elimination Decreased hepatic accumulation Decreased tumor or abscess uptake
Clindamycin	Localization of RP in bowel
Calcium gluconate, IM injections	Soft tissue accumulation of RP
Ampicillin, sulfonamides, sulfinpyrazone, ibuprofen, cephalosporins, hydrochlorothiazide, methicillin, erythromycin, rifampin, pentamidine, phenylbutazone, gold salts, allopurinol, furosemide, phenazone, phenobarbital, phenytoin, phenindione	Increased accumulation of RP in the kidneys
Chemotherapeutic agents, antibiotics	Localization of RP in the thymus

Ansel`S Pharmaceutical Dosage Forms and Drug Delivery system 10`th p666

Practice of Nuclear Pharmacy –
Provision of Drug Information and Consultation

- Drug interactions associated with radiopharmaceuticals.
- Precaution associated with the use of radiopharmaceuticals.
- Regulatory requirement affecting the use of radiopharmaceuticals.
- This information can be used for educational purpose , for setting policies ,and procedures , and for diagnostic or therapeutic value in the care of patients.

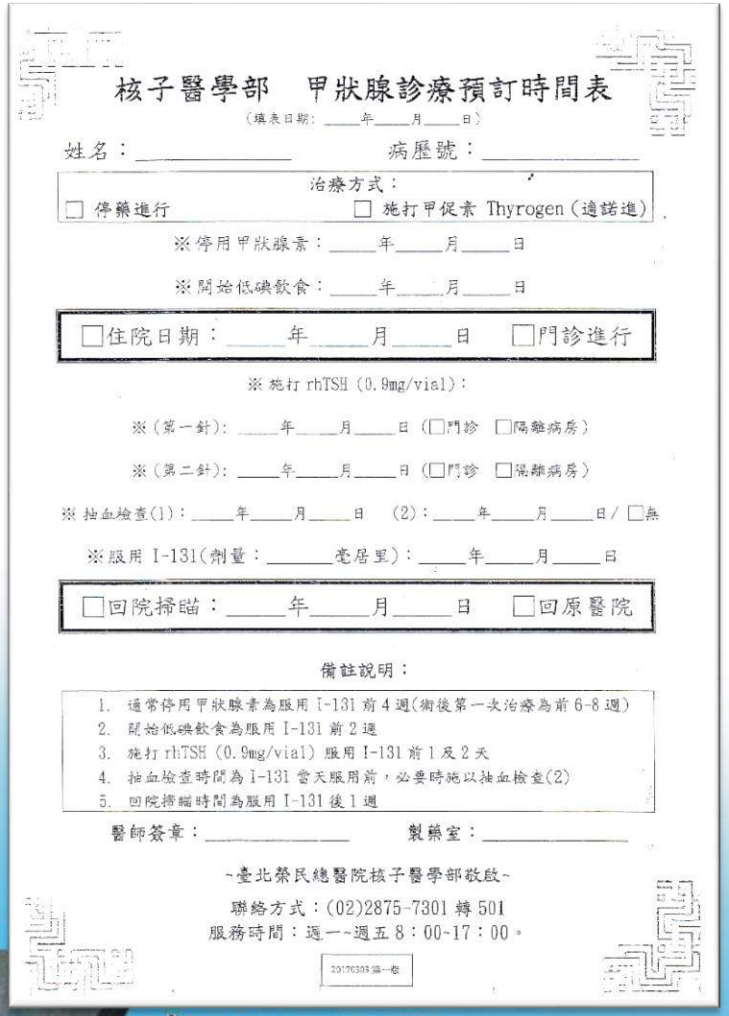


"Default" I-131 Release Criteria
< I-131 30mCi administered,
or < 70 μSv/hr at one meter
→ **FREE TO GO.**

臺北榮民總醫院
Taipei Veterans General Hospital

Preparing for radioactive iodine treatment

Practice of Nuclear Pharmacy –
Provision of Drug Information and Consultation



核子醫學部　甲狀腺診療預訂時間表

（填表日期：____年____月____日）

姓名：_____　病歷號：_____

治療方式：

☐ 停藥進行　☐ 施打甲促素 Thyrogen（適諾進）

※停用甲狀腺素：____年____月____日

※開始低碘飲食：____年____月____日

☐住院日期：____年____月____日　☐門診進行

※ 施打 rhTSH（0.9mg/vial）：

※（第一針）：____年____月____日（☐門診　☐隔離病房）

※（第二針）：____年____月____日（☐門診　☐隔離病房）

※ 抽血檢查(1)：____年____月____日　(2)：____年____月____日 / ☐無

※服用 I-131(劑量：_____毫居里)：____年____月____日

☐回院掃瞄：____年____月____日　☐回原醫院

備註說明：

1. 通常停用甲狀腺素為服用 I-131 前 4 週(術後第一次治療為前 6-8 週)
2. 開始低碘飲食為服用 I-131 前 2 週
3. 施打 rhTSH（0.9mg/vial）服用 I-131 前 1 及 2 天
4. 抽血檢查時間為 I-131 當天服用前，必要時施以抽血檢查(2)
5. 回院掃瞄時間為服用 I-131 後 1 週

醫師簽章：_____　製藥室：_____

~臺北榮民總醫院核子醫學部敬啟~

聯絡方式：(02)2875-7301 轉 501

服務時間：週一~週五 8：00~17：00。

20170303 第一版

臺北榮民總醫院核醫部

小劑量碘-131 治療 輻射安全衛教單

（未超過 30mCi）

警告：未懷孕者才能接受本治療。如果您無法確認是否懷孕，請立刻聯絡您的主治醫師。

一般說明：

1. 全世界通例，小於 30mCi 治療是不需要住院的，請遵照**醫事人員**（醫師、藥師、護理師、醫檢師、放射師）指示依規定時間及方法自行服藥、飲食及生活起居。
2. 碘-131 會放出加馬射線及貝他粒子，除治療您的病症外，對他人健康亦有所影響，因此請務必遵守規定，以保護您的親友及跟您相處的熟人或陌生人。
3. 碘-131 在您體內時，貝他粒子不會影響他人，但是加馬射線有很強的穿透力，因此要跟其他人員保持距離。
4. 防護三原則：距離越遠越好，接觸時間越短越好，良好的屏蔽（金屬、混凝土、無縫磚牆，越厚實越好）。
5. 您體內的碘-131，絕大部份都會從尿液排出，因此必須完全避免讓其他人接觸到您的尿液。

服藥後遵行事項【請遵行至少 2 日（48 小時）】（最好能延伸至一週）：

1. 服藥後請立即返家，禁止逗留於公共場所，**居家照顧規範以醫師、及其他醫事人員指示為優先**。
2. 避免長時間與其他人接觸（即 1 公尺以內）。
3. **完全**避免接觸**幼兒及孕婦**。
4. 分床睡眠 2 夜，**禁止有性行為**。
5. 如有男女間親密行為，在 6 至 12 月內應做有效之**避孕措施**。
6. 上廁所後手必須洗乾淨。如有尿液滴灑在馬桶外，請用衛生紙擦拭後丟入馬桶沖走，每次如廁後必須沖水 2 次。（如非化糞池或連接衛生下水道之廁所，糞尿嚴禁拿來施肥）
7. 每天至少飲用 10 杯 250ml 之水、飲料或湯。
8. 內衣請先在水槽或水盆中漂洗後再丟入洗衣機內。
9. 飲食及盥洗用具必須單獨使用。

備註：（2~9 項係參照美國 MAYO CLINIC MANUAL OF NUCLEAR MEDICINE ^{131}I Therapy （30mCi or More）制定）

Radiation isolation ward

臺北榮民總醫院核醫部

大劑量碘-131 治療輻射安全衛教單

(大於 30mCi)

