Prinsip Dasar Produksi Senyawa Bertanda/ Radiofarmaka

Rien Ritawidya

Pelatihan Petugas Keahlian Pada Fasilitas Produksi Radioisotop dan atau Radiofarmaka dari Siklotron

10 Juli – 23 Juli 2026
Direktorat Pengembangan Kompetensi BRIN - 2026

Biodata

Nama	Rien Ritawidya
Tempat, Tanggal Lahir	Jakarta, 29 December 1982
Pekerjaan	Peneliti di Bidang Radiofarmasi
Pendidikan	S3 Farmasi, Universität Leipzig S2 Farmasi, Universitas Indonesia S1, Kimia-Universitas Indonesia
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Latar Belakang

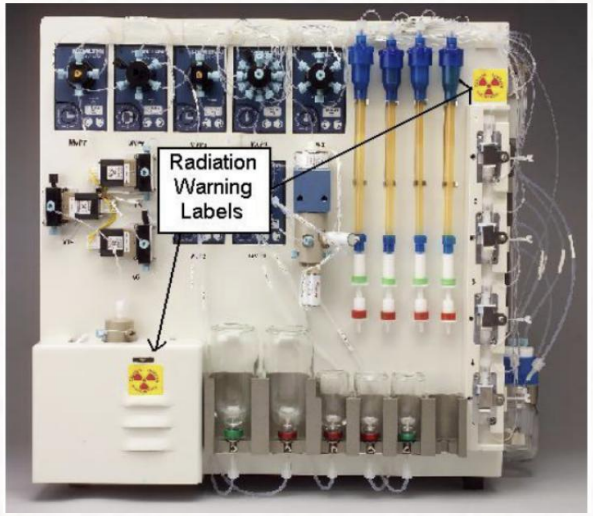
Kebutuhan radiofarmaka PET seperti [^{18}F]FDG dan yang semakin meningkat

Mengurangi ketergantungan import radiofarmaka PET

Meningkatkan kompetensi dalam produksi radiofarmaka berbasis PET seperti [^{18}F]FDG

Tujuan

Setelah mengikuti mata Pelatihan ini, peserta diharapkan mampu memahami prinsip dasar radiofarmaka PET ^{18}F[FDG] dan radiofarmaka ^{68}Ga



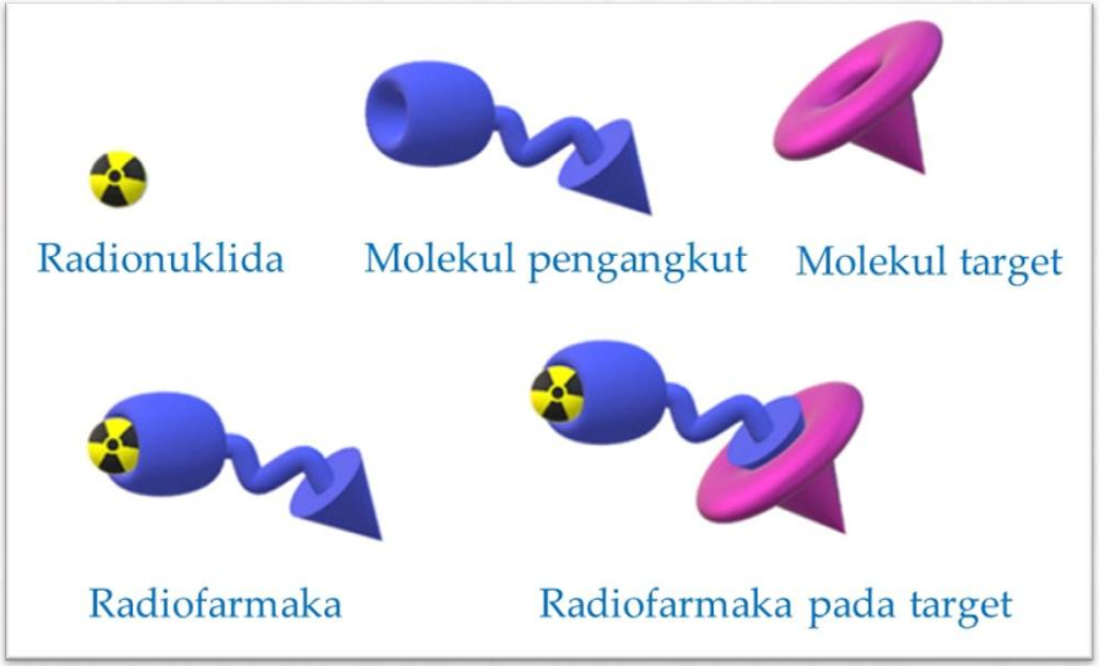
Pokok Bahasan

1. Radiofarmaka PET
2. Prinsip Radiofarmaka PET
3. Radionuklida PET
4. Aspek Radiokimia dan Prinsip Penandaan dengan ^{18}F
5. Pendahuluan Radiofarmaka ^{68}Ga
6. Produksi ^{68}Ga
7. Aspek Radiokimia dan Prinsip Penandaan dengan ^{68}Ga

1 Radiofarmaka *Positron Emission Tomography* (PET)

Radiofarmaka

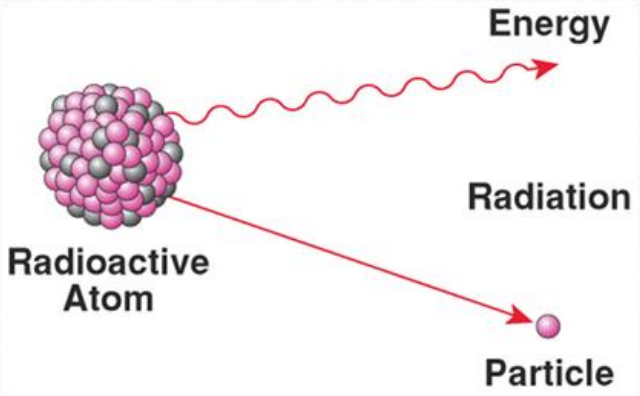
Radiofarmaka adalah sekelompok farmasi atau obat yang mengandung radionuklida atau isotop radioaktif dan digunakan sebagai agen diagnostik dan terapeutik.



Radionuklida / Radioisotop : unsur yang memiliki inti atom yang tidak stabil.

