^{68}Ga/^{177}Lu物性及化性與在PSMA-11的調製

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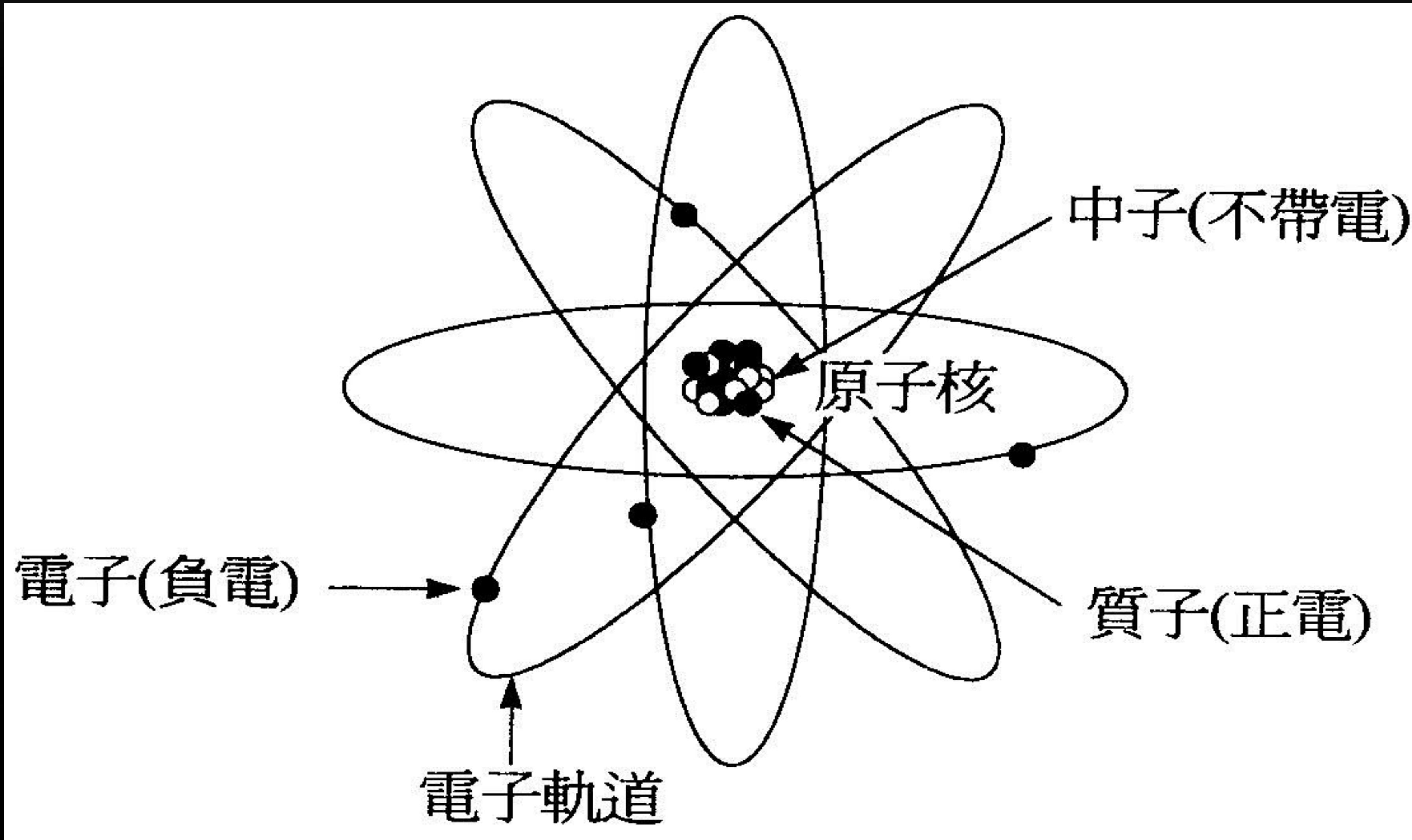
Outline

- Fundamental nuclear physics
- Radioisotope produce
- $^{68}Ge/^{68}Ga$ Generator reviews
- $^{68}Ge/^{68}Ga$ Generator Eluate quality and chemistry
- Chelating agent
- Radionuclide therapy
- Peptide receptor radionuclide therapy
- 68Ga-PSMA-11 produce

Fundamental nuclear physics

原子結構示意圖



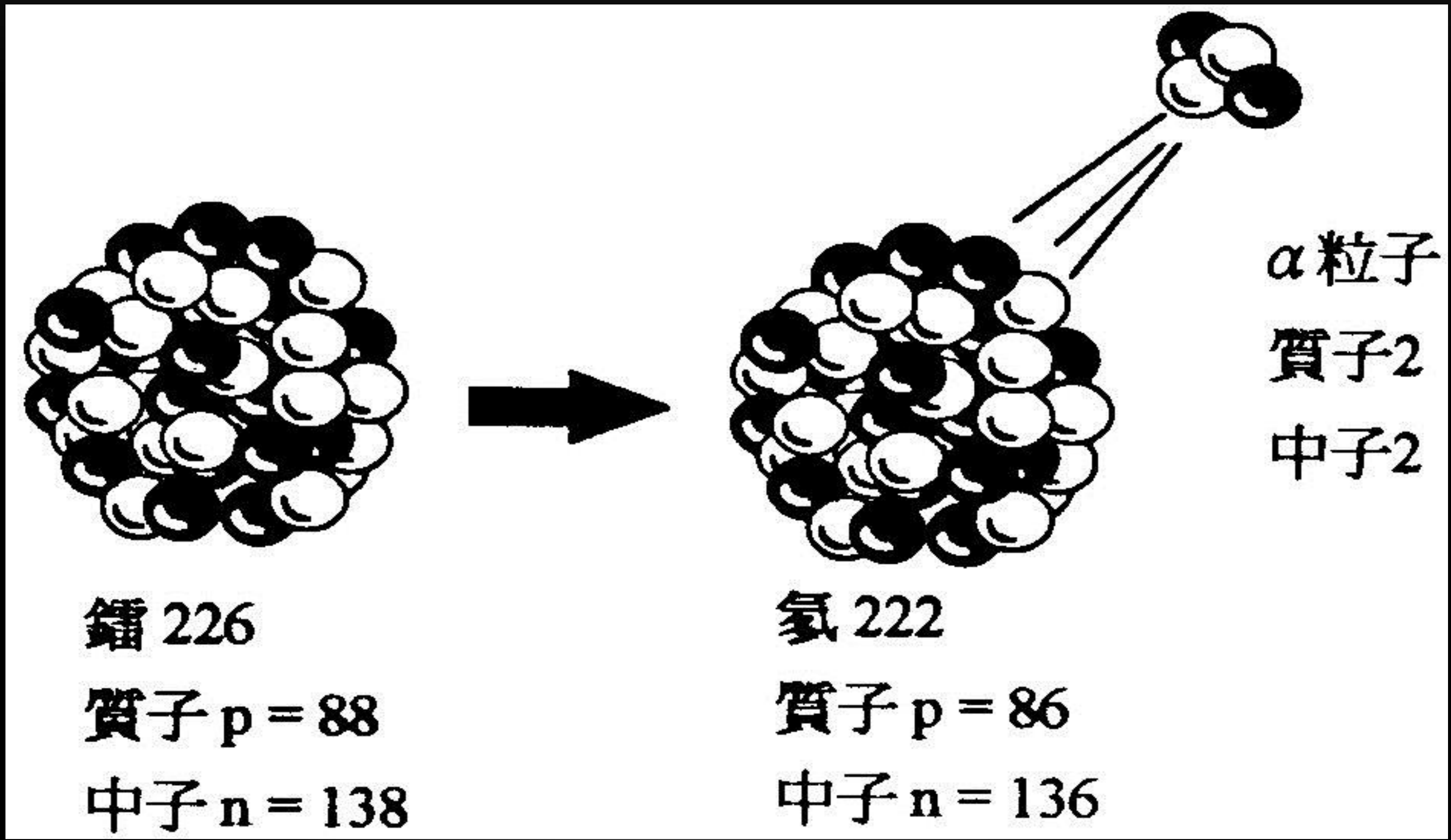
Nuclide (核種)

- An atomic species characterized by specific values of the atomic number (*Z*, 原子序) and the mass number (*A*, 質量數)
- Symbolized as $^{A}_{Z}\mathbf{X}$ (*e.g.* $^{12}_{6}\mathbf{C}$, $^{14}_{6}\mathbf{C}$)

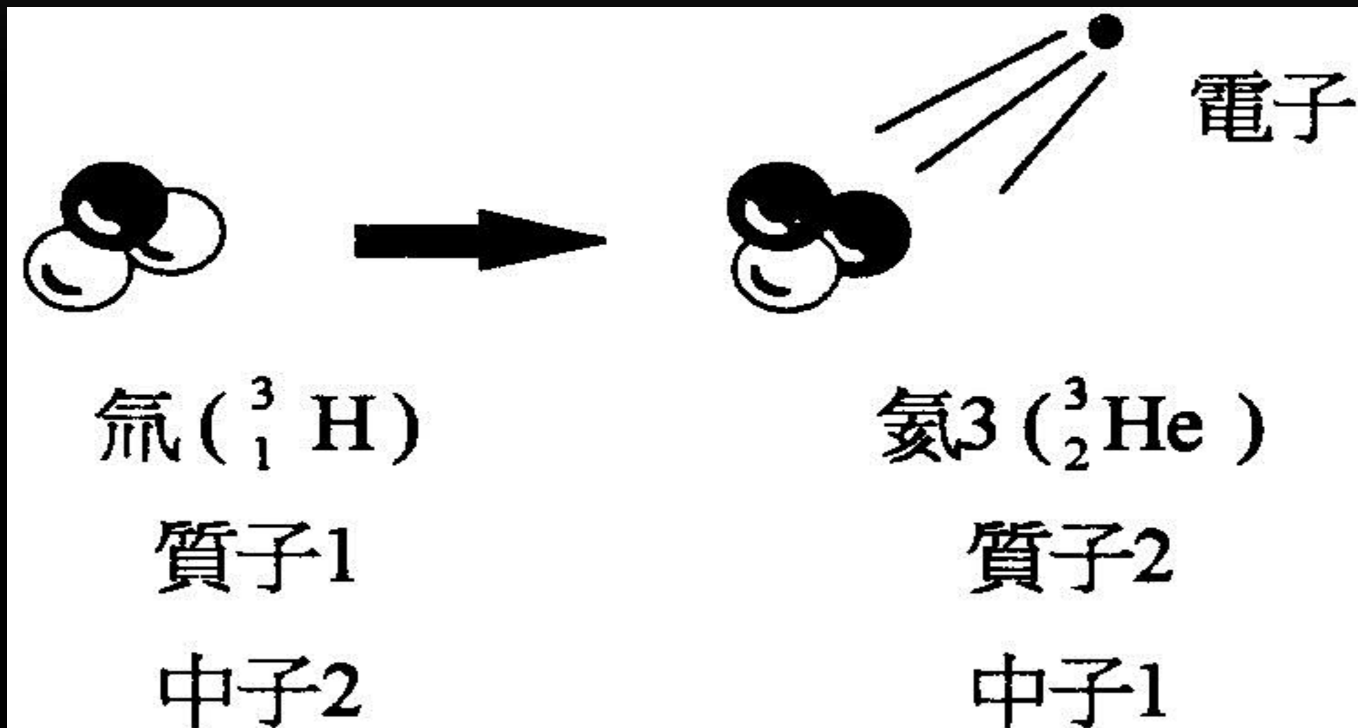
Radionuclide（放射核種)

- An atomic that has excess nuclear energy, making it unstable.
- This excess energy can be released by emitting from the nucleus as γ-radiation or particles (α-particle or β-particle) from the nucleus.