警告：未懷孕者才能接受本治療。如果您無法確認是否懷孕，請立刻告知護理人員聯絡您的主治醫師。

住院期間：

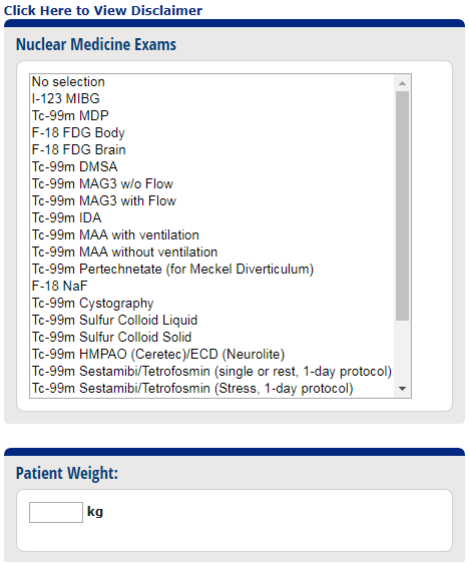
1. 請遵照**醫事人員**（醫師、藥師、護理師、醫檢師、放射師）指示依規定時間及方法服藥、飲食及生活起居。
2. 請依護理人員指示做好垃圾分類。
3. 若想嘔吐，請先至浴室並儘量吐入馬桶內。
4. 服藥後至出院期間，如有大量體液（尿液及嘔吐物）不慎留在房間內，請勿自行處理，應先通知護理人員再依指示處理。
5. 出院當日，請依輻射防護人員指示，先坐在桌邊等待病房門開啟，開啟後請站立在待測點（距門口 1 米處紅色標誌），由輻射防護人員測量剩餘輻射量。(測量時間約 1 分鐘)
6. 如果剩餘輻射量符合外釋標準，輻射防護人員會通知護理人員辦理出院作業程序，請靜候護理人員通知。
7. 任何輻射防護問題，請以電話或呼叫器告知護理站。

出院後【請遵行至少 2 日（48 小時)】：

1. 出院後請立即返家，禁止逗留於公共場所，**居家照顧規範以醫師、護理師指示為優先**。
2. **避免**長時間與其他人接觸（即 1 公尺以內）。
3. **完全**避免接觸**幼兒及孕婦**。
4. 分床睡眠 2 夜，**禁止有性行為**。
5. 如有男女間親密行為，在 **6 至 12 月內**應做有效之**避孕措施。**
6. 上廁所後手必須洗乾淨。如有尿液滴灑在馬桶外，請用衛生紙擦拭後丟入馬桶沖走，每次如廁後必須沖水 2 次。(如非化糞池或連接衛生下水道之廁所，糞尿嚴禁拿來施肥)
7. 每天至少飲用 10 杯 250ml 之水、飲料或湯。
8. 內衣請先在水槽或水盆中漂洗後再丟入洗衣機內。
9. 飲食及盥洗用具必須單獨使用。

備註：(2~9 項係參照美國 MAYO CLINIC MANUAL OF NUCLEAR MEDICINE ^{131}I Therapy （30mCi or More）制定)

Practice of Nuclear Pharmacy - Monitoring patient outcome



- Patient safety and optimal outcomes are the goal of the nuclear pharmacist and a central tenet of pharmaceutical care.
- Ensure that patient are selected appropriately for radionuclide therapy and monitored after therapy to prevent complication .
- Breast milk excretion of radiopharmaceuticals

With few exceptions ,very small fractions of administered doses of radiopharmaceuticals are excreted in milk.

Only ^{99m}Tc-Sodium Pertechnetate 、^{131}I-Sodium Iodide 、^{67}Ga-Citrate may exhibit cumulative exeretions >10% .

It is generally agreed that a reasonable dose criterion for interrupting breast—feeding is 0.1rem effective dose to infant.

Table 11.3 Limits of activities that require instructions to breast-feeding patients and record keeping

Radiopharmaceutical	Activity above which instructions are needed [mCi (MBq)]	Activity above which record is needed [mCi (MBq)]	Recommended duration of cessation of breast-feeding
^{131}I-NaI	0.004 (0.01)	0.002 (0.07)	Complete cessation
^{123}I-NaI	0.5 (20)	3 (100)	
^{123}I-MIBG	2 (70)	10 (400)	12 h (4 mCi/150 MBq)
^{99m}Tc-DTPA	30 (1000)	150 (6000)	
^{99m}Tc-MAA	1.3 (50)	6.5 (200)	12.6 h (4 mCi/150 MBq)
^{99m}Tc-pertechnetate	3 (100)	15 (600)	12 h (12 mCi/440 MBq)
^{99m}Tc-DISIDA	30 (1000)	150 (6000)	
^{99m}Tc-sestamibi	30 (1000)	150 (6000)	
^{99m}Tc-MDP	30 (1000)	150 (6000)	
^{99m}Tc-PYP	25 (900)	120 (4000)	
^{99m}Tc-RBC in vivo	10 (400)	50 (2000)	6 h (20 mCi/740 MBq)
^{99m}Tc-RBC in vitro	30 (1000)	150 (6000)	
^{99m}Tc-sulfur colloid	7 (300)	35 (1000)	6 h (12 mCi/440 MBq)
^{99m}Tc-MAG3	30 (1000)	150 (6000)	
^{99m}Tc-WBC	4 (100)	15 (600)	12 h (12 mCi/440 MBq)
^{67}Ga-citrate	0.04 (1)	0.2 (7)	1 month (4 mCi/150 MBq)
^{111}In-WBC	0.2 (10)	1 (40)	1 week (0.5 mCi/20 MBq)
^{201}Tl	1 (40)	5 (200)	2 weeks (3 mCi/110 MBq)

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IAEA Safety Standards
for protecting people and the environment

Radiation Protection and Safety in Medical Uses of Ionizing Radiation
Jointly sponsored by
IAEA ILO FAO WHO

Specific Safety Guide
No. SSG-46

IAEA

Practice of Nuclear Pharmacy - Monitoring patient outcome

Appendix II

RECOMMENDATIONS FOR AVOIDANCE OF PREGNANCY FOLLOWING RADIOPHARMACEUTICAL THERAPY

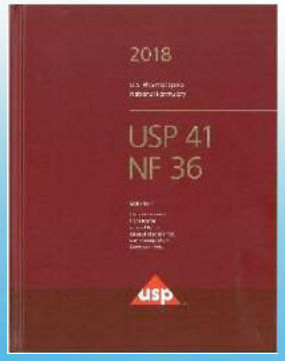
Nuclide and form	Disease	All activities up to[a] (MBq)	Avoid pregnancy (months)
^{32}P phosphate	Polycythaemia and related disorders	200	3
^{89}Sr chloride	Bone metastases	150	24
^{90}Y colloid	Arthritic joints	400	0
^{90}Y antibody or ^{90}Y-octreotid	Cancer	4000	1
^{131}I iodide	Benign thyroid disease	800	6–12
^{131}I MIBG[b]	Malignancy	7500	3
^{153}Sm colloid	Bone metastases	2600	1

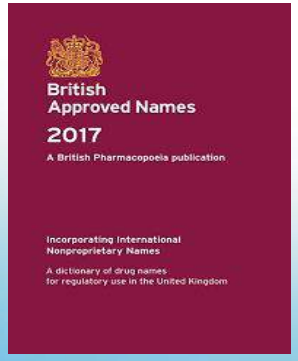
a The administration of activities smaller than those indicated in column 3 does not imply that the advisory period specified in column 4 can be reduced.
b Metaiodobenzylguanidine.

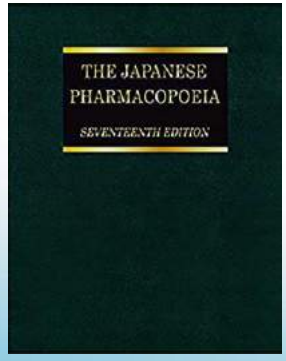
https://www-pub.iaea.org/MTCD/Publications/PDF/PUB1775_web.pdf

Pharmacopoeia

- 中華藥典
- U.S. Pharmacopoeia
- European Pharmacopoeia
- British Pharmacopoeia
- Japanese Pharmacopoeia