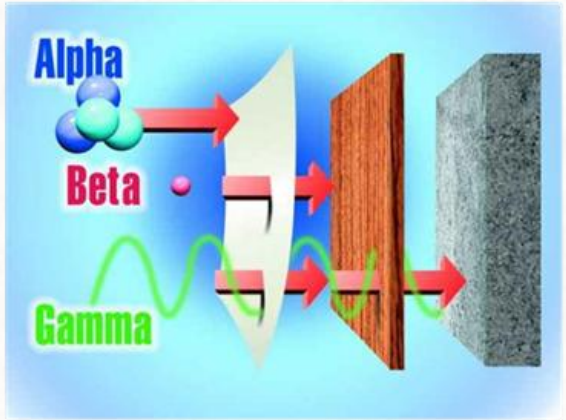
Radionuklida dan sifat-sifatnya

1. memancarkan radiasi



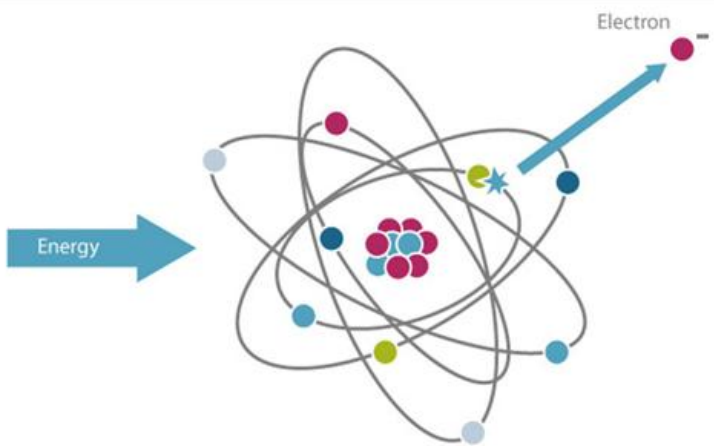
bilheal.bilkent.edu.tr

2. Daya tembus tinggi



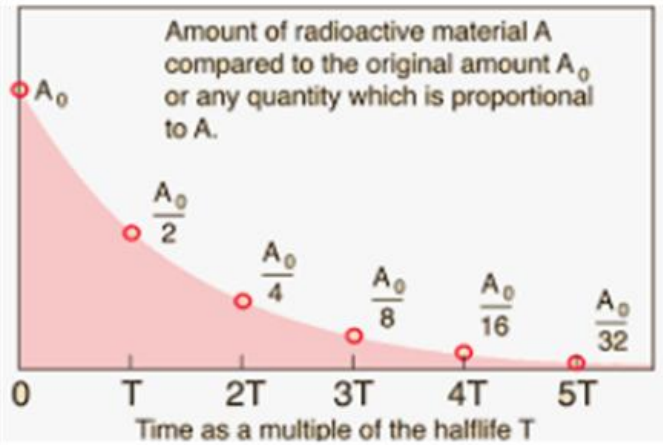
http://igcsechemistry2012.weebly.com

3. Dapat menyebabkan ionisasi

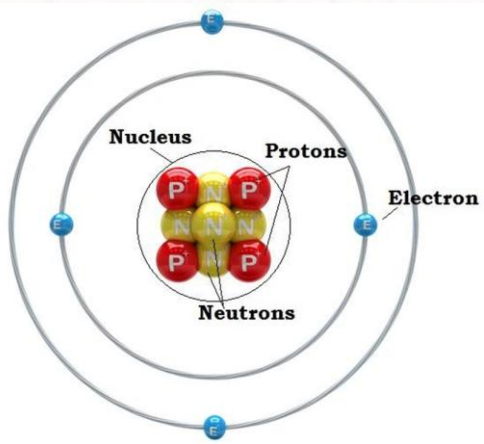


http://www.medicalradiation.com/

4. Memiliki waktu paro



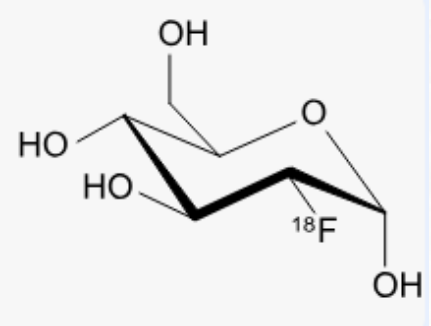
http://hyperphysics.phy-astr.gsu.edu



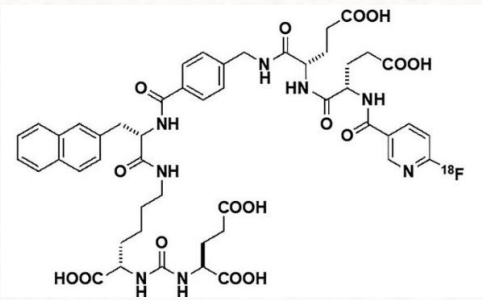
Radiofarmaka PET

- Radiofarmaka PET adalah farmaka atau senyawa biologis yang salah satu atau lebih atom penyusunnya mengandung radionuklida pemancar positron (β^+).

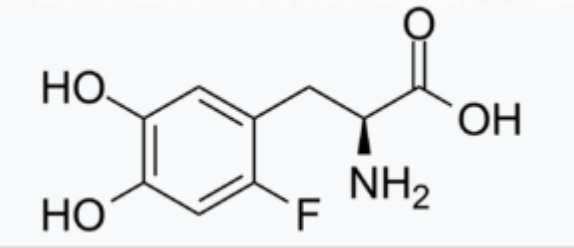
***Fluorodeoxyglucose* [^{18}F]FDG**



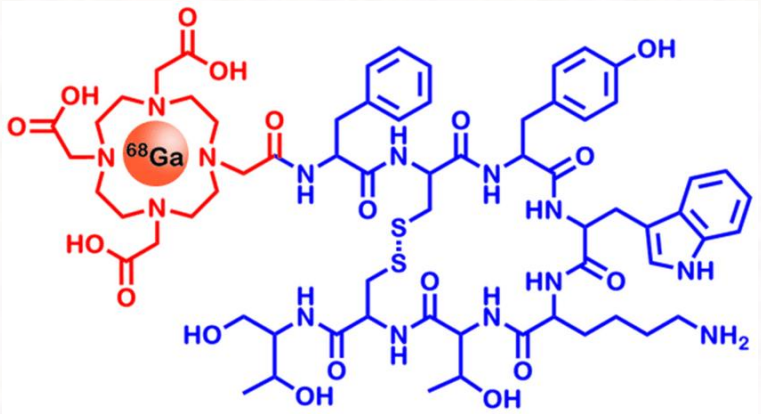
[^{18}F]-PSMA 1007



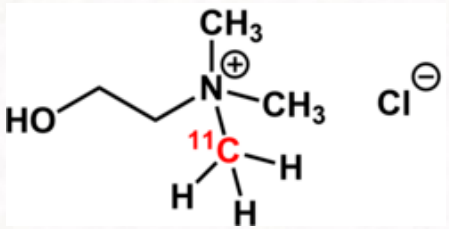
[^{18}F]-DOPA



[^{68}Ga]Ga-DOTA-TATE



[^{11}C]Choline



Tateishi, *Japanese Journal of Clinical Oncology,* 2020, 50(4)349–356
Weber et al. *Int. J. Mol. Sci.* **2015**, *16*(3), 4918-4946

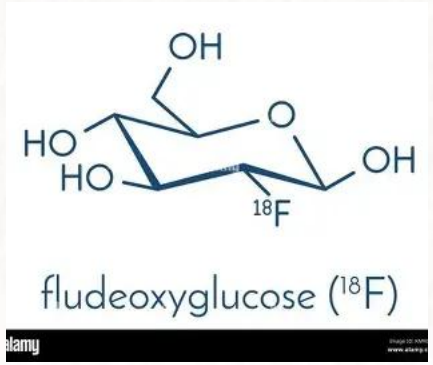
FDA-APPROVED PET RADIOPHARMACEUTICALS

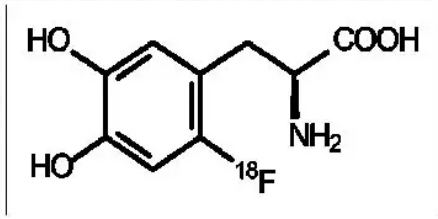
Radiotracers for Positron Emission Tomography (PET) Imaging