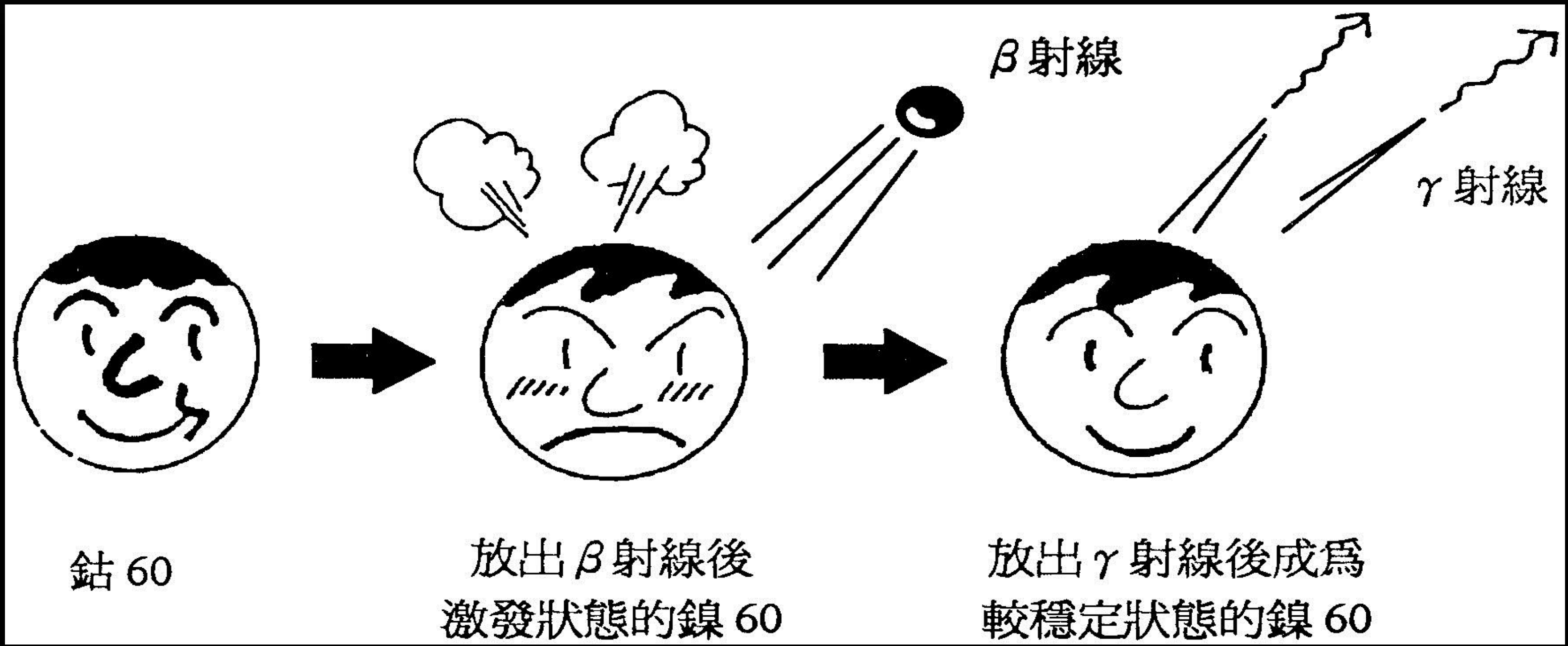
α-粒子輻射



β-粒子輻射



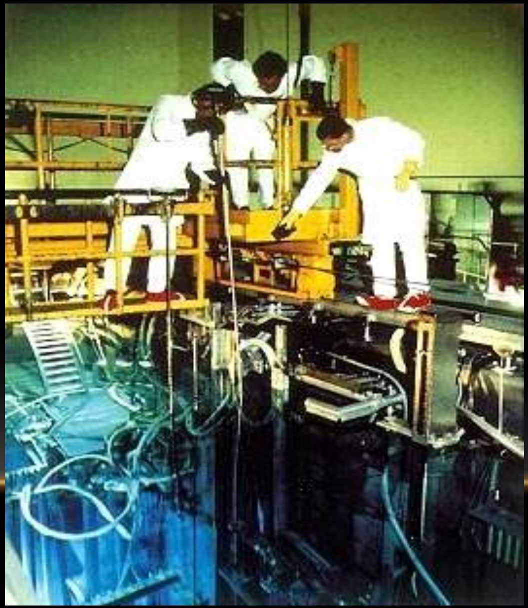
γ-射線



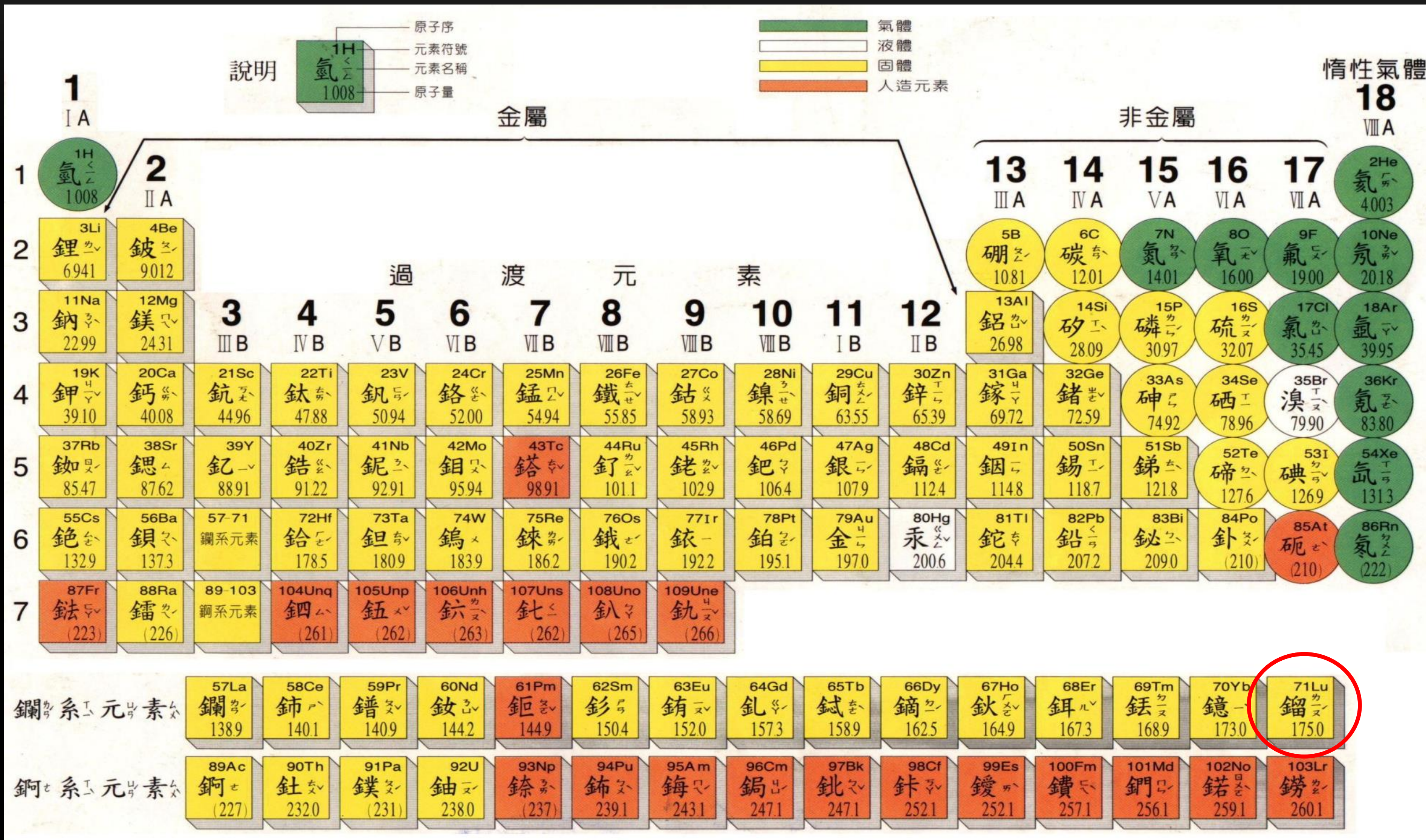
Radioisotope produce

Lutetium-177 (Lu-177)

生產：　在核子反應器內以中子束照射 Lu-176 靶產生
物理半衰期：6.647天
衰變模式：β^- 衰變
最大 β^- 能量：0.498 MeV
主要 γ 能量：112.95 keV (6.17%), 208.37 keV (10.36%)



Lutetium (Lu; 鎦)



Inorganic chemistry of Lu

- Electrons arranged in the [Xe]4f145d16s2 configuration.

- Lu atoms lose the two outermost electrons as well as the only 5d electron, thereby generating a +3 metal cationic species.

- Lutetium salts as well as their aqueous solutions, with the common exception of the iodide, are colorless and form white crystalline solids upon drying. While the nitrate, sulfate, and acetate salts are water soluble and crystallize with water molecules to form hydrates, the oxide, hydroxide, fluoride, carbonate, phosphate, and oxalate are insoluble in water.

Physical properties of Lu-177

- Lu-177 has a physical half-life of 6.647 days. Lu-177 emits β-rays that have a short range in soft tissue (average 0.23 mm, max. 1.7 mm) and γ-rays.
- The The radionuclide is produced by the Lu-176(n,γ)Lu-177 reaction. Lu is a rare earth element with the atomic number 71.

Half-life	Type of decay	Maximum energy (MeV) of β rays and percentage emitted	Photon energy (MeV) and percentage emitted	Percentage of internal conversion electrons emitted	Effective dose rate constant ($\mu Sv \cdot m^2 \cdot MBq^{-1} \cdot h^{-1}$)
6.647 days	β^-	0.176–12.2% 0.385–9.1% 0.498–78.6% Other	0.113–6.4% 0.208–11.0% Other 0.0555–4.5% Hf-Kα 0.0637–1.2% Hf-Kβ	14.5% 0.73%	0.00517

Cited from Radioisotope Pocket Data Book (11th ed.), Japan Radioisotope Association, 2011

Gallium (Ga-68)

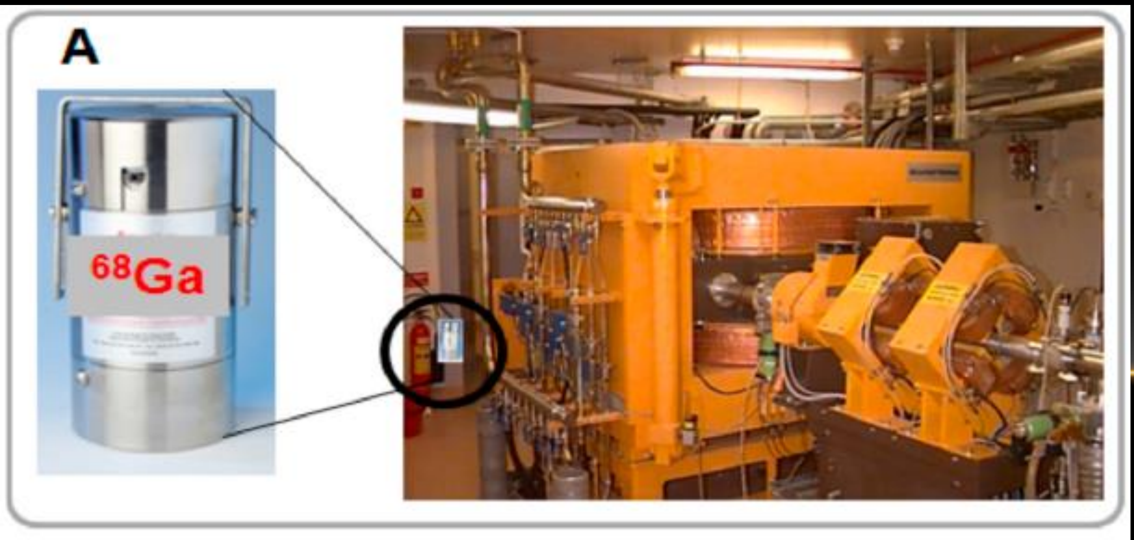
生產：　　　　1. 在68Ge/68Ga Generator母核68Ge衰變成68Ga