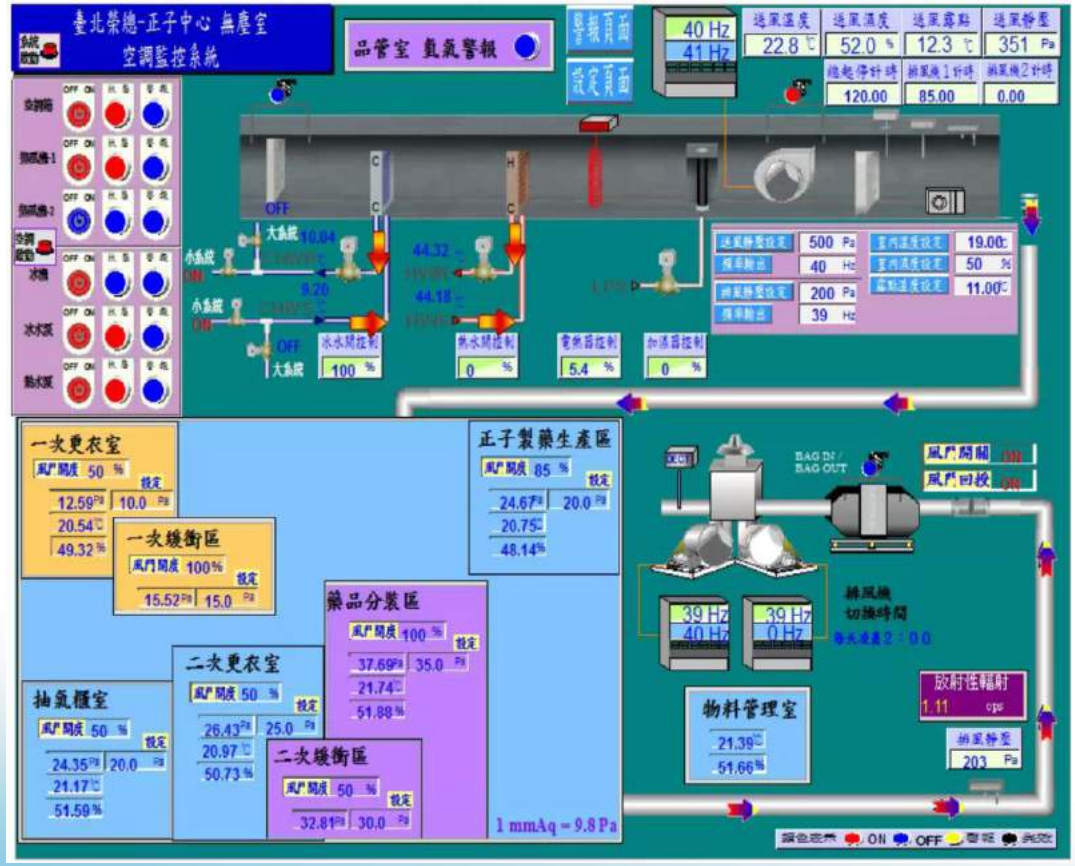




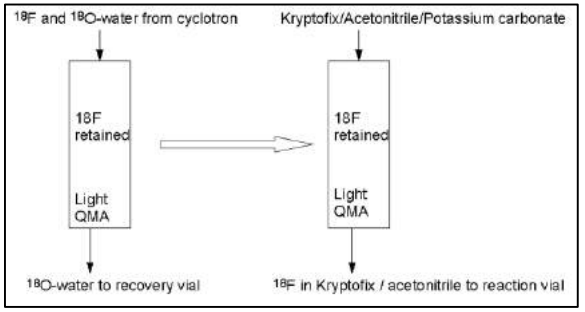


Microbiological control and monitoring of aseptic processing environments

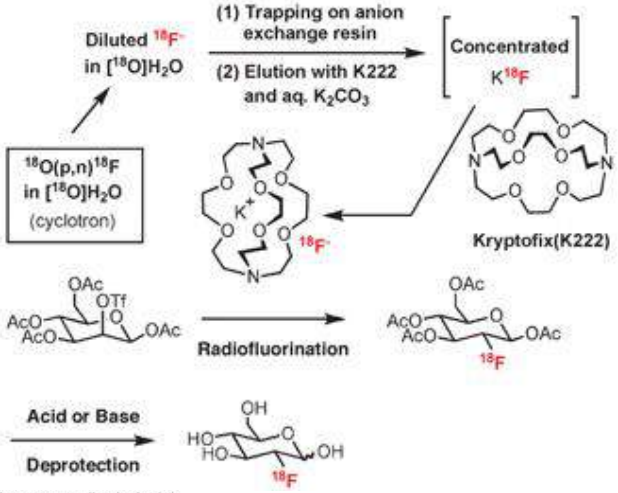
- Cleanroom Operations
- Viable and non-viable airborne particles
- Air flow patterns
- Temperature and humidity
- Air pressure differential
- Containment of hazardous aerosols



2-[^{18}F]-fluoro-2-deoxy-D glucose (^{18}FDG)synthesis overview

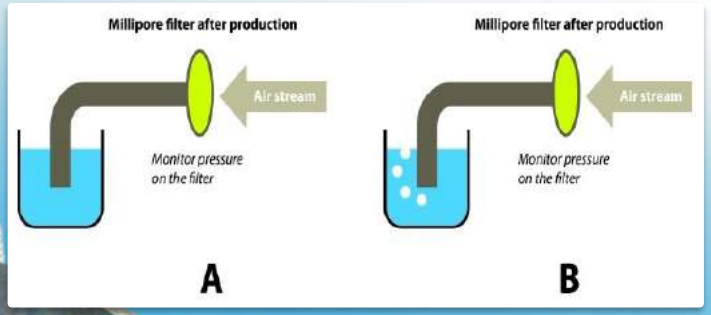


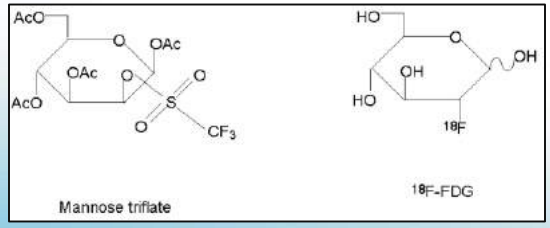
- ^{18}F ions are trapped on the anion exchange cartridge (QMA)
- O-18 water passes through and retained (re-use)
- ^{18}Fwashed off the QMA into the reaction vial by K222/acetonitrile mix
- Solvents dried (@95° C) in the reaction vial (under nitrogen flow & vacuum)
- Reconstituted mannose triflate added to dry residue in the reaction vial
- Nucleophilic reaction occurs (@85° C). Critical step
- Water flushed through reaction vial
- [^{18}F]fluoro-tetra-O-acetyl-D-glucose trapped on C-18 cartridge, ^{18}F ions to waste
- Alkaline hydrolysis [NaOH] (to remove protective acetyl groups) occurs on C-18 cartridge to form ^{18}F FDG
- Alkaline FDG neutralised by citrate buffer and not retained on C-18
- FDG solution purified by 2nd C-18 cartridge, trapping hydrolysed compounds
- FDG solution then passes through a Alumina N cartridge to remove remaining free ^{18}F ions
- Finally, FDG solution passes through a sterile 0.22µm filter into a sterile collection vial



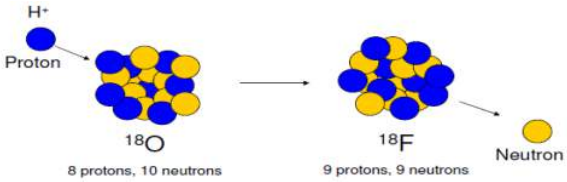
Removal of protective groups (hydrolysis):
Acidic or basic hydrolysis
Reagents:
HCl (1M); >100°C; Time: ~8 min. or
NaOH (1-2M); Room Temperature on resin cartridge; or at ~50°C in solution; Time: ~3 min.