			Indication / Primary Use
1	^{11}C	Carbon-11 choline	Prostate cancer
2	^{64}Cu	Cu-64 dotatate (Detectnet™)	Neuroendocrine tumors (NET)
3	^{18}F	Fluorine-18 florbetaben (Neuraceq™)	Amyloid imaging (Alzheimer's disease)
4	^{18}F	Fluorine-18 florbetapir (Amyvid™)	Amyloid imaging (Alzheimer's disease)
5	^{18}F	Fluorine-18 flortaucipir (Tauvid™)	Tau imaging (Alzheimer's disease)
6	^{18}F	Fluorine-18 flotufolastat (POSLUMA®)	Prostate cancer (PSMA)
7	^{18}F	Fluorine-18 fluciclovine (Axumin™)	Prostate cancer
8	^{18}F	Fluorine-18 fludeoxyglucose (FDG)	Oncology (many cancers)
9	^{18}F	Fluorine-18 fluorodopa	Neuroendocrine tumors; brain tumors
10	^{18}F	Fluorine-18 fluoroestradiol (Cerianna™)	Estrogen receptor positive (ER+) breast cancer
11	^{18}F	Fluorine-18 flurpiridaz (Flyrcado™)	Cardiac perfusion imaging
12	^{18}F	Fluorine-18 flutemetamol (Vizamyl™)	Amyloid imaging (Alzheimer's disease)
13	^{18}F	Fluorine-18 piflufolastat (PYLARIFY®)	Prostate cancer (PSMA)
14	^{18}F	Fluorine-18 sodium fluoride	Bone imaging (metastases, fracture, etc.)
15	^{68}Ga	Gallium-68 DOTATATE (Netspot™)	Neuroendocrine tumors (NET)
16	^{68}Ga	Gallium-68 DOTATOC	Neuroendocrine tumors (NET)
17	^{68}Ga	Ga-68 gozetotide (Illuccix®, Locametz®)	Prostate cancer (PSMA)
18	^{13}N	Nitrogen-13 ammonia	Myocardial perfusion imaging
19	^{82}Rb	Rubidium-82 chloride (Cardiogen-82®)	Myocardial perfusion imaging

Radiofarmaka PET untuk Aplikasi Klinis di Kedokteran Nuklir

Oncology

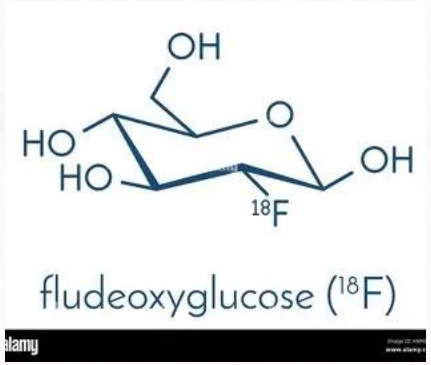




^{18}F-FDOPA (fluorodopamine)

^{18}F-NaF

Cardiology

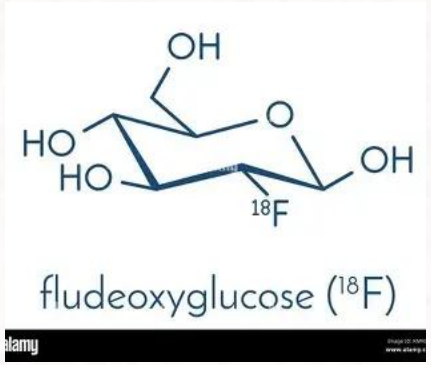


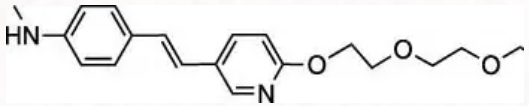
^{15}O-H_2O

^{13}N-NH_3

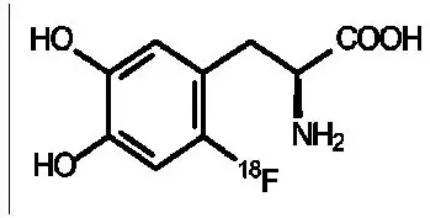
^{82}Rb-chloride

Neurology

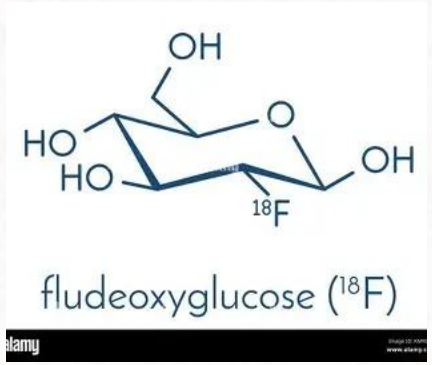


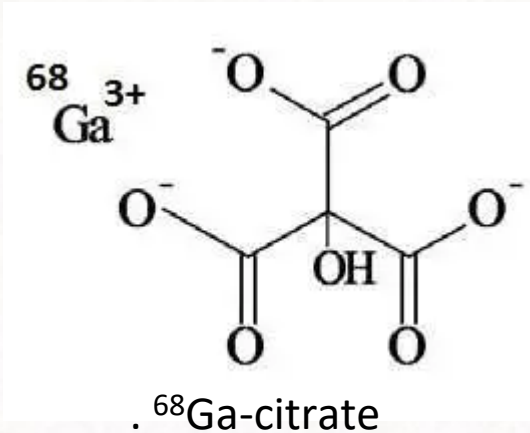


Fluorbetapir



Inflammation





. ^{68}Ga-citrate

TABLE 3. IMPORTANT DIFFERENCES BETWEEN Tc-99m AND PET RADIOPHARMACY

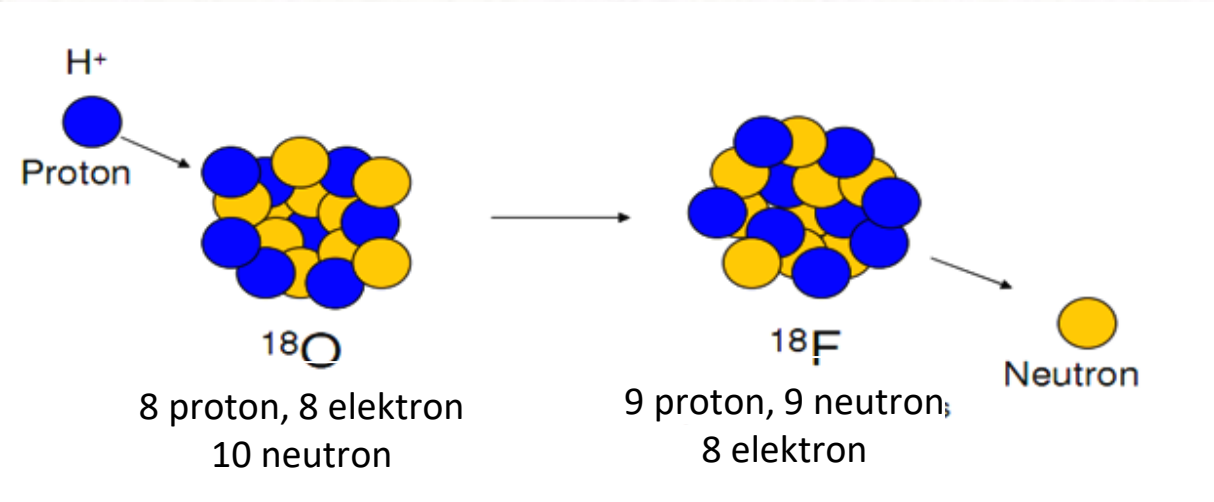
Tc-99m radiopharmacy	PET radiopharmacy
$T_{1/2}$ = 6 h	$T_{1/2}$ = 110 min for F-18, 20 min for C-11, 10 min for N-13 and 2 min for O-15
Sterile $^{99m}TcO_4$ produced on-site from a generator	Isotope produced on-site from a cyclotron
Tc-99m radiopharmaceuticals are complexes of Tc-99m and a chelating agent attached to biologically active molecules with the desired properties, and easy to prepare, with no chemical synthesis.	PET radiopharmaceuticals are biologically active molecules that are synthesized with the PET isotope attached covalently at a specific site within the molecule.
'Cold' sterile reagent and Tc-99m available in separate sterile vials — preparation requires addition of sterile $^{99m}TcO_4^-$ with a 'cold kit' and good mixing (no further processing or minimal without opening the vial)	Rapid chemical synthesis of the PET radiopharmaceutical is necessary using special precursors (to reduce synthesis time) for F-18 and C-11 labelled radiopharmaceuticals. Only simple molecules possible with N-13 and O-15
Quality control (QC) of radiopharmaceutical is minimal since the cold kit used for making the Tc-99m radiopharmaceutical is certified to be sterile and free of endotoxins.	Quality control is more elaborate, since the PET radiopharmaceutical is synthesized every day.
'Parametric release' permitted if quality assurance (QA) is validated	'Parametric release' permitted if QA is validated
The radiopharmaceutical prepared can be used throughout the day — for at least eight hours.	Because of the short physical half-life of its isotope, ^{18}F-RP has to be used within a few hours, perhaps requiring multiple syntheses on the same day. In the case with ^{11}C radiopharmaceutical, each synthesis could cover one or two patients.
γ = 140 keV, 20 mm lead shielding is adequate.	β^+ emitters, $\gamma = 2 \times 511$ keV; 70 mm lead shielding required
Multipatient dose in a single vial possible. Up to 12.95 GBq (350 mCi) of Tc-99m	Preferred as maximum of two to three doses in a vial. Doses preferred in syringes, ready to inject to minimize handling
Should be sterile	Should be sterile
Endotoxin levels below 175/V[a] (IU)[b]	Endotoxin levels below 175/V (IU)