　　　　　　　2. 迴旋加速器生產

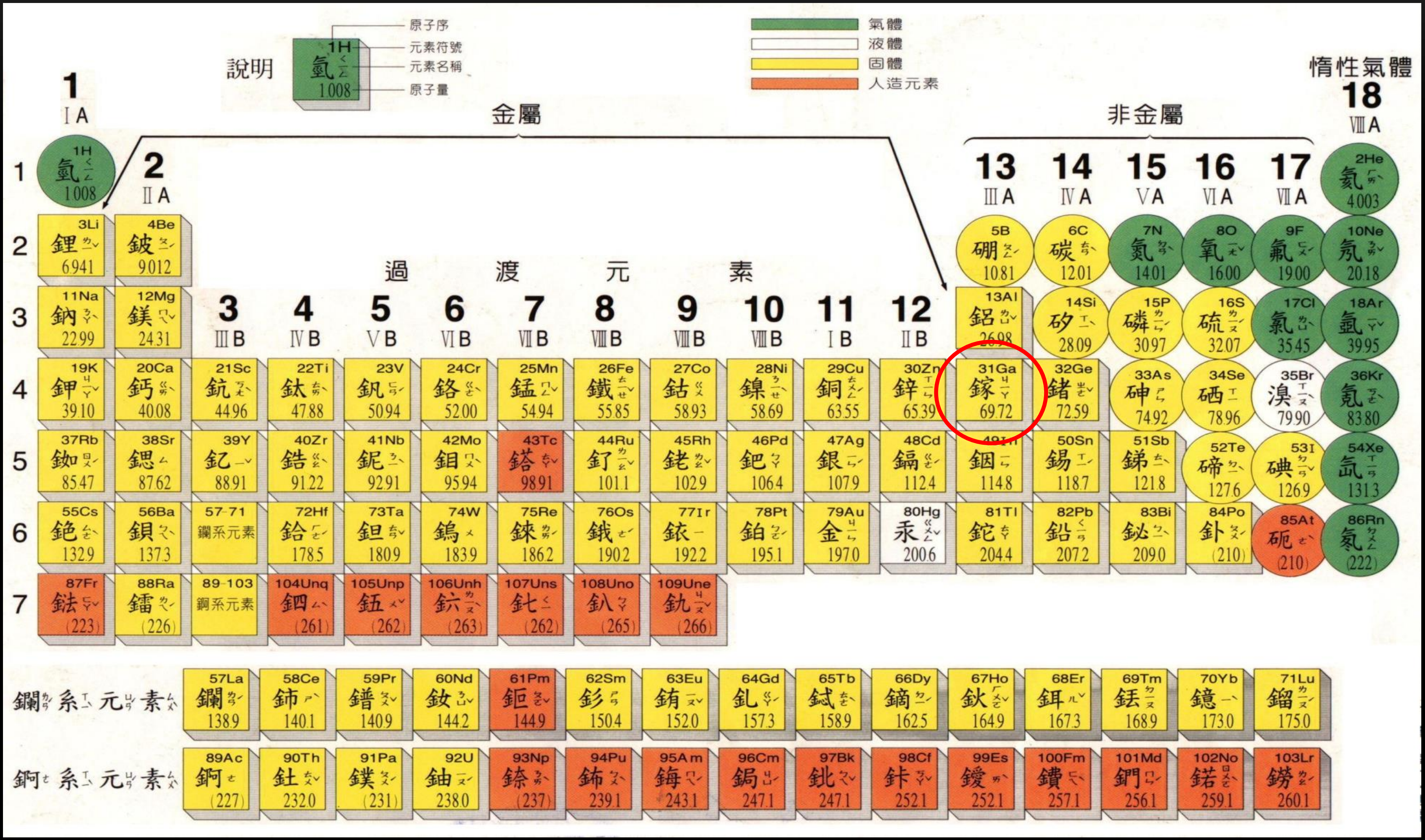
物理半衰期：　67.71分鐘

衰變模式：　　β^+ 衰變

主要γ能量：　兩道511 KeV 互毀光子



Gallium (Ga; 鎵)



說明
原子序
元素符號
元素名稱
原子量
氣體
液體
固體
人造元素
金屬
非金屬
惰性氣體
過渡元素
鑭系元素
錒系元素
31Ga
鎵
69.72

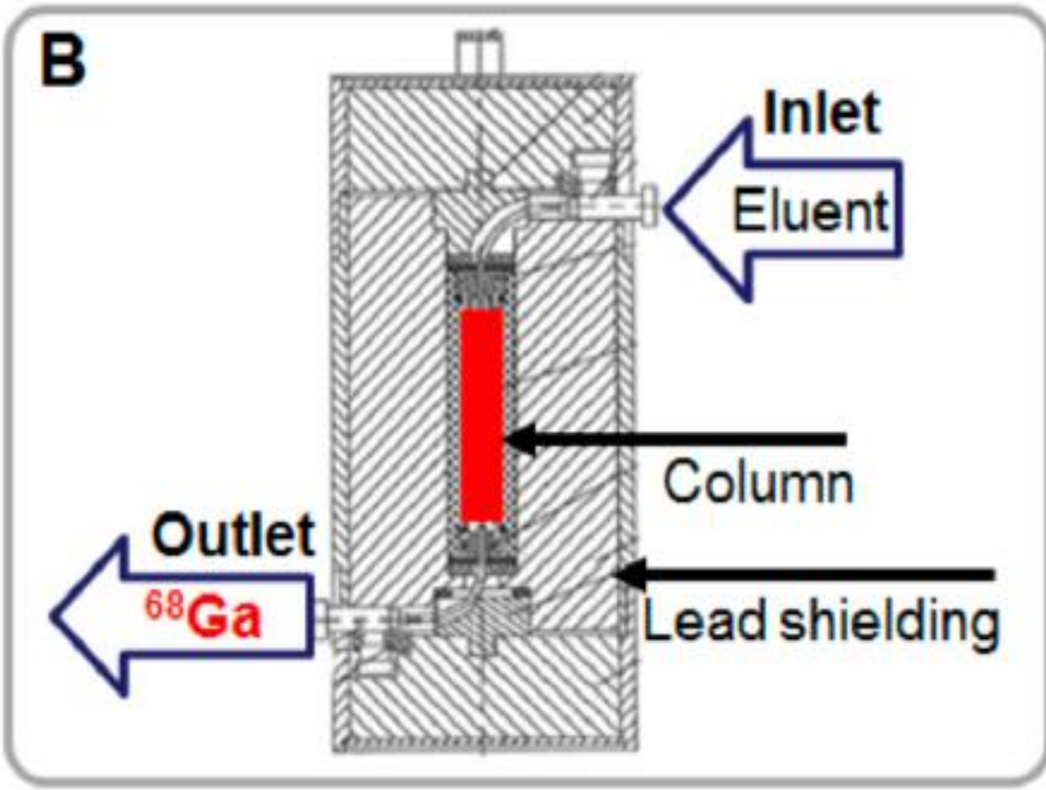
^{68}Ge/^{68}Ga Generator

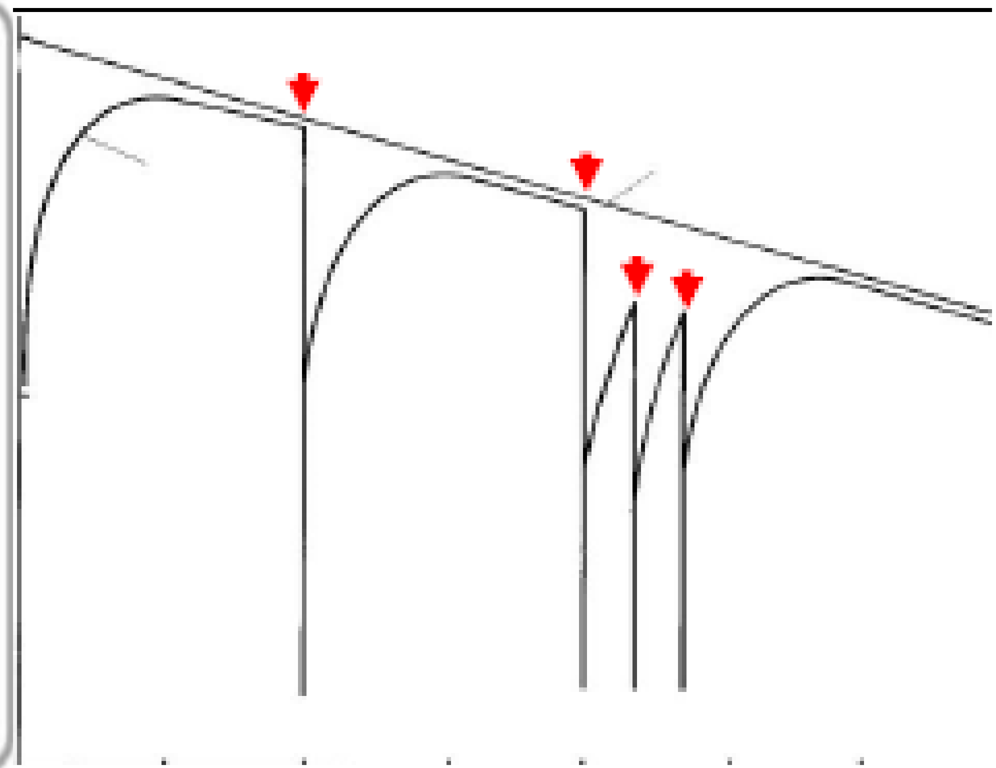
$$^{68}_{32}Ge + \,_{-1}^{0}e \rightarrow \,^{68}_{31}Ga + \nu$$

$$^{68}_{31}Ga \rightarrow \,^{68}_{30}Zn + \beta^{+} + \nu; p \rightarrow n + \beta^{+} + \nu$$

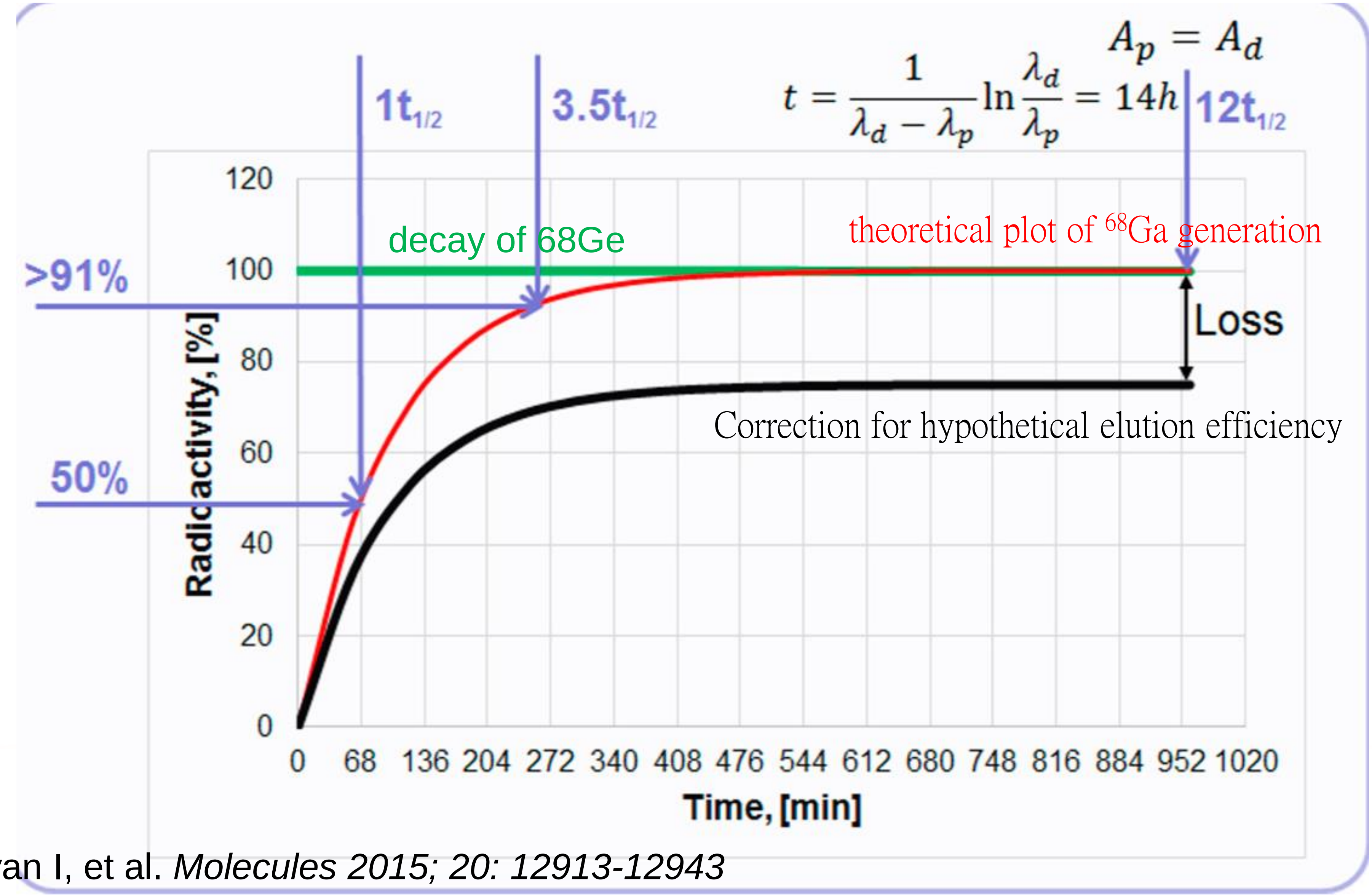
$$\frac{t_{1/2}(^{68}_{32}Ge)}{t_{1/2}(^{68}_{31}Ga)} = 5762$$