0.22µm Membrane Filter Integrity test





Biomed Imaging Interv J. 2006 Oct-Dec; 2(4)



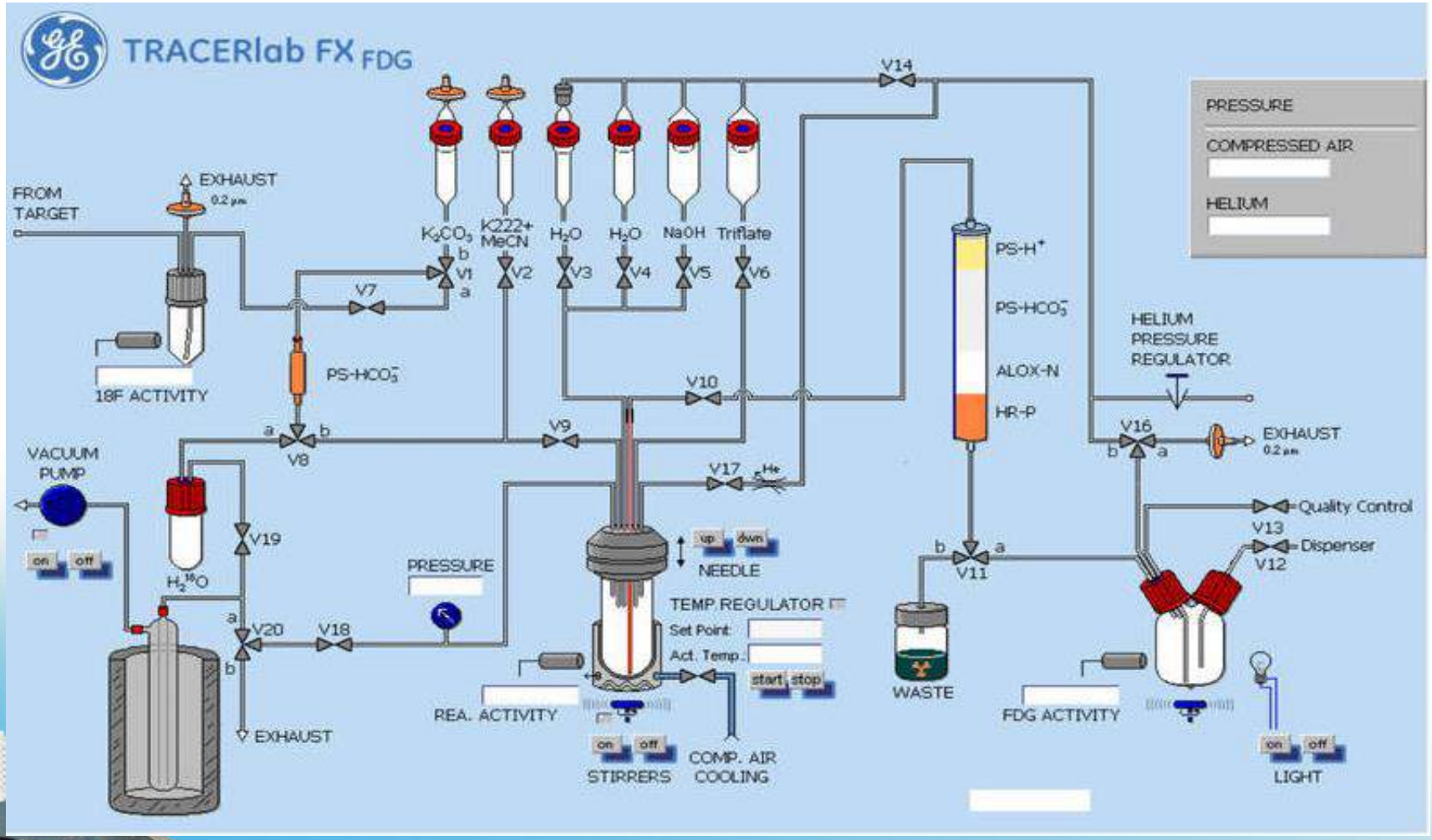
Production routes fluorine-18

REACTION	$^{18}O(p,n)^{18}F$	$^{16}O(^{3}He,p)^{18}F$	$^{20}Ne(d,\alpha)^{18}F$	$^{18}O(p,n)^{18}F$
Target	$H_2{}^{18}O$	H_2O	Ne (200 μmol F2)	$^{18}O_2$, Kr (50 μmol F2)
Particle Energy 〔Mev〕	16 → 3	36 → 3	14 → 3	16 → 3
Main product form	$^{18}F^-_{aq}$	$^{18}F^-_{aq}$	〔^{18}F〕F2	〔^{18}F〕F2
Exp.yield 〔GBq/μAh〕	2.22	0.26	0.4	1.0
Specific activity 〔MBq/μmol〕	≈ 600 x10^3	≈ 50 x10^3	≈ 100	≈ 600

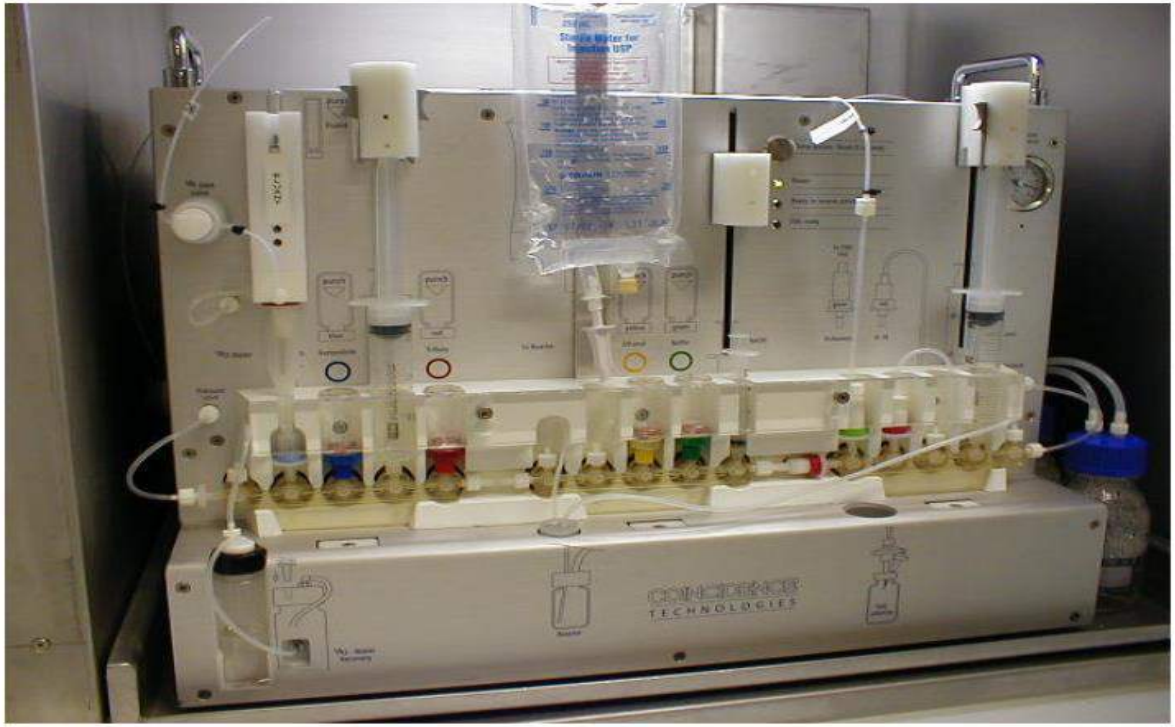
Radiochemical yields of ^{18}F-FDG using various automated synthetic procedures

Cyclotron	Automated module	Type of hydrolysis	Synthesis time (min)	^{18}F-FDG yield. (End of synthesis)
GE PET-trace	FDG II Microlab	Alkali	35	44
MC17 Scanditronix	Coincidence TracerLab MX FDG	Alkali	27	58.9
MC17 Scanditronix	Anatech RB86 Robot	Alkali	48	63
IBA 18/9	Nuclear interface	Acidic	16	48
GE MINI Trace	GE Fastlab	Alkali	25	70

2-[^{18}F]-fluoro-2-deoxy-D glucose (^{18}FDG) -Synthesis – Automation Software



2-[^{18}F]-fluoro-2-deoxy-D glucose (^{18}FDG) - Synthesis /Hardware kit / Reagent kit



Tracer Lab MX FDG

PET- Synthesis module in a hot cell

- The synthesis is carried out in a synthesis module which is remotely controlled via a PC in a lead-shielded hot cell.

PET- Dispensing isolator

- Provide an cGMP Grade A (class 100) air environment in each module.
- Shielded drawer for vial/syringe handing.
- Interlocking 50mm lead Shielding with 100mm lead glass window.
- Ball mounted remote manipulator with grippers optimised for PET dispensing operations.