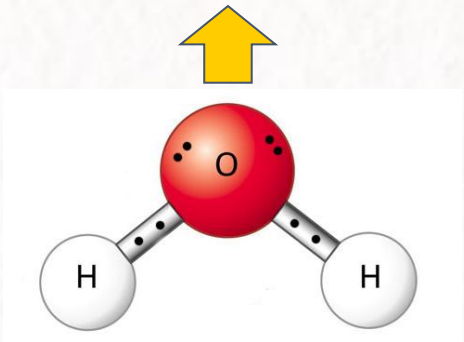
[a] V: Maximum recommended dose.
[b] IU: International units.

IAEA TechDoc STI/PUB/1344; ISBN 978-92-0-107008-1 Strategies for Clinical Implementation and Quality Management of PET Tracers

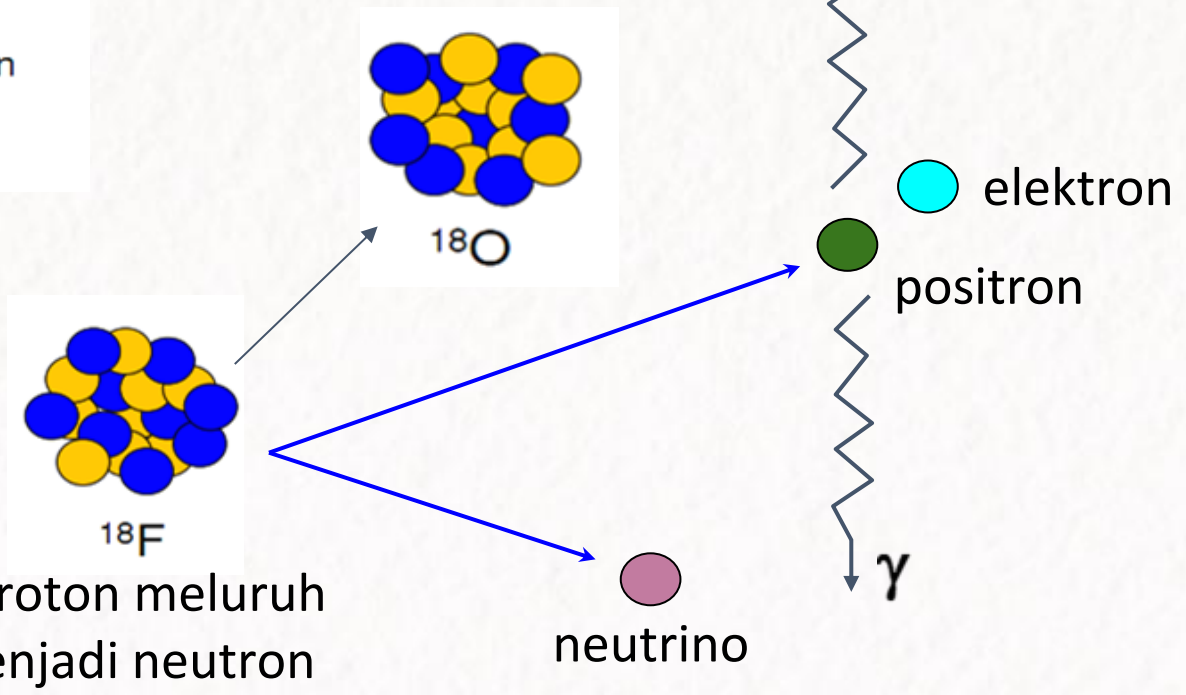
2 Prinsip pencitraan PET dengan radiofarmaka PET