- 14hr for equilibrium
- 4hr for achieve 91%





Equilibrium with ^{68}Ge decay and ^{68}Ga accumulation



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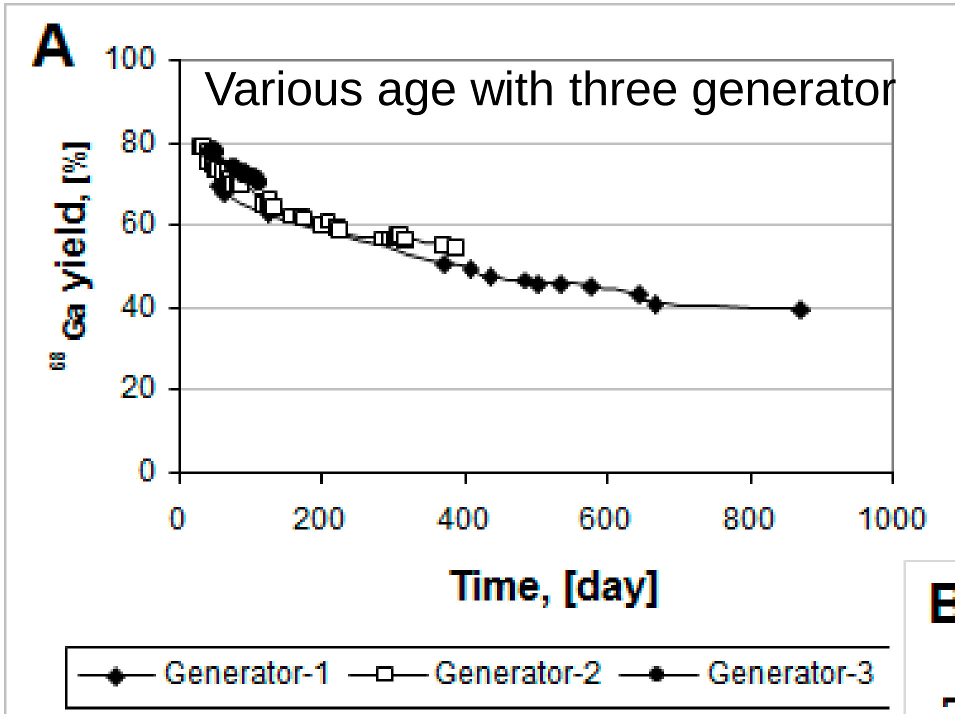
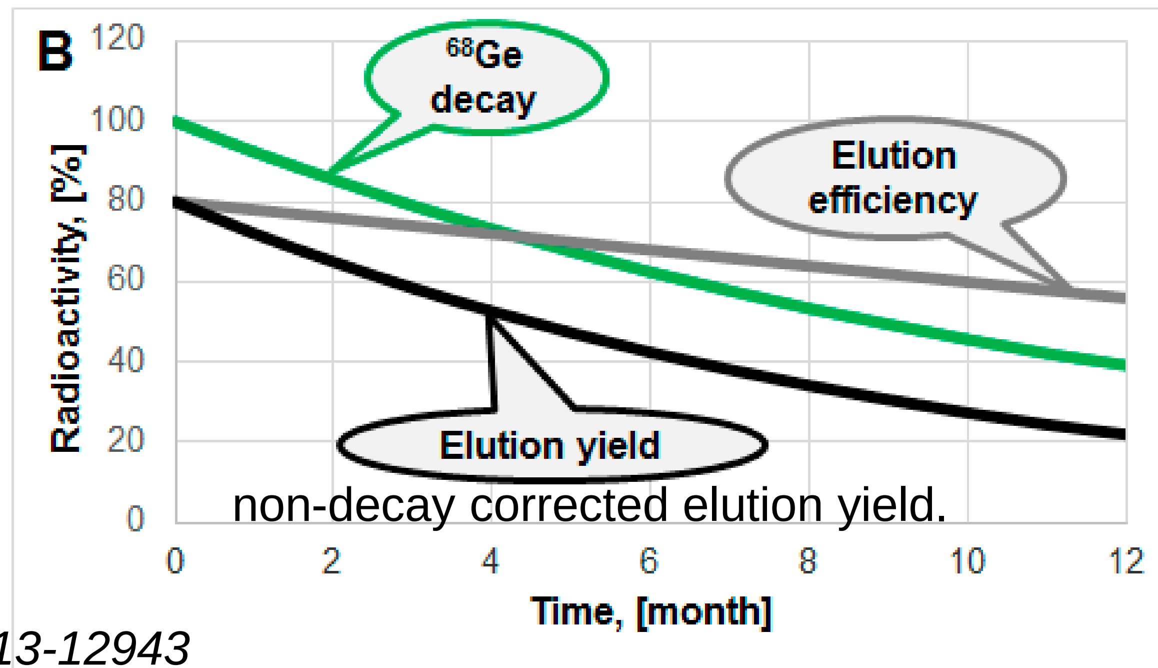
$^{68}Ge/^{68}Ga$ Generator elution efficiency



29 months 14 months 3 months

- Highly reproducible and robust performance

- The elution efficiency depends on the 68Ge breakthrough and column matrix, and may drop in time course, however the 68Ge-decay component is larger



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$^{68}Ge/^{68}Ga$ Generator Column

- 1. Radiation resistance; 2.chemical stability of the column material; 3.eluate sterility; 4.apyrogenecity; 5. ^{68}Ge breakthrough; 6.eluent type; 7. elution profile.
- Most of the generators use acidic eluent since it provides cationic Ga(III) for the further direct chemistry.

Various sorbents and respective eluents used in column based $^{68}Ge/^{68}Ga$ generators.

$^{68}Ge/^{68}Ga$ Generator Column Matrix

Inorganic (Eluent)		Organic (Eluent)
	Wildly used for less radiolysis	
SnO_2 (1 M HCl)	95% of ^{68}Ga in 2 mL	*N*-methylglucamine (0.1 M HCl; 0.1 M NaOH; citrate; EDTA)
TiO_2 (0.1 M HCl)		Pyrogallol-formaldehyde (0.3 M HCl)
CeO_2 (0.02 M HCl)		Nanoceria-polyacrylonitrile (0.1 M HCl)
ZrO_2 (0.1 M HCl)		^{68}Ge breakthrough of $<10^{-5}\%$
Zr-Ti ceramic (0.5 M NaOH/KOH; 4 M HCl; acetate; citrate)	^{68}Ge breakthrough of $<10^{-3}\%$	
Nano-zirconia (0.01 M HCl)		

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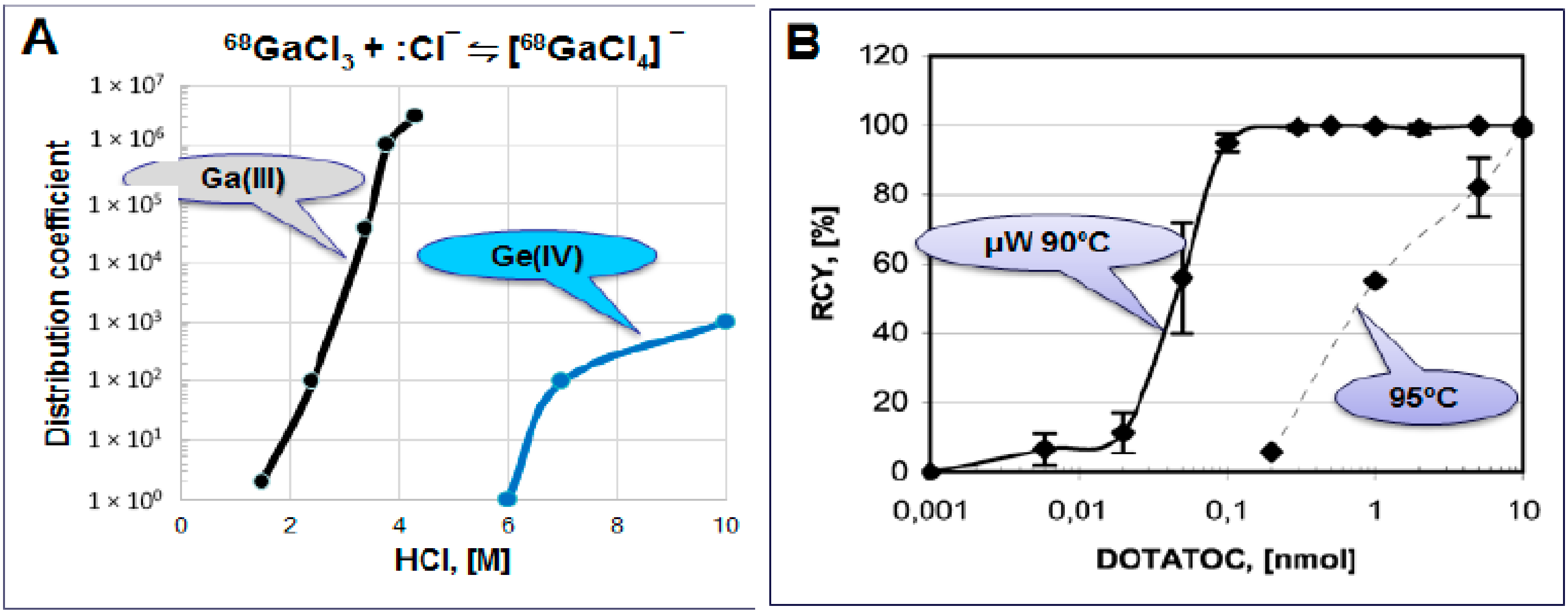
Basic methods of 68Ge/68Ga generator eluate utilization.

Method	Eluent	Volume	Cation Impurity Reduction	^{68}Ge Elimination
Full volume, 5–8 mL	H_2O/HCl	>5000 µL	Not purified	none
Fractionation, 1 mL	H_2O/HCl	1000 µL	Not purified	none
Eluate Concentration and Purification				
Anion exchange	H_2O	200 µL	One step: Al (>99%), In (>99%), Ti (90%)	Complete
Cation exchange	Acetone/HCl	400 µL	Two steps: Zn (×10^5), Ti (×10^2), Fe (×10)	10^4 fold
	NaCl/HCl	500 µL	NA	NA
	EtOH/HCl	1000 µL	Two steps: Ti (11%), Fe (×7)	400 fold
Combined cation/anion exchange	●Acetone/HCl ●H_2O/HCl	1000 µL	NA	10^5 fold

$^{68}GaCl_3$ and ligand labeling chemistry

- **(A)** Distribution coefficient D for the adsorption of Ga(III) and Ge(IV) chloride anions on an anion-exchange resin;
- **(B)** Influence of the DOTA-TOC amount on thedecay-corrected radiochemical yield of the 68Ga complexation reaction in HEPES buffer system using the full available ^{68}Ga radioactivity in 200 µL volume obtained after the pre-concentration and purification step.

Solid line: 1 min microwave heating at 90 ± 5 ˚C,
dashed line: 5 min conventional heating at 95 ˚C.