1.Physicochemical Tests

- Physical characteristics
- pH
- Radionuclidic purity
- Radiochemical purity

2.Biological Tests

- Sterility test
- Apyrogenicity test

Physical characteristics

- Recognize the color and state of Radiopharmaceutical
- Colloidal or aggregated preparations：
  size identify visualization of the reticuloendothelial system： 10nm ~ 1 μm
- ^{99m}Tc-sulfur colloid：80 ~500nm
- ^{99m}Tc-MAA，Tc-label albumin microsphere： 10 ~90μm
  (checked with hemocytometer under a light microscope)
  larger than 150 μm → pulmonary arterial blockade → embolism smaller than 10 μm → localize in the reticuloendothelial system

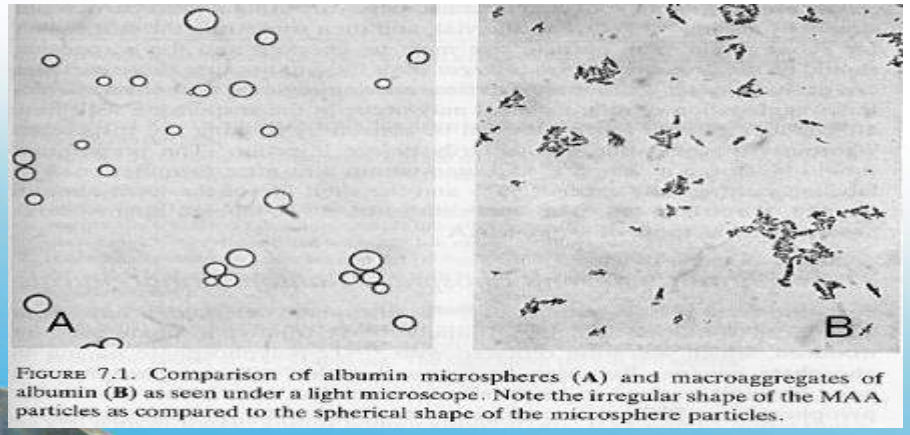
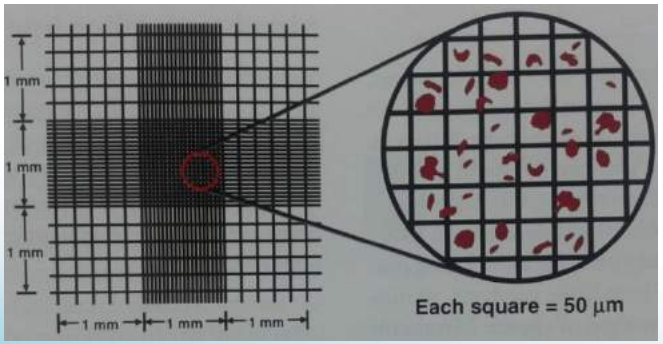
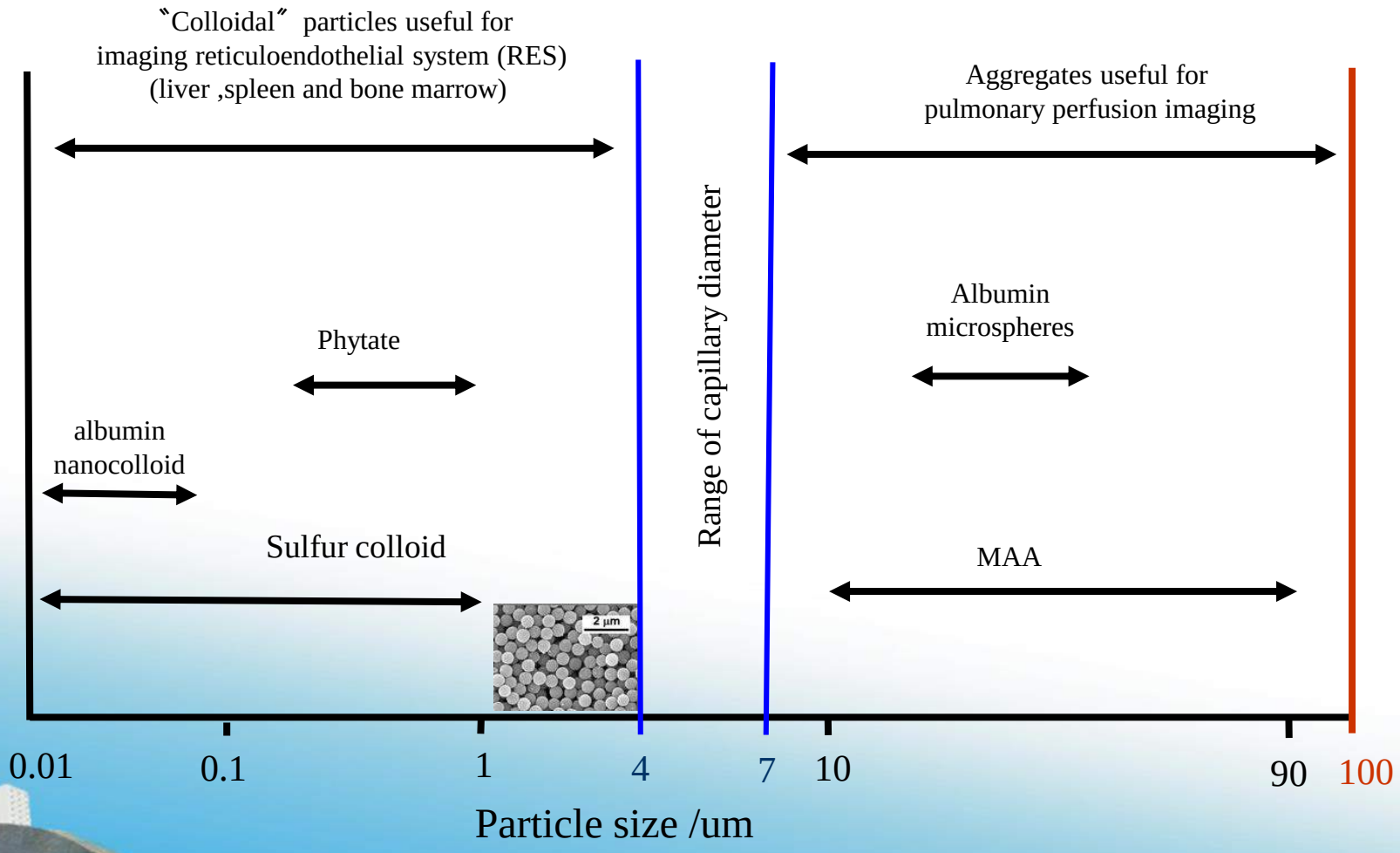


FIGURE 7.1. Comparison of albumin microspheres (A) and macroaggregates of albumin (B) as seen under a light microscope. Note the irregular shape of the MAA particles as compared to the spherical shape of the microsphere particles.

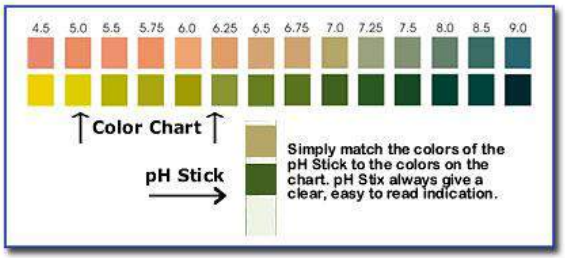




Nuclear pharmacy .H M Chilton et al;41

PH

- Ideal pH radiopharmaceutical should be7.4 (pH of the blood)
- However， radiopharmaceutical can vary between 2 ~ 9 because of high buffer capacity (緩衝能力) of blood.



	PH
$Na^{99m}TcO_4$	4.0 ~ 8.0
MDP	5.0 ~ 6.0
DTPA	4.0 ~ 4.5
DMSA(III)	2.5 ~ 3.5
DMSA(V)	7.5 ~ 8.0
MAA	5.0 ~ 8.0
Phytate	6.0 ~ 7.0
PYP	4.5 ~ 5.5
DISIDA	4.0 ~ 5.0
Trodat-1	6.5 ~ 8.5
ECD	7.2 ~ 8.0
MIBI	5.3 ~ 5.9
In-111 Pentetreotide	3.8 ~ 4.3

Radionuclidic purity

- Impurity sources from：

  ^{99}Mo-^{99m}Tc generator：^{99}Mo breakthrough from the alumina column

  ^{131}I / ^{18}F/ ^{11}C/ ^{13}N /^{68}Ga：contain many other isotopes

- Radionuclidic purity is determined by measuring the half-live and characteristic radiation emitted by individual radionuclides.