Proses Terbentuknya Positron dari ^{18}F



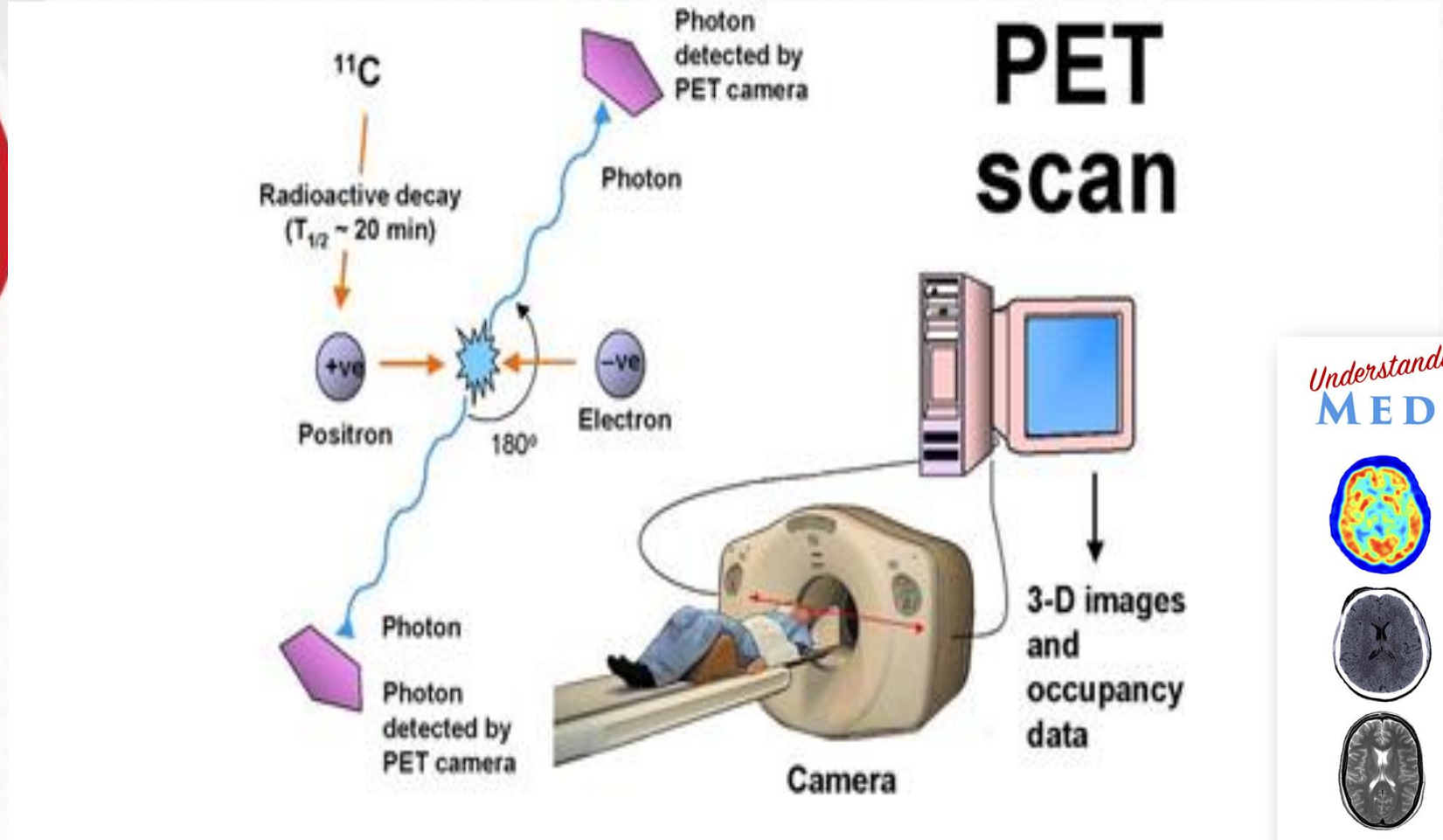


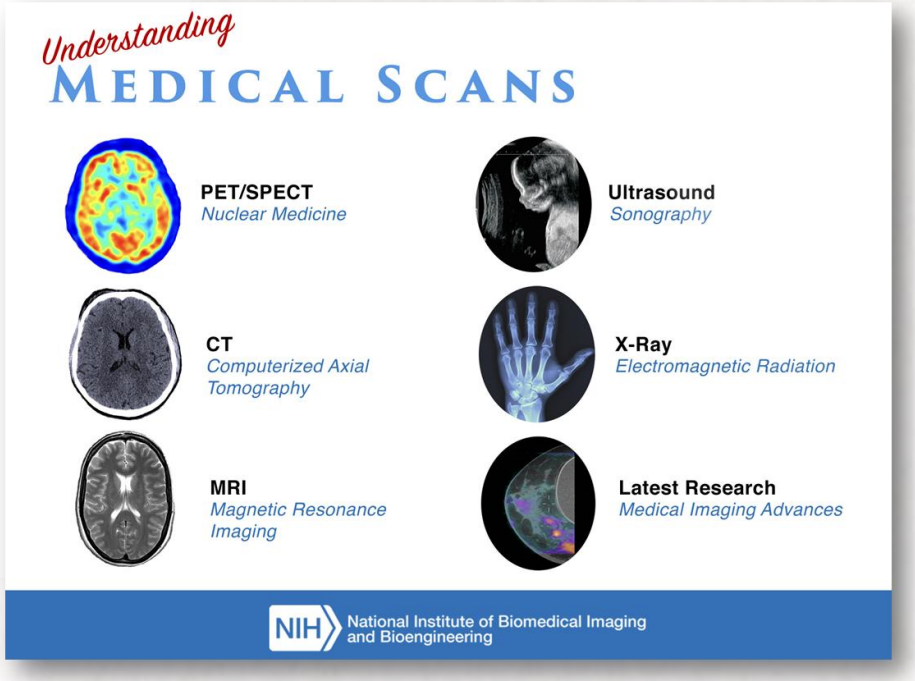
Molekul air ($H_2{}^{18}O$) sebagai target iradiasi Cyclotron



1 proton meluruh menjadi neutron

Prinsip Pencitraan (Imaging) dengan Radiofarmaka PET





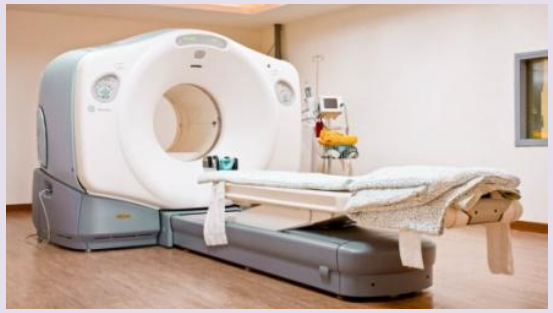
Sumber: (IAEA Technical Tecdoc Series No. 1968, 2021)

Modalitas Pencitraan

MRI

CT-scan

https://pantirapih.or.id/rspr/mri-magnetic-resonance-imaging/



Positron Emission Tomography (PET)

Single-photon emission computed tomography (SPECT)

https://www.siemens-healthineers.com/en-us/molecular-imaging/spect-and-spect-ct

Hybrid modalities imaging

SPECT/CT
PET/MRI

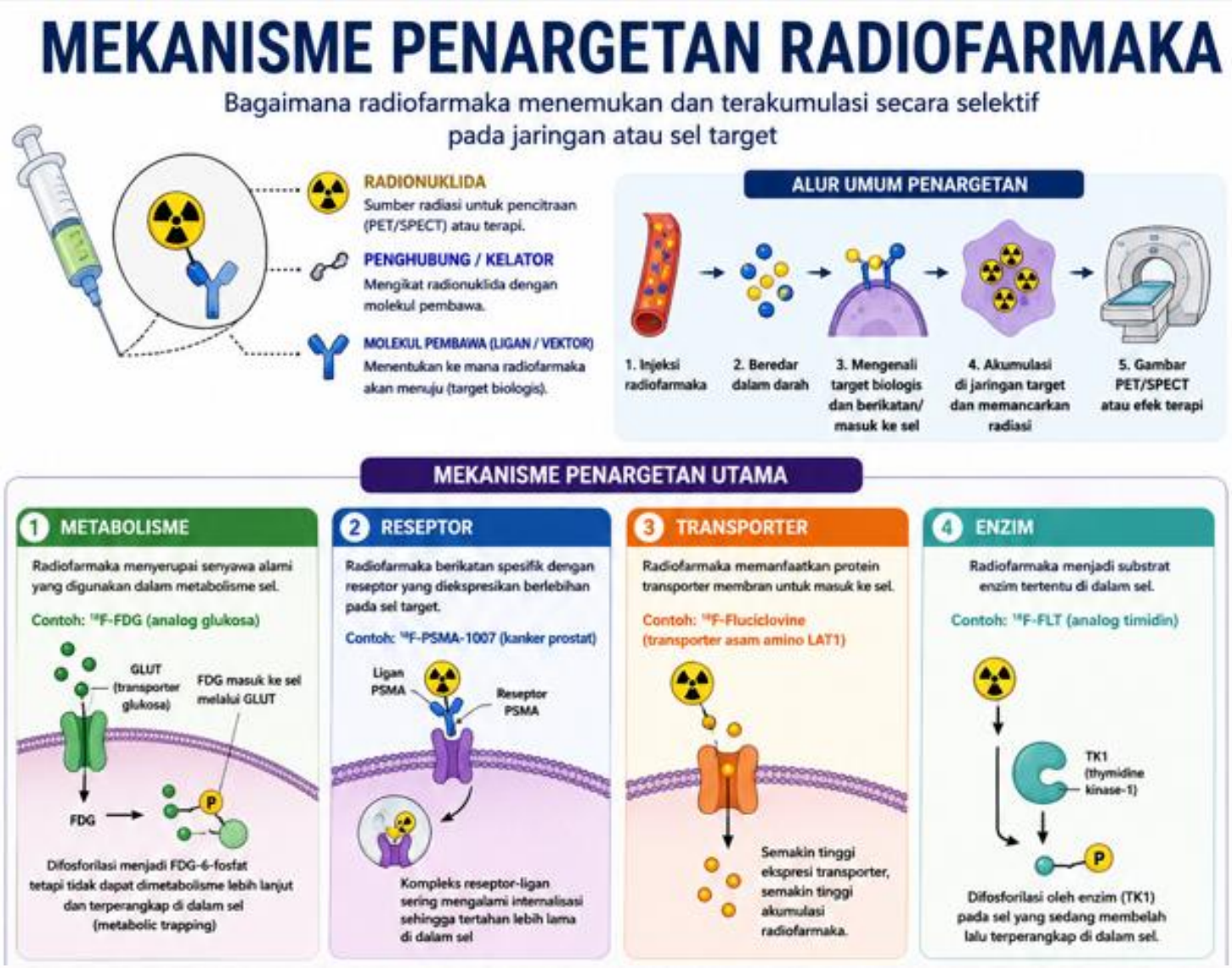
- ✓ Monitoring metabolic processes in living subjects
- ✓ Measurement of chemical changes before anatomical signs of a disease
- ✓ **Require probe or radiotracer**: compound labeled with γ radionuclide (SPECT)
  - β+ (positron) for PET