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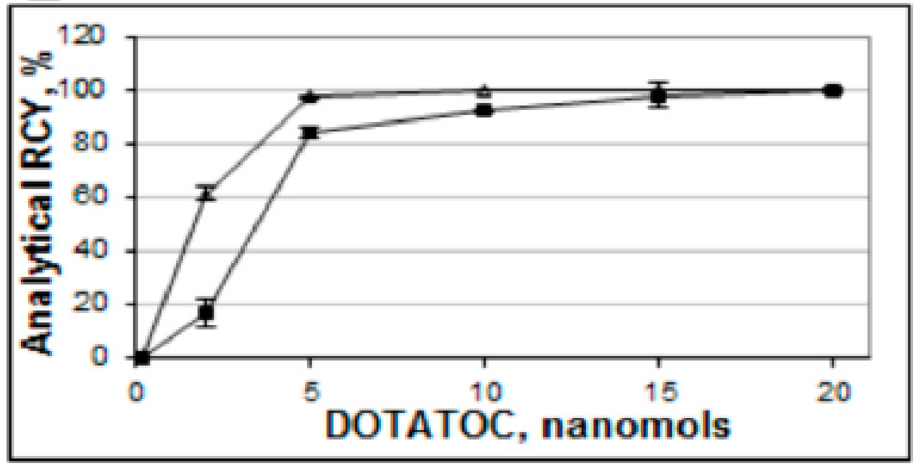
$^{68}Ge/^{68}Ga$ Generator Eluate quality and chemistry

A

pH	Species	Solubility
0-3	Ga^{3+}; $[Ga(H_2O)_6]^{3+}$	soluble
3-7	$Ga(OH)_3$	insoluble
>7	$[Ga(OH)_4]^-$	soluble

B



(A) Table showing formation of various species dependent on pH;

(B) Influence of the buffering system (■ sodium acetate, Δ HEPES) on the 68Ga radioactivity incorporation for different DOTA-TOC quantities (1 min microwave heating at 90 ± 5 °C). The reaction was conducted using the 1 mL peak fraction of the original generator eluate;

(C) Table comparing characteristics of acetate and HEPES buffers.

C

	HEPES buffer	Acetate buffer
Biocompatible	+	+
Toxicology (LD_{50})	Quail: 316 mg/kg)	Rat: 90 mL/kg
Stabilizing agent	+	+
Transchelation	+	+
pH	+	+
Human use	–	+
Purification	Required	Not required
QC	Required	Not required

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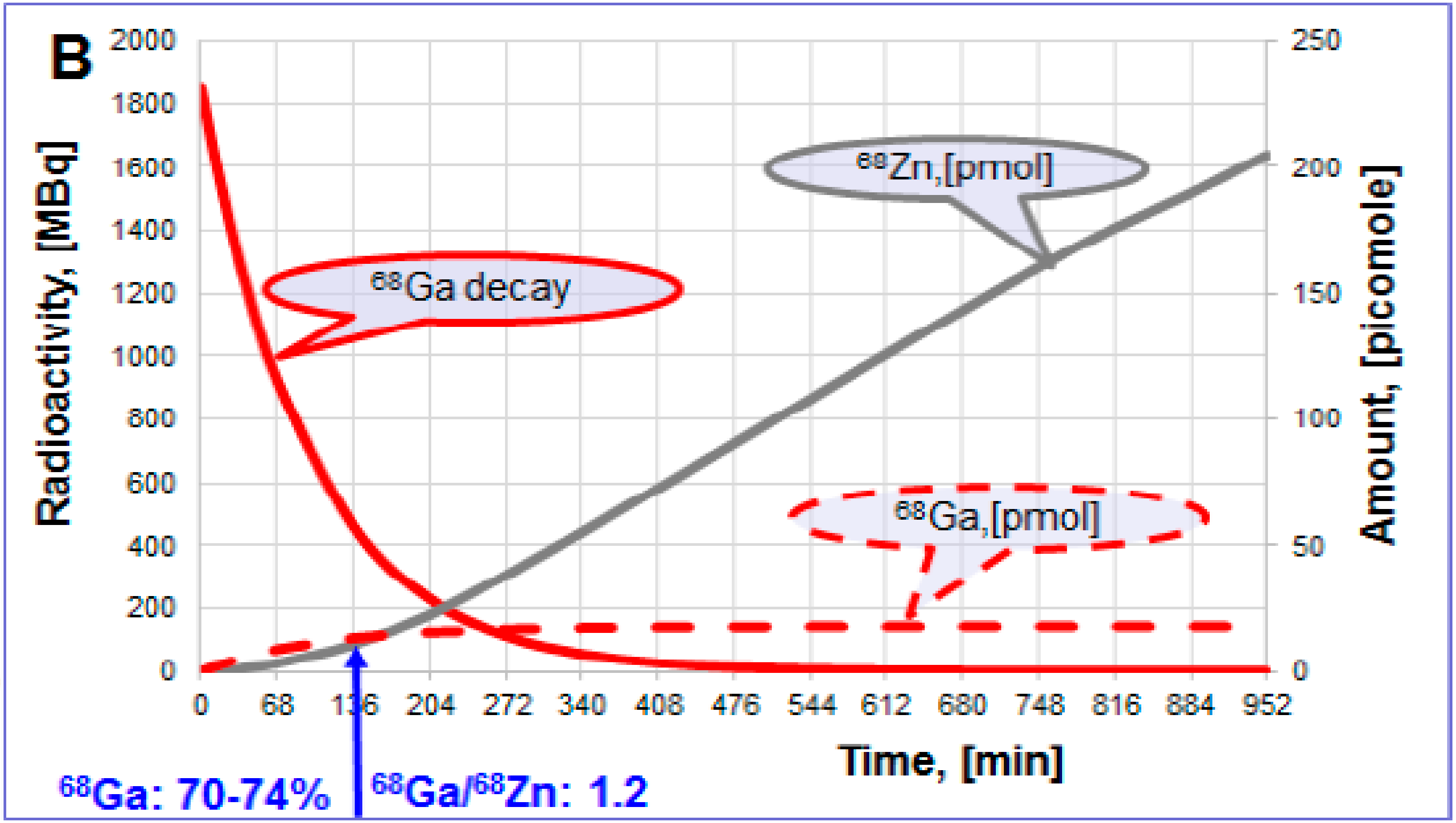
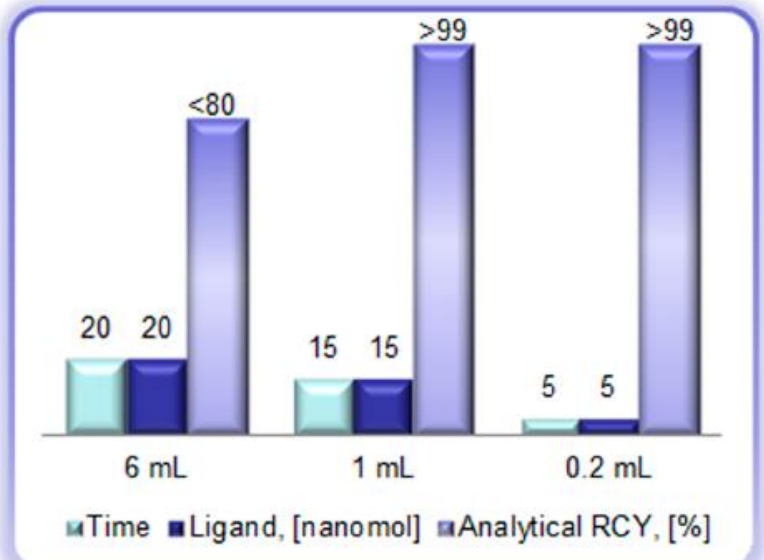
^{68}Ge/^{68}Ga Generator Eluate quality and chemistry

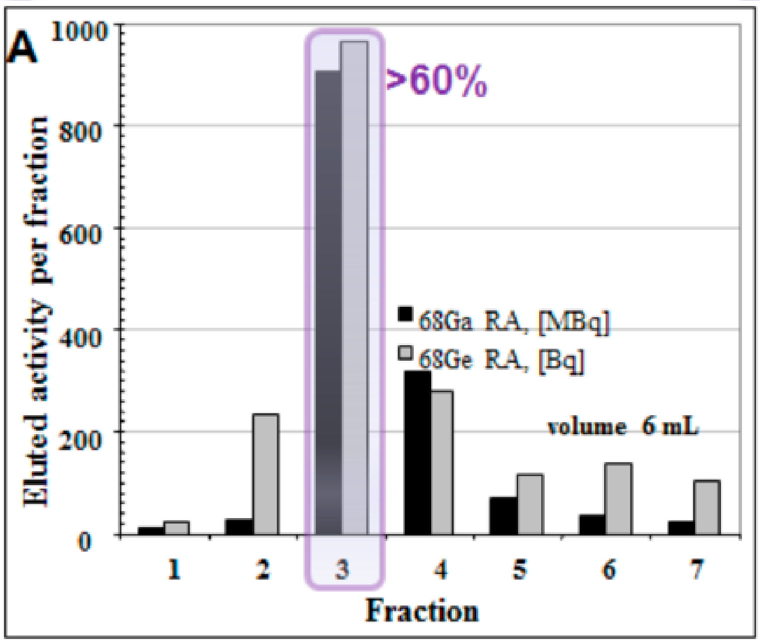
(A) Zn(II) forms thermodynamically stable complex with DOTA derivatives and interferes 68Ga-labeling reaction, especially in the excessively high concentration;
(B) Theoretical graphs (50 mCi generator) showing 68Ga decay (MBq) and accumulation of radioactive 68Ga and stable Zn(II) in picomoles within the time frame of secular equilibrium.

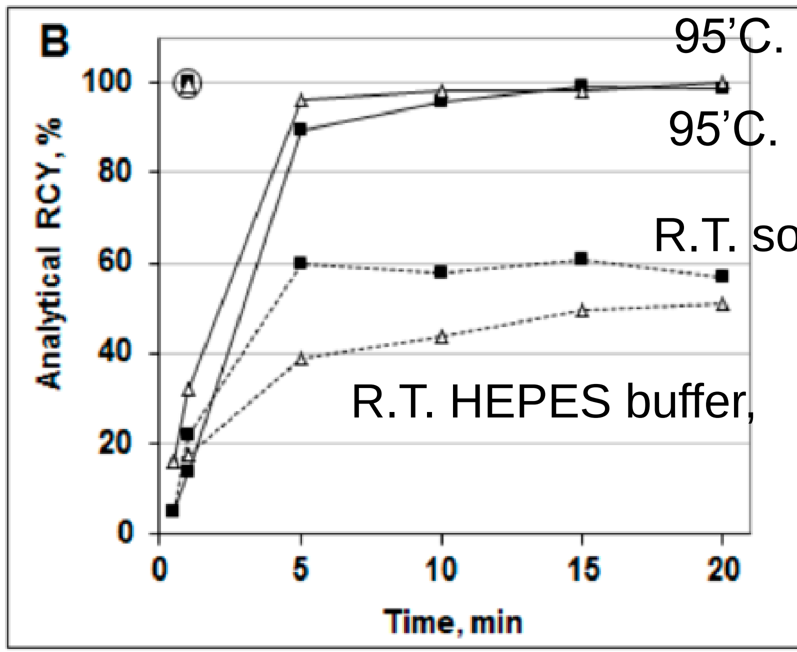


$^{68}Ge/^{68}Ga$ Generator Eluate quality and chemistry



- Reaction heating time (min), ligand amount (DOTA-TOC, (nanomole)), and analytical radiochemical yield (%) of the [68Ga]Ga-DOTA-TOC synthesis.
- Fraction 3 (1 mL) contains over 60% of the available 68Ga radioactivity; The profiles for the 68Ga elution and the 68Ge breakthrough are similar; the 68Ge breakthrough is ~10^{-3}%.
- 1. Eluate volume, 2. HCl eluent molarity, 3. content of metal cationic impurities influence the efficiency of 68Ga-labeling chemistry. 4.pH prevention of Ga(III) precipitation and colloid formation, 5. radiolysis of vector molecules,





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$^{68}Ge/^{68}Ga$ Generator Development

- Efficient separation of the daughter and parent elements due to their different chemical properties;
- Physical half-life of parent allowing rapid daughter regrowth after generator elution; stable granddaughter with no radiation dose to the patient;
- Long shelf-life; effective shielding of the generator, minimizing radiation dose to the user and expenses of hot cells; sterile and pyrogen-free output of the generator
- Mild and versatile chemistry of the daughter 68Ga amenable to automation and kit preparation.

Table 3. Milestones of $^{68}Ge/^{68}Ga$ generator development.