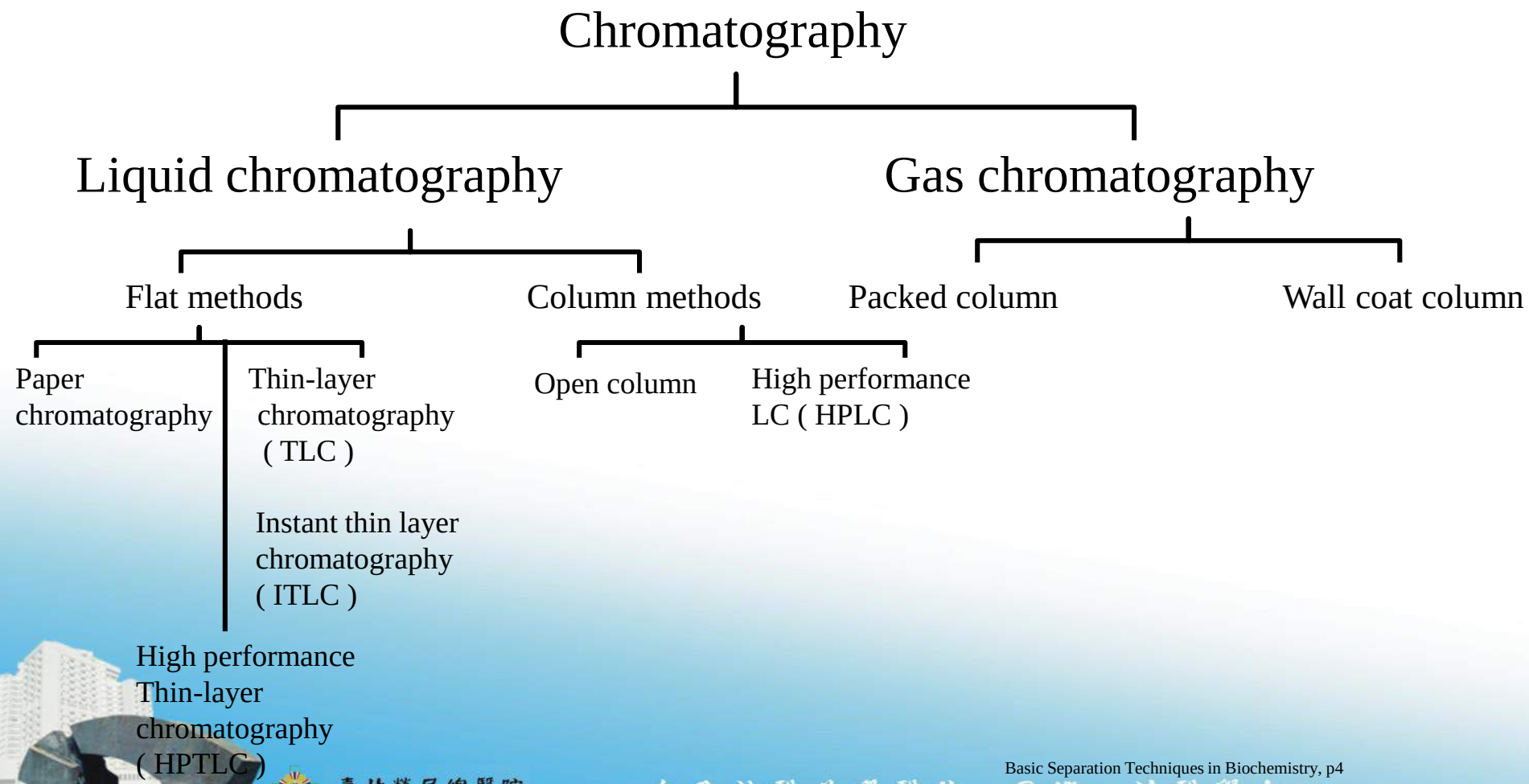
  γ-ray emission radionuclides ：checked with Multi-Channel Analyzer

  pure β emission radionuclides ：checked with β-spectrometer or a liquid scintillation counter

Radiochemical purity (RCP)

- Radiochemical impurities arise from decomposition due to
  1. action of solvent
  2. change in temperature or pH
  3. light
  4. presence of oxidizing or reducing agents
  5. radiolysis(輻射分解)
- Analytical methods
  - Paper chromatography (PC)
  - Thin-layer chromatography (TLC)
  - Instant thin-layer chromatography (ITLC)
  - High performance liquid chromatography (HPLC)
  - ⋮

Branches of chromatography according to mobile phase and physical apparatus



Paper and Thin-Layer Chromatography

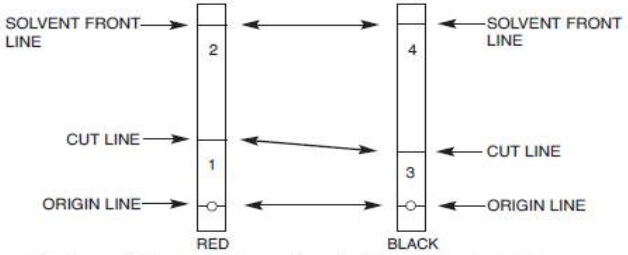
- The electrostatic forces (adsorption and capillary action) of the stationary phase and the polarity of the mobile phase are the two determining factors in the separation of different radiochemical components in a sample 。

- Rf = Retardation factor

$$Rf = \frac{\text{The distance traveled by the analyte}}{\text{The total distance traveled by the mobile phase}}$$

INTRODUCTION

Tec-Control is a miniaturized chromatography system for the radiochemical purity evaluation of specific radiopharmaceuticals.



Each red (150-001) and each black (150-005) chromatography strip have three distinct lines: an origin line, a cut line, and a solvent front line. For user convenience the back of each strip is marked with a soluble dye, located close to the line, that will migrate with the solvent front. The technologist can easily see the solvent front via the movement of the dye. Use a 10ml Wheaton Serum Vial as a developing vial. This test requires the technologist to "spot" approximately 10 microliters of the radiopharmaceutical sample onto the chromatography strip. This is easily accomplished using a 26G needle and syringe. One drop equals a volume of 0.01 cc (10µl or ten microliters).

NOTE: The Acetone HPLC grade solvent (Sigma-Aldrich part # 27972-5) and distilled H20 required to complete this procedure must be purchased separately.

Tec-Control Solvent Vendor:
Sigma-Aldrich Chemical Company
800-558-9160 www.sigmaaldrich.com

Customers outside the USA should visit the Sigma-Aldrich web site to locate a regional office.

NOTE: For each of the following procedures the strip should be placed on top or away from the well detector depending on count rate. If the strip is placed in the well, the dead time of the detector will give erroneous results.

NOTE: Black strip development time will take less than 1 minute.

NOTE: Red strip development time will take less than 1 minute.

DETERMINATION OF FREE PERTECHNETATE IN Tc-99m LABELED MAA, SULFUR COLLOID, STANNOUS CHLORIDE, ALBUMIN COLLOID AND GLUCOHEPTONATE

1. Add 1cc of acetone solvent to a developing vial.
2. Using a red chromatography strip, spot approximately 10 microliters of the test sample onto the bottom line (origin) of the test strip.
3. Immediately place the test strip into the developing vial containing acetone, and develop until the solvent front migrates to top line (solvent front).
4. Remove strip from the vial and allow to dry.
5. Cut strip at central line (cut line), producing sections 1 and 2.
6. Using a gamma counter, count background and calculate the net counts by subtracting the background counts from the number of counts registered for each strip section.

CALCULATION

% free pertechnetate

$$= \left[\frac{\text{(net cts sect. 2)}}{\text{(net cts sect. 1) + (net cts sect. 2)}} \right] \times 100$$

Artifacts in planar chromatography

- Reaction with the support，especially by drying the spots.
- Splashing when spotting.
- Grease from fingers.
- Strips touching wet walls of the developing chamber.
- Incorrect mobile phase.
- Insufficient mobile phase to allow full development to the required solvent front.