Anatomical (Organ Imaging)
Structural Imaging

Functional imaging (Organ Function Imaging)

https://www.healthline.com/health/pet-scan#purpose

Targeted Diagnostic and Therapy

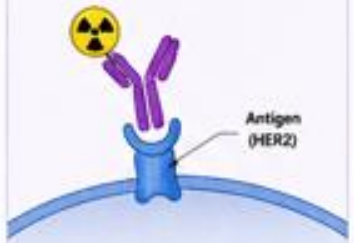


Targeted Diagnostic and Therapy …cont'd

5 ANTIGEN (ANTIBODI)

Antibodi mengenali antigen spesifik pada permukaan sel target.

Contoh: ^{89}Zr-trastuzumab (HER2)

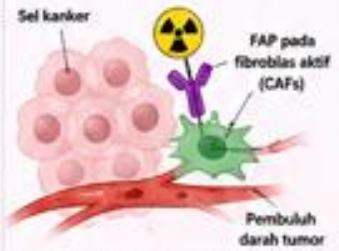


Ikatan antigen–antibodi sangat spesifik sehingga radiofarmaka terakumulasi pada sel target.

6 MIKROLINGKUNGAN TUMOR

Radiofarmaka mengenali komponen atau kondisi khas di lingkungan tumor.

Contoh: ^{68}Ga-FAPI (menargetkan FAP pada cancer-associated fibroblasts)



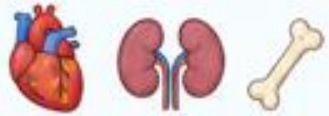
Radiofarmaka berikatan dengan FAP pada stroma tumor (bukan langsung pada sel kanker) sehingga memberikan kontras tinggi dan distribusi luas di berbagai tumor.

7 PERFUSI / FUNGSI ORGAN

Radiofarmaka terakumulasi karena sifat fisiologis organ tertentu.

Contoh:

- ^{99m}Tc-MIBI → perfusi & potensial membran mitokondria (miokard)
- ^{99m}Tc-DTPA → filtrasi glomerulus (ginjal)
- ^{99m}Tc-MDP → ikatan pada hidroksiapatit (tulang)



Akumulasi bergantung pada perfusi, filtrasi, atau afinitas terhadap jaringan.

FAKTOR YANG MEMPENGARUHI PENARGETAN

- Ekspresi target (reseptor, transporter, enzim, antigen)
- Perfusi / aliran darah ke jaringan target
- Sifat radiofarmaka (lipofilisitas, ukuran molekul, muatan, stabilitas)
- Konkuren biologis (glukosa, asam amino, dll.)
- Waktu pencitraan yang optimal

RANGKUMAN

Spesifisitas penargetan hampir seluruhnya ditentukan oleh molekul pembawa (ligan/vektor), sedangkan radionuklida berfungsi sebagai "pelapor" untuk pencitraan atau "penghancur" untuk terapi.

Target sama → mekanisme sama
Radionuklida berbeda → radiasi berbeda
(pencitraan atau terapi)

CONTOH: TARGET SAMA, RADIONUKLIDA BERBEDA

TUJUAN AKHIR

PENCITRAAN
Memberikan informasi akurat mengenai lokasi, karakteristik, dan tingkat keparahan penyakit.

TERAPI
Memberikan radiasi terarah untuk menghancurkan sel penyakit dengan efek samping minimal.

INGAT: Radiofarmaka yang baik = radionuklida yang tepat + molekul pembawa yang spesifik + farmakokinetik yang optimal → hasil pencitraan berkualitas tinggi atau terapi yang efektif dan aman.

3 Radionuklida PET

Radionuklida Positron

Radionuklida	Waktu paruh	Energi β^+ maks (MeV)	Reaksi Nuklir	Jangkauan Maksimum (mm)	Availability atau ketersediaan
^{18}F	110 menit	0,635	$^{18}O(p,n)^{18}F$	2,4	Siklotron
^{11}C	20 menit	0,961	$^{14}N(p,\alpha)^{11}C$	4,1	Siklotron
^{13}N	10 menit	1,72	$^{15}C\,(p,n)^{13}N$	7,3	Siklotron
^{15}O	2 menit	1,19	$^{15}N(p,n)^{15}O$	5,1	Siklotron
^{68}Ga	68 menit	1,899	$^{68}Zn(p,n)^{68}Ga$	14,1	Siklotron dan Generator
^{89}Zr	78,4 jam	0,395	$^{89}Y(p,n)^{89}Zr$		Siklotron

Kenapa Fluorine-18 (^{18}F) ?