Time Period	Milestone
1950–1970	First $^{68}Ge/^{68}Ga$ generator Clinical applications: ^{68}Ga-EDTA; ^{68}Ga-citrate; ^{68}Ga-colloid
1970–1980	Further development of $^{68}Ge/^{68}Ga$ generator: $^{68}Ga(III)$
1990s	Commercial generator: $^{68}Ga(III)$
2000s	Clinical use with advent of SST ligands
2011	GMP generators
2014	Marketing authorization

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Commercial $^{68}Ge/^{68}Ga$ Generator

- 1. long shelf-life of 1–2 year; 2. stable column matrixes; 2. cationic chemical form of 68Ga(III)
- Variation in the1. molarity of HCl elution; 2.metal cation content; 3. mental cation content and ^{68}Ge breakthrough.

	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

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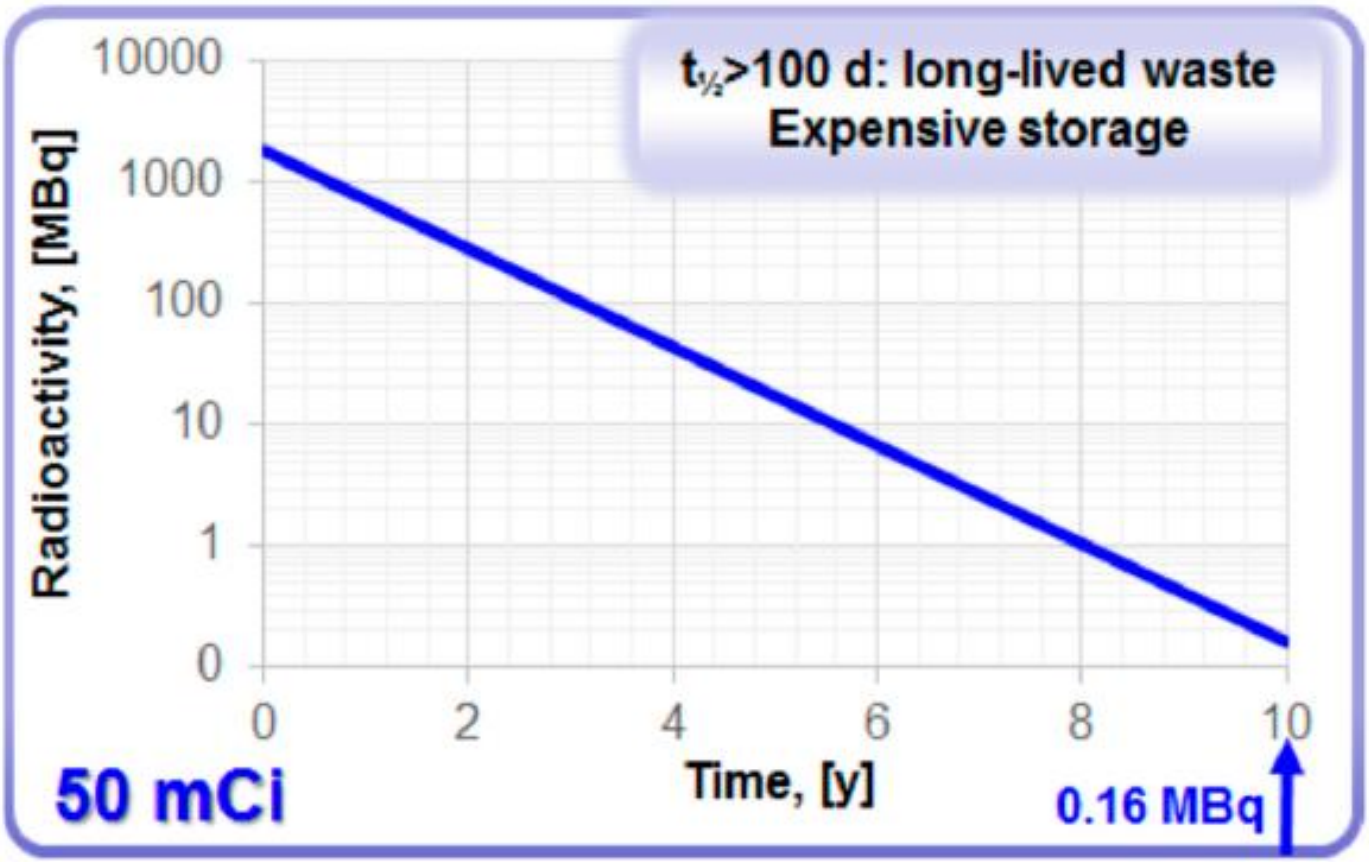
Commercial $^{68}Ge/^{68}Ga$ Generator

➢ long shelf-life may raise concern with regard to
1. Radiolytic stability of column material,
2. Sterility of the eluate,
3. Long-lived ^{68}Ge waste management.



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BIFUNCTIONAL CHELATING AGENT

Table 1 Overview on Structures of the Sole Chelate Chelators (CL), Their Thermodynamic Complex Formation Stability Constant (log K) and Typical Reaction Parameters to Achieve the High-Radiochemical Yields (RCY) Mentioned of the ^{68}Ga Ligand Complexes. Also, Those Derivatives Are Included, Where ^{67}Ga Was Applied Instead of ^{68}Ga.

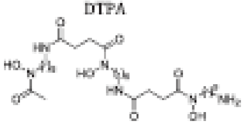
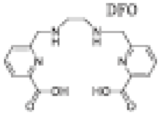
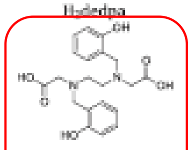
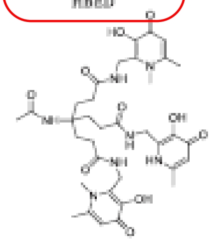
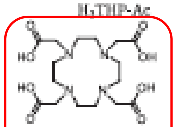
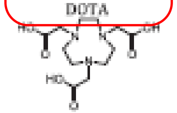
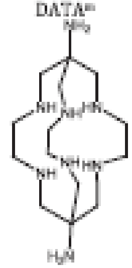
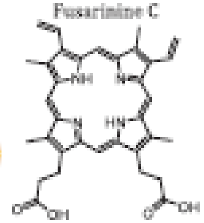
CL	log K_{GaL}	Typical Radiolabeling (Buffer, pH, Reaction Time, and Reaction Temperature)	RCY (%)	Ref
 DTPA	24.3			7
 DFO	28.6	0.1 M ammonium acetate (pH = 4.5), 5 min, RT	98	8,9
 H_2dedpa	28.1	0.1 M sodium acetate, 10 min, RT	97	10,11
 HBED	38.5	2.1 M HEPES buffer (pH = 4.2), 4 min, ≈ 95°C/RT	99	12,13
 H_3THP-Ac	–	1 M ammonium acetate, 5 min, RT	99	14
 DOTA	21.3	1 M HEPES buffer (pH = 4.8), 5 min, ≈ 95°C	>90	2,15
 NOTA	31.0	1 M HEPES (pH = 3.5), 10 min, ≈ 95°C	>95	1,16

Table 1 (continued)

CL	log K_{GaL}	Typical Radiolabeling (Buffer, pH, Reaction Time, and Reaction Temperature)	RCY (%)	Ref
 AAZTA	22.2	1 M sodium acetate (pH = 4.5), 10 min, RT	>95	17,18
 DATA[m]	21.7	0.2 M sodium acetate, 1 min, RT	>95	19
 $[NH_2]_2$-sar	–	0.1 M sodium acetate, 35 min, ≈ 85°C	98	20
 Fusarinine C	–	2 M sodium acetate (pH = 5), 5 min, RT	98	21
 Porphyrins	–	sodium acetate (pH = 4.5), 45 min, ≈ 120°C/MW	33	22

MW, microwave; RT, room temperature.

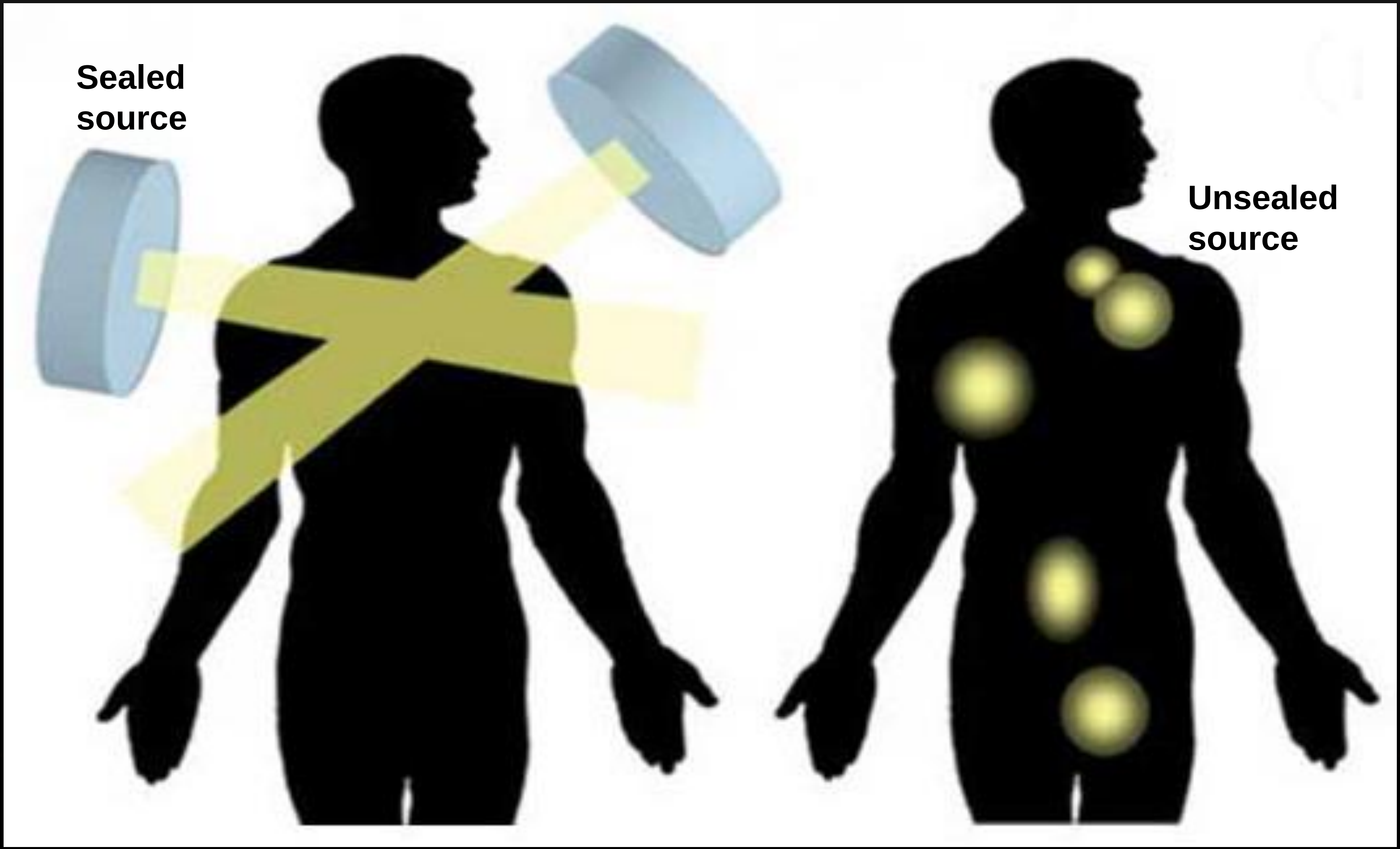
HBED-CC BIFUNCTIONAL CHELATING AGENT

- Acyclic radiometal chelator N,N'-bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N'-diacetic acid (HBED-CC) was first coupled with tetrazine and after successful synthesis, the compound was labeled with 68Ga.
- Aim of the study was to discover the potential of this compound to pass the cell membrane and to determinate its properties. The synthesis of HBED-CC-tetrazine was successfully optimized with good yields in a range of 65-85 %.
- Radiosynthesis of [68Ga] Ga-HBED-CC-tetrazine was also optimized using different temperatures, reaction times and precursor amounts. All conditions resulted in good radiochemical yields. Optimized conditions for radiolabeling turned out to be in 85 degrees for 20 minutes which resulted in 97 % of radiochemical yield with over 98 % radiochemical purity. The properties of the labeled compound [68Ga] Ga-HBED-CC-tetrazine were tested, such as lipophilicity and the stability of the compound in a presence of iron.