TABLE 14-2 Effect of Wet versus Dry Spot on Minichromatography Results (% Activity) for ^{99m}Tc-Labeled Compounds in ITLC-SG/Acetone System

Radiopharmaceutical	Wet Spot[a]		Dry Spot[a]	
	Origin	Solvent Front	Origin	Solvent Front
^{99m}Tc-gluceptate (^{99m}Tc-GH)[b]	74.01	25.99	99.81	0.19
^{99m}Tc-pentetate (^{99m}Tc-DTPA)[b]	60.04	39.96	99.70	0.30
^{99m}Tc-pyrophosphate (^{99m}Tc-PYP or ^{99m}Tc-PPi)[b]	85.37	14.63	99.39	0.61
^{99m}Tc-medronate (^{99m}Tc-MDP)[b]	82.60	17.40	99.82	0.18

[a]Results are means of five determinations on 5 cm ITLC-SG strips.
[b]Common chemical abbreviation.
Source: Reference 34.

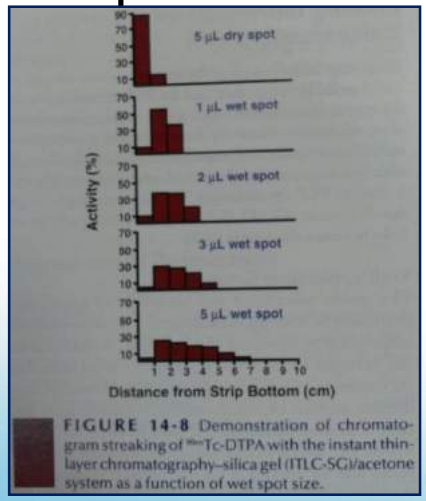


FIGURE 14-8 Demonstration of chromatogram streaking of ^{99m}Tc-DTPA with the instant thin-layer chromatography–silica gel (ITLC-SG)/acetone system as a function of wet spot size.

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Determination of the radiochemical purity of a radiopharmaceutical by ITLC using two different solvent

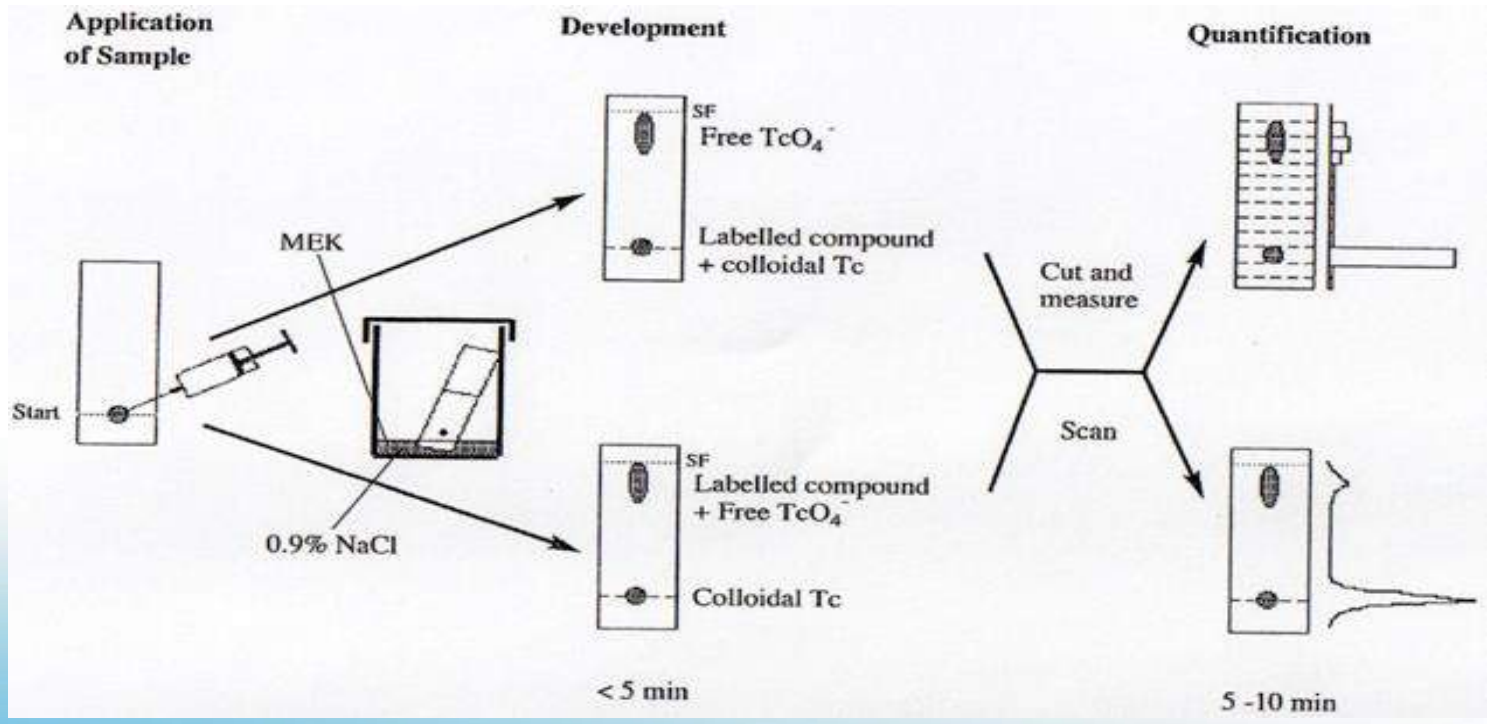

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TABLE 8.1. Chromatographic data of ^{99m}Tc labeled radiopharmaceuticals

^{99m}Tc labeled radiopharmaceuticals	Stationary phase	Solvent	R_f		
			$^{99m}TcO_4$	^{99m}Tc Complex	Hydrolyzed ^{99m}Tc
^{99m}Tc PYP	ITLC SG	Acetone	1.0	0.0	0.0
	ITLC SG	Saline	1.0	1.0	0.0
^{99m}Tc HDP	ITLC SG	Acetone	1.0	0.0	0.0
	ITLC SG	Saline	1.0	1.0	0.0
^{99m}Tc MDP	ITLC SG	Acetone	1.0	0.0	0.0
	ITLC SG	Saline	1.0	1.0	0.0
^{99m}Tc DTPA	ITLC SG	Acetone	1.0	0.0	0.0
	ITLC SG	Saline	1.0	1.0	0.0
^{99m}Tc SC	ITLC SG	Acetone	1.0	0.0	0.0
^{99m}Tc MAA	ITLC SG	Acetone	1.0	0.0	0.0
^{99m}Tc Gluceptate	ITLC SG	Acetone	1.0	0.0	0.0
	ITLC SG	Saline	1.0	1.0	0.0
^{99m}Tc DISIDA	ITLC SA	20% NaCl	1.0	0.0	0.0
^{99m}Tc Mebrofenin	ITLC SG	Water	1.0	1.0	0.0
^{99m}Tc DMSA	ITLC SA	Acetone	1.0	0.0	0.0
^{99m}Tc sestamibi	Al_2O_3 coated Plastic plate	Ethanol	0.0	1.0	0.0
^{99m}Tc HMPAO	ITLC SG	Butanone (MEK)	1.0	1.0 (Primary)	0.0
	ITLC SG	Saline	1.0	0.0	0.0
	Whatman 1	50% Acetonitrile	1.0	1.0	0.0
^{99m}Tc tetrofosmin	ITLC SG	Acetone: dichloromethane (35:65 v/v)	1.0	0.5	0.0
^{99m}Tc MAG3	Whatman 3 MM	Acetone	1.0	0.0	0.0
	Whatman 3 MM	Water	1.0	1.0	0.0
^{99m}Tc bicisate	Whatman 3 MM	Ethylacetate	0.0	1.0	0.0
^{99m}Tc nanocolloid	Whatman ET 31	Saline	0.8	0.0	0.0

TABLE 8.2. Chromatographic data of radiopharmaceuticals other than ^{99m}Tc complexes[a]