- Waktu paruh yang cukup: Tidak terlalu pendek dan tidak terlalu panjang (110 menit)
- Energi positron yang rendah: Memungkinkan scanning dengan resolusi tinggi (635 KeV)
- Dapat diproduksi dengan jumlah besar dalam bentuk [^{18}F]fluoride
- Dapat diperoleh dalam aktivitas molar yang tinggi

Produksi ^{18}F

The database now contains details on the
production and contact details for 1279 cyclotrons (from 20 companies) in 95 Member States
Source: IAEA Tech doc

Produced in cyclotron:
a particle accelerator

Nuclear reaction → $^{18}O(p,n)^{18}F$

https://www.slideshare.net/liegecreative/opportunits-de-financement-de-la-transition-nergtique-liege-creative-080617

- Target gas $^{18}O_2$ → $[^{18}F]F_2$ gas untuk reaksi electrophilic fluorination→ (100−600 MBq/µmol = 2.7 – 16.2 mCi) **radiofarmaka aktivitas jenis (SA) yang kecil.**
- Target $^{18}O_2$ cair → fluoride anion $[^{18}F]F^-$ untuk reaksi nucleophilic fluorination (>370 GBq/batch = 10 Ci/batch) → **radiofarmaka SA yang besar**

O. Jacobson, D.O. Kiesewetter, and X. Chen. *Bioconjugate Chem.* **2015**, *26*, 1–18

Produksi ^{18}F

- Specific activity, SA (aktivitas jenis)

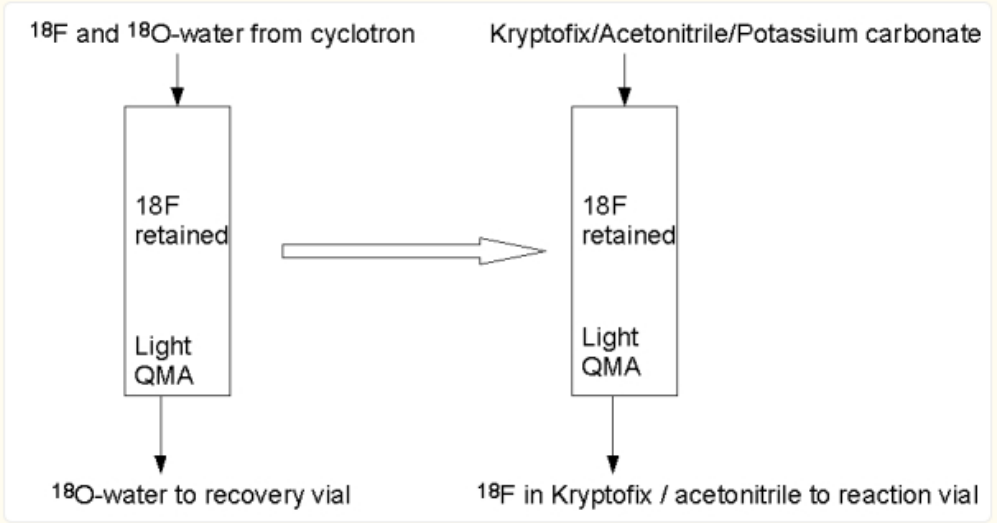
  Jumlah radioaktivitas per massa senyawa

SA yang tinggi penting:

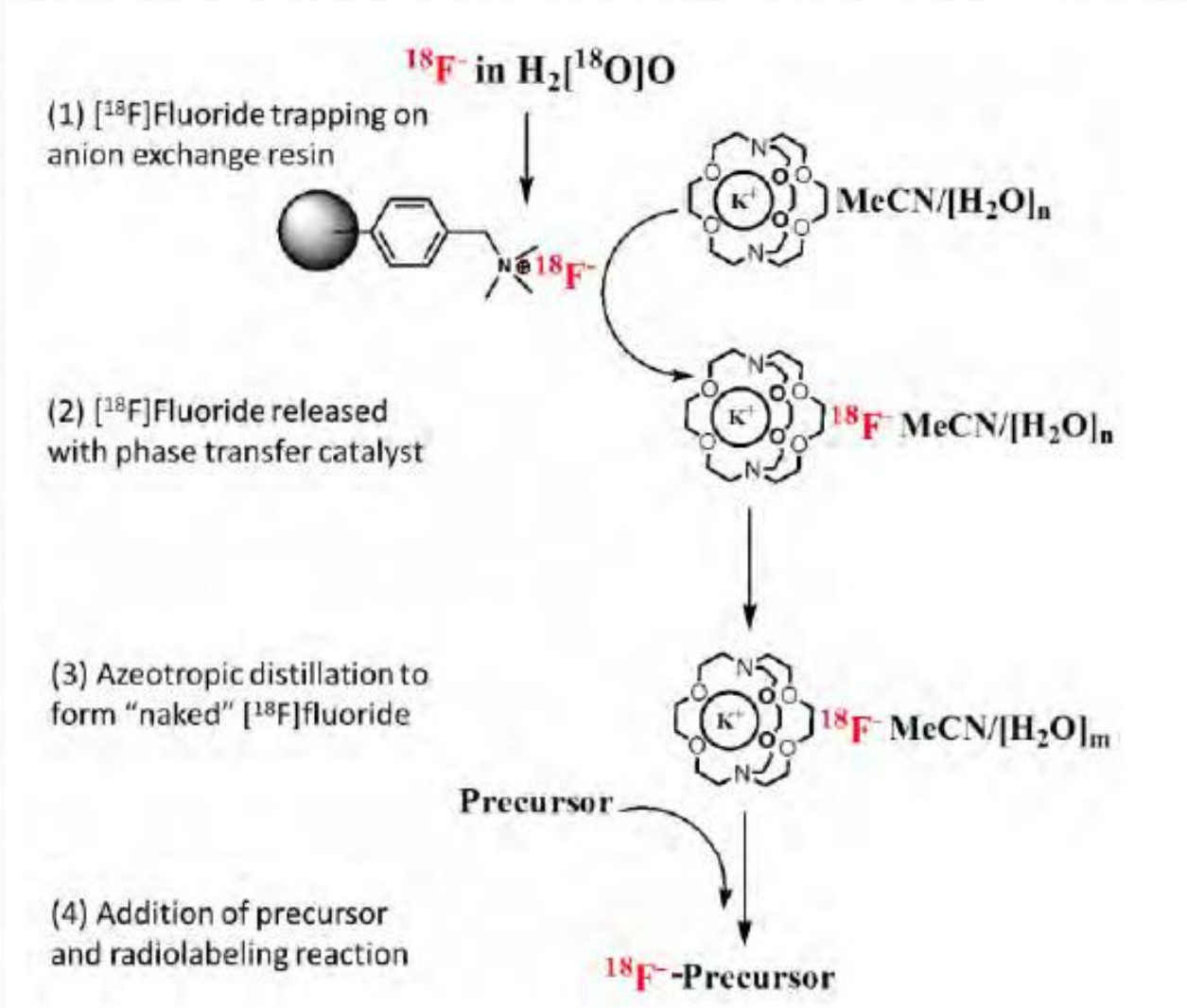
- Menghindari saturasi receptor target
- Reduksi sinyal PET
- Efek farmakologis

4 Aspek Radiokimia dan Prinsip Penandaan dengan ^{18}F

Tahapan penyiapan radiofarmaka ^{18}F



Yu S. Review of F-FDG Synthesis and Quality Control. Biomed Imaging Interv J. 2006 Oct;2(4):e57



Pei Yuin Keng, Melissa Esterby and R. Michael van Dam, **Emerging Technologies for Decentralized Production of PET Tracers**

Strategi sintesis radiofarmaka berbasis ^{18}F

- Cepat, maksimal 2 half-life (<4 h): labeling, deprotection, purification and formulation step.
- Memasukkan atau *introduce* atom radioaktif **^{18}F** perlu precursor
- Sintesis kimia organik stoikiometri ordenya mMolar
- Reaksi sintesis radiotracer **^{18}F** tidak stoikiometri (nmol)
- Suhu reaksi yang tinggi
- Proses optimasi (waktu dan suhu reaksi, solvent dan konsentrasi)

Prinsip Sintesis Radiokimia Radiofarmaka atau tracer ^{18}F

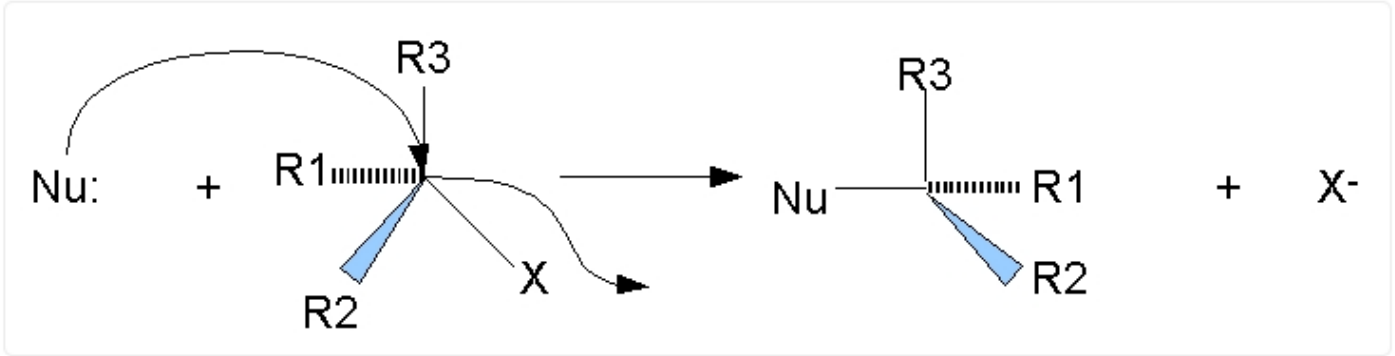
- Direct fluorination

  1. Electrophilic fluorination

  2. Nucleophilic fluorination

- In direct fluorination

  Prostetic groups → Penandaan **^{18}F** -peptida



Nucleophilic substitution: Nu = nucleophilic molecule, X = leaving group.

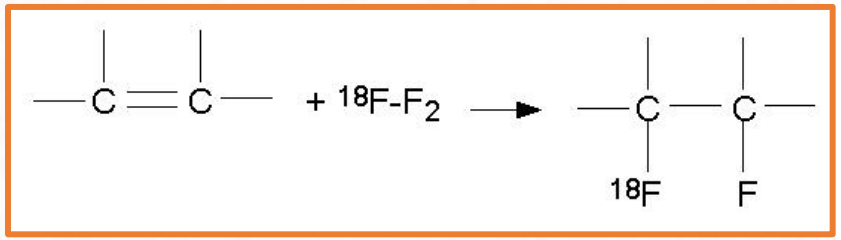
A comparison of various leaving groups

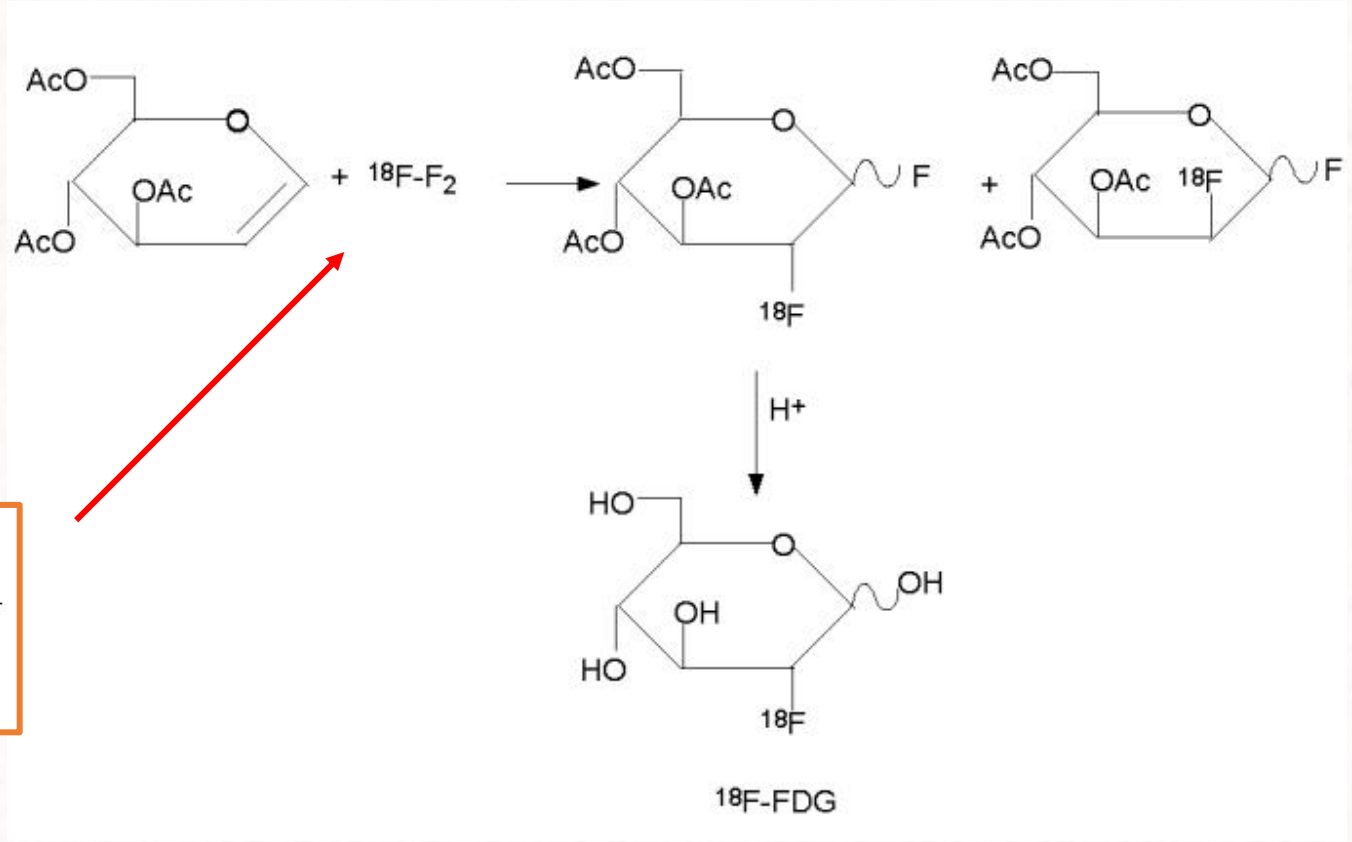
Leaving group Properties	
Trifates	very good leaving group
Toyslate	
Mesylate	
Iodide	moderate leaving group
Bromide	
Chloride	poor leaving group

Yu S. Review of F-FDG Synthesis and Quality Control. Biomed Imaging Interv J. 2006 Oct;2(4):e57

Prinsip Sintesis Radiokimia Radiofarmaka atau tracer ^{18}F

1. Electrophilic fluorination

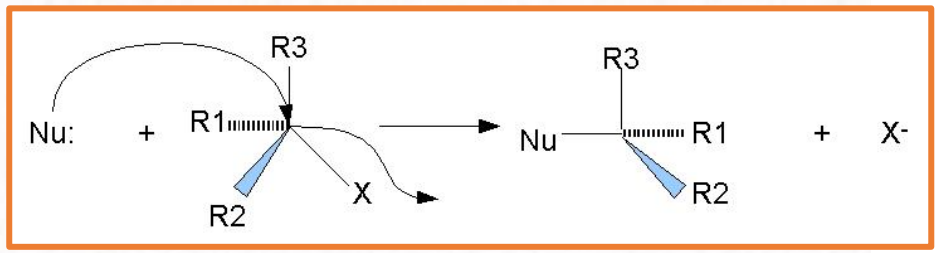