Radionuclide Therapy（放射核種治療）

- A form of treatment that delivers therapeutic doses of radiation to malignant tumors.
- For example, by administration of a radiolabeled molecule designed to target certain tumor cells, and kill them by radiation energy.

Radiation Therapy (放射線治療) | Radionuclide therapy (放射核種治療)



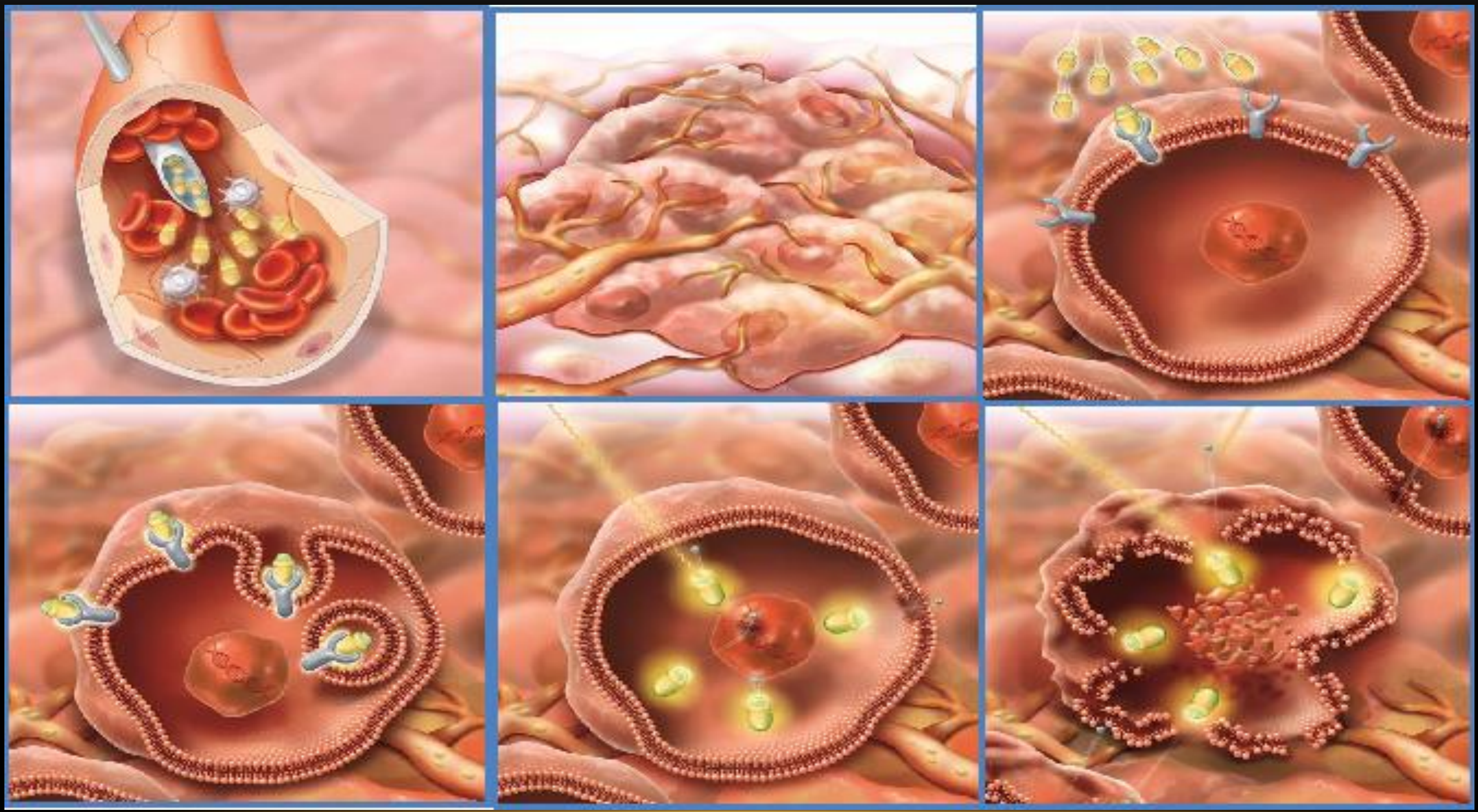
Radionuclides for Therapy

Radionuclide	Decay mode
I-131	$\beta + \gamma$
P-32	β
Sr-89	β
Re-186	β
Sm-153	$\beta + \gamma$
Ra-223	α
Y-90	β
Lu-177	$\beta + \gamma$

Peptide Receptor Radionuclide Therapy (PRRT)
（胜肽受體放射核種治療）

- A type of unsealed source radiotherapy.
- Using a radiopharmaceutical which targets peptide receptors to deliver localized radiation treatment.
- Typically for neuroendocrine tumors (NETs).

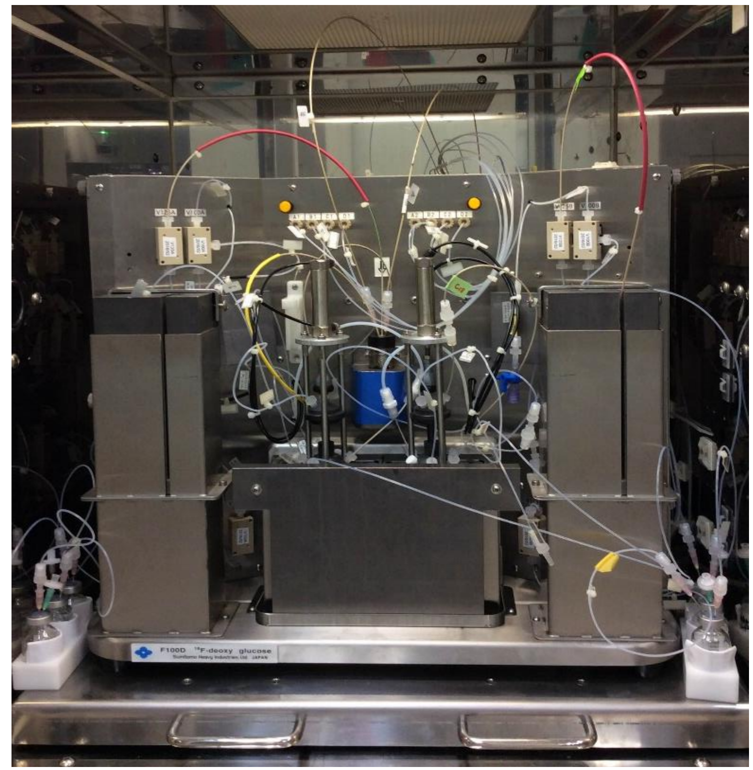
PRRT: Mode of Action

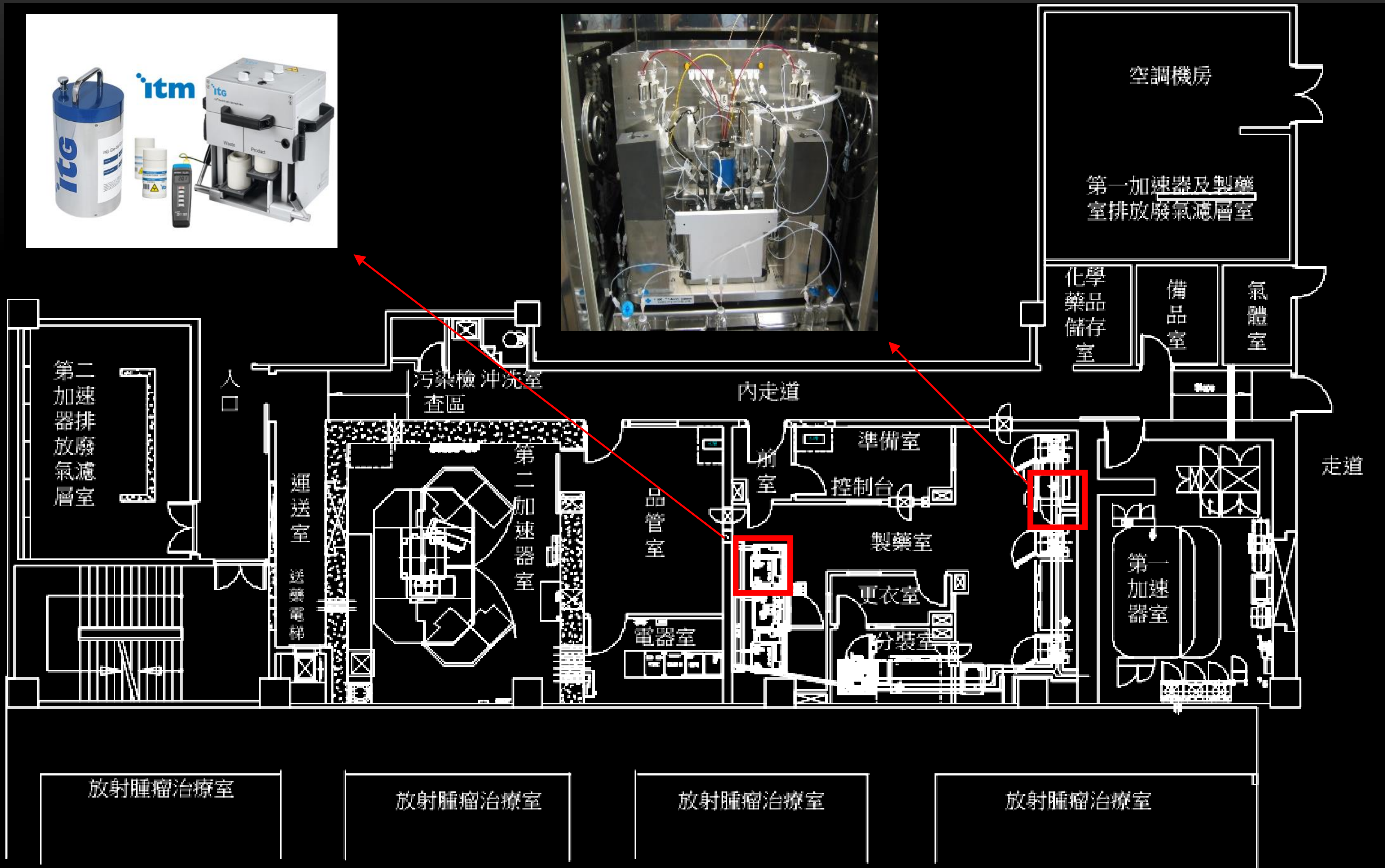


^{68}Ga-PSMA-11合成設備

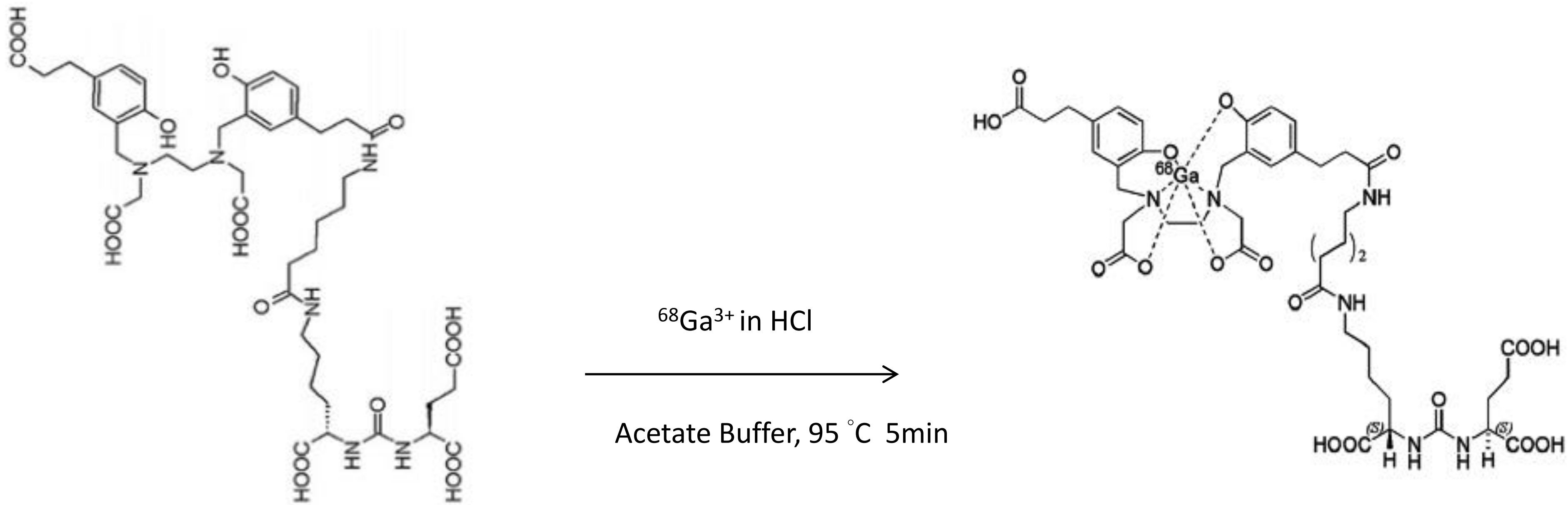
發生器： itG ^{68}Ge/^{68}Ga Generator

合成器： Sumitomo F100D Module B side




itm
itG
空調機房
第一加速器及製藥室排放廢氣濾層室
化學藥品儲存室
備品室
氣體室
第二加速器排放廢氣濾層室
入口
污染檢查區
沖洗室
內走道
運送室
送藥電梯
第二加速器室
品管室
前室
準備室
控制台
製藥室
更衣室
分裝室
電器室
第一加速器室
走道
放射腫瘤治療室
放射腫瘤治療室
放射腫瘤治療室
放射腫瘤治療室