Radiopharmaceuticals	Stationary phase	Solvent	R_f Values	
			Labeled product	Impurities
^{125}I RISA	ITLC SG	85% Methanol	0.0	1.0 (I)
^{131}I MIBG	Silica gel plated plastic	Ethylacetate:ethanol (1:1)	0.0	0.6 (I)
^{131}I NaI	ITLC SG	85% Methanol	1.0	0.2 (IO_3)
^{51}Cr sodium chromate	ITLC SG	*n* Butanol saturated with 1 N HCl	0.9	0.2 (Cr^{3+})
^{67}Ga citrate	ITLC SG	$CHCl_3$:acetic acid (9:1)	0.1	1.0
^{111}In DTPA	ITLC SG	10% Ammonium acetate: methanol (1:1)	1.0	0.1 (In^{3+})
^{111}In capromab[b] pendetide	ITLC SG	Saline	0.0	1.0 (In^{3+})
^{18}F FDG[b]	Silica gel	CH_3CN/H_2O (95:5)	0.37	0.0
^{90}Y , ^{111}In ibritumomab tiuxetan[b]	ITLC SG	0.9% NaCl sol	0.0	1.0

[a]Data are adapted from Procedure manual Radiochemical purity of radiopharaceuticals using Gelman Seprachrom™ (ITLC™) chromatography. Gelman Science, Inc., Ann Arbor, Michigan, 1977

[b]Data are from package insert

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Characterization and Quality Control Analysis of ^{99m}Tc-Bicisate

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TABLE 1
Radiochemical Purity of ^{99m}Tc-ECD Stored at Room Temperature

Analysis method	% RCP at time after reconstitution (mean ± SE)			Accuracy of method (%)
	30 min	120 min	360 min	
Baker-Flex SG/EtAc	98.3 ± 0.8 (n=5)	—	—	1.8
W17/EtAc	97.8 ± 0.3 (n=19)	98.8 ± 0.8 (n=3)	98.7 ± 0.3 (n=3)	1.3
C18/saline, regular	98.2 ± 0.2 (n=19)	98.0 ± 0.5 (n=3)	99.0 ± 0.4 (n=3)	1.0
C18/saline, fast	93.8 ± 0.4 (n=19)	93.8 ± 0.5 (n=3)	94.8 ± 0.4 (n=3)	1.8
ITLC SG/saline	97.4 ± 0.1 (n=3)	98.6 ± 0.0 (n=3)	97.0 ± 0.3 (n=3)	0.2
SAX/WFI	96.0 ± 1.2 (n=3)	—	—	2.1

SG = silica gel; EtAc = ethylacetate; W17 = Whatman 17; SAX = strong anion exchange.

CONCLUSION

The RCP of ^{99m}Tc-ECD was found to be 98% by the manufacturer-recommended Baker-Flex silica gel/ethyl acetate method, the same as values derived by other analysis methods such as Whatman 17/ethyl acetate, Amprep C18/saline, and ITLC silica gel/saline. The lengthy analysis time of ITLC silica gel/saline was inconvenient, and the strong anion exchange/WFI method underestimated the percentage of ^{99m}Tc-ECD. The simpler, faster and safer Amprep C18/saline system, eluted at a regular flow rate is recommended as the method of choice for routine quality control analyses of ^{99m}Tc-ECD.

Sterility test

- 1. To prove that radiopharmaceuticals are in essence free of viable microorganisms.
- Incubate the radiopharmaceutical sample in

(1) fluid thioglycollate medium at 30 ~ 35℃ for 14 days

(2) sobean-casein digest medium for incubation at 20 ~ 25℃ for 14 days

培養基	試驗微生物	培養14天	
	菌種	培養溫度	培養狀態
硫醇乙酸鹽培養基 Fluid Thioglycollate Medium (FTM)	金黃色葡萄球菌 (Staphylococcus aunreus)	30 ~ 35℃	有氧
	綠膿桿菌 (Pseudomonas aeruginosa)		
	產芽孢梭菌 (Clostridium sporogenes)		無氧
大豆分解蛋白質-乾酪素 Soybean-Casein Digest (SCD)	枯草桿菌 (Bacillus subtilis)	20 ~25℃	有氧
	白色念珠菌 (Candida albicans) (fungi)		
	黑麴菌 (Aspergillous niger) (fungi)		

Apyrogenicity test

- Pyrogens include any substance capable of eliciting a febrile (or fever) response upon injection or infection 。
- The severity of response is dependent upon the amount of pyrogen administered。
  (Hypotension 、 Myalgia 、 headache 、 nausea、 sepsis …)
- The USP set a limit for radiopharmaceutical at 175EU/ V 。
  (EU=Endotoxin Units) (V = maximum dose in ml)
- Sterile ≠ Pyrogen free
- Pyrogen (熱原) ≠ Endotoxin (內毒素)

Apyrogenicity test

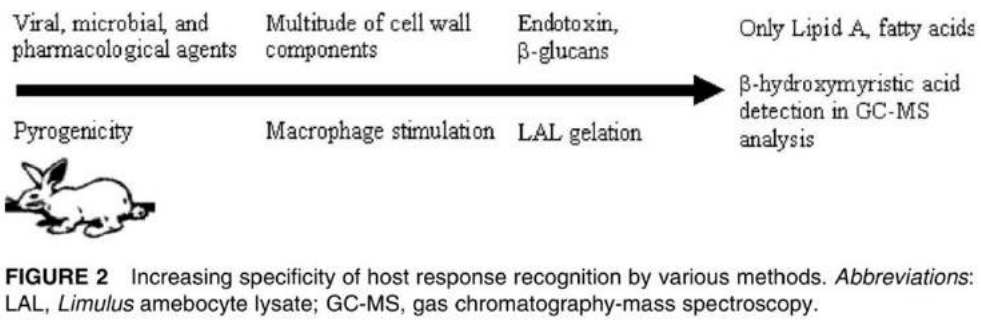


FIGURE 2 Increasing specificity of host response recognition by various methods. *Abbreviations*: LAL, *Limulus* amebocyte lysate; GC-MS, gas chromatography-mass spectroscopy.

- Pyrogen Test - In vivo test

  Rabbit fever test

- Bacterial Endotoxin Test (BET) -In vitro test

  Limulus Amebocyte Lysate (LAL) test

Primary ways in which drug products inhibit the LAL test are :

1、Suboptimal pH
2、Aggregation or adsorption of control Endotoxin spikes
3、Unsuitable cation concentrations
4、Enzyme or protein modification
5、Non-specifc LAL activation (sometime an interference mechanism can not be determined .)

Limitations of the LAL test :

Meperidine HCl 、Promethazine HCl 、Oxacillin sodium 、 Sulfisoxazole .

In vitro limulus amebocyte lysate(LAL) test

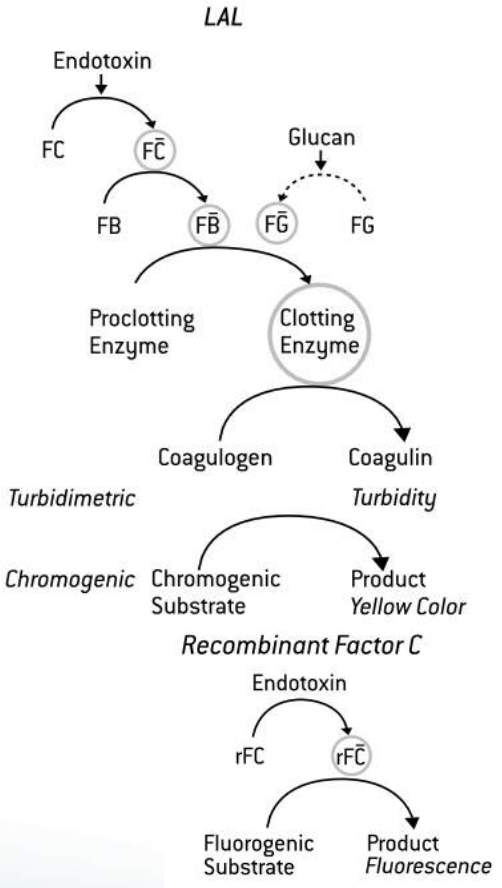
- Semi-quantitative method ：

  Gel-clot techniques (濁度法)

- Quantitative method：

  Photometric techniques (呈色法)

  - Turbidimetric techniques
    - End-point
    - Kinetic
  - Chromogenic techniques
    - End-point
    - Kinetic
  - Fluorescent Assays - End-point



Chromogenic Endotoxin Test

- Incubating Microplate Readers (ELx808™) (FLx800™)
- 無熱源水 (LAL Reagent Water)
- 標準品(Control Standard Endotoxin (CSE) E. Coli)
- 內毒素呈色劑 (Pyrochrome®)
- PyroGene™ rFC Kit
- Pyrogen-Free 96-well plates