^{68}Ga-PSMA-11合成反應



PSMA-11 (10µg)

^{68}Ga-PSMA-11 acetate

^{68}Ga-PSMA-11調製步驟說明

Generator及分裝器準備

1. Generator淘洗
2. 分裝器組裝

合成器準備

1. 確認合成器已清洗完畢
2. 更換反應器(內含前驅物)
3. 安裝Cartridge及各組件
4. 試劑添加

品管準備

1. HPLC condition
2. HPLC注射standard
3. 內毒素儀準備
4. GC準備
5. TLC準備
6. MCA檢測準備

執行生產

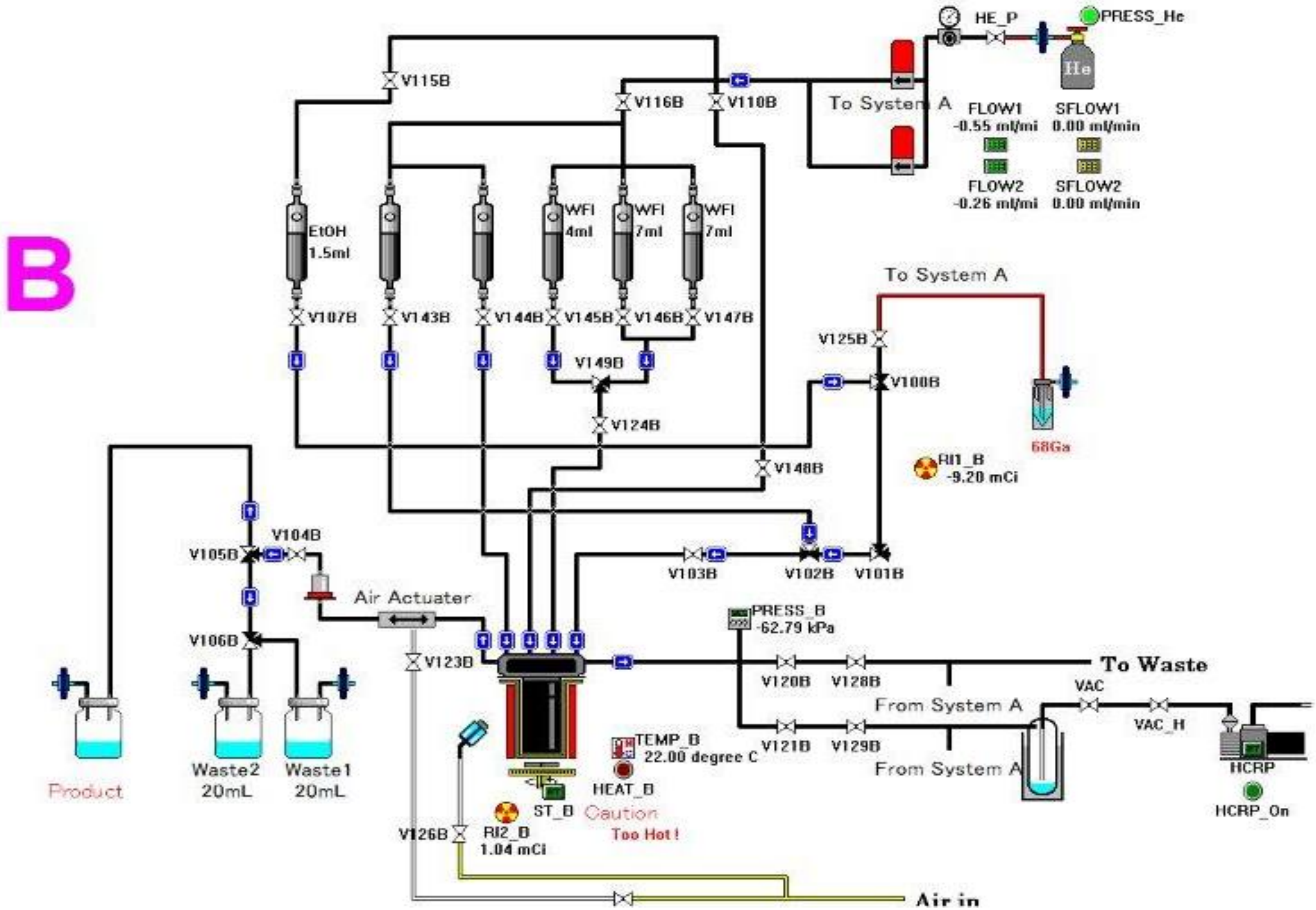
無菌分裝

藥物品管

濾膜完整性測試

藥物放行

^{68}Ga-PSMA-11自動合成系統

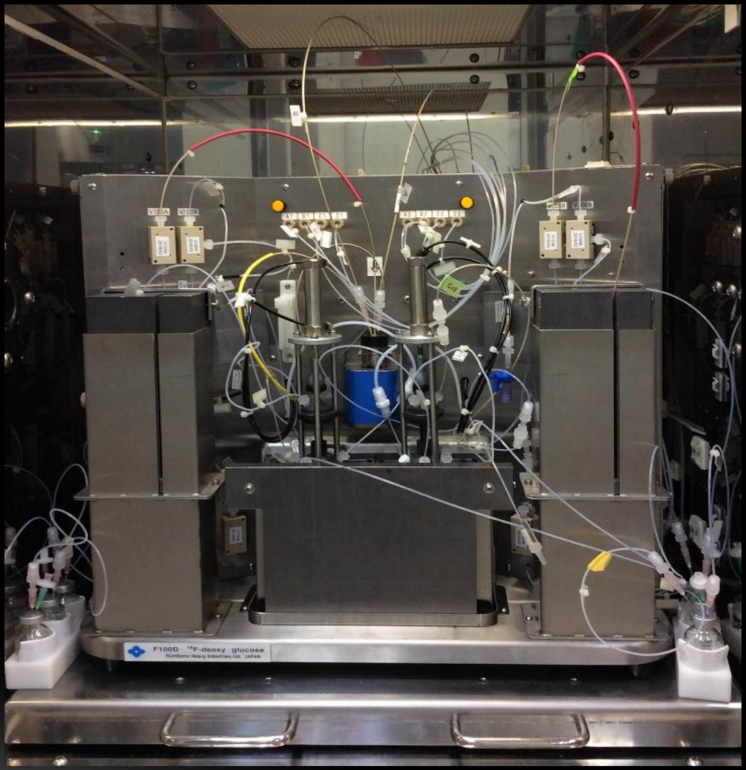


^{68}Ga-PSMA-11檢驗規格(QC)

Items	Specification
Appearance	Clear, colorless solution with no visible particulate matter
Ethanol content	$\leq$ 10 %
pH	4.0 < pH < 8.0
Radiochemical purity	≥ 95%
Chemical identity (API)	Relative retention with reference Standard= about 1.0 RRT = 1.00 ± 0.05 (95%-105%)
Radiochemical impurity (^{68}Ga in colloidal form)	≤ 3%
Radionuclidic identity (^{68}Ga)	62 min ≤ $T_{1/2}$ ≤ 74 min
Strength	≥ 0.13 mCi/mL
Radionuclidic Purity	≥ 99.9% in 0.511 MeV, 1.077 MeV, 1.022 MeV, 1.883 MeV and Compton scatter
Radionuclidic impurity (examined for at least 48 h)	Radionuclidic impurities ≤0.001%
Bacterial endotoxin	≤ 11.6 EU/mL
Sterility	Meet the requirements of the test

2017年開始自動化生產

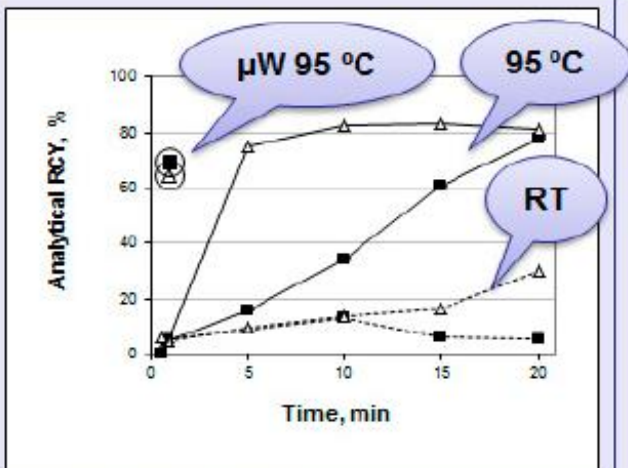
- ItG 68Ge/68Ga Generator
- Sodium Acetate Buffer
- Yield=38.06 ±8.23% (n=75)

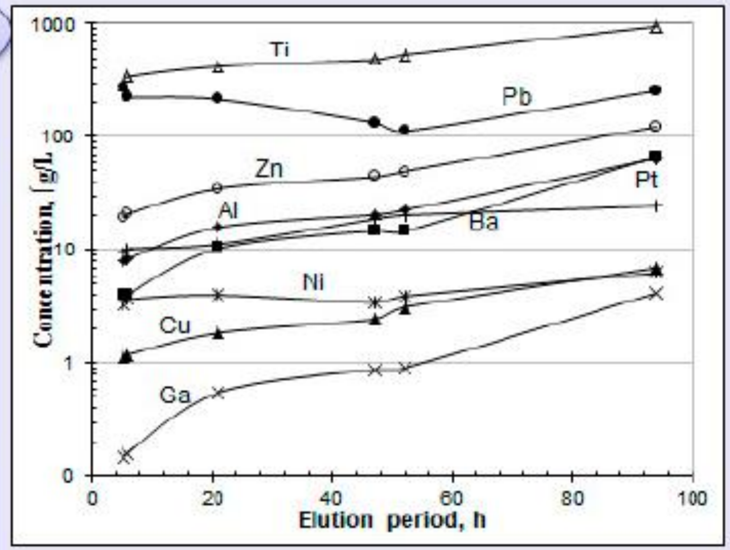


Thank you for your attention

$^{68}Ge/^{68}Ga$ Generator Eluate quality and chemistry

➢ 1. eluate volume, 68Ga radioactivity concentration, 2. HCl eluent molarity, 3. content of metal cationic impurities influence the efficiency of 68Ga-labeling chemistry. 4.pH prevention of Ga(III) precipitation and colloid formation, 5. radiolysis of vector molecules,

<table>
<tr><th>A) Large eluate volume</th><th>B) Metal contamination</th><th>C) ^{68}Ge breakthrough</th></tr>
<tr><td>

^{68}Ga-DOTA-TOC
^{68}Ga-eluate: 6 ml
■ sodium acetate, Δ HEPES</td>
<td>
</td>
<td>$t_{½}(^{68}Ge) = 270.95$ d

$[^{68}Ge] < 0.001\%$</td></tr>
<tr><td>• Fractionation
• Concentration</td>
<td>• Regular elution
• Elution 3-4 hours prior to the synthesis
• Eluate purification</td>
<td>• Regular elution
• Eluate purification
• Product purification</td></tr>
</table>

What is different $^{68}Ge/^{68}Ga$ generator with $^{99}Mo/^{99m}Tc$ generator?

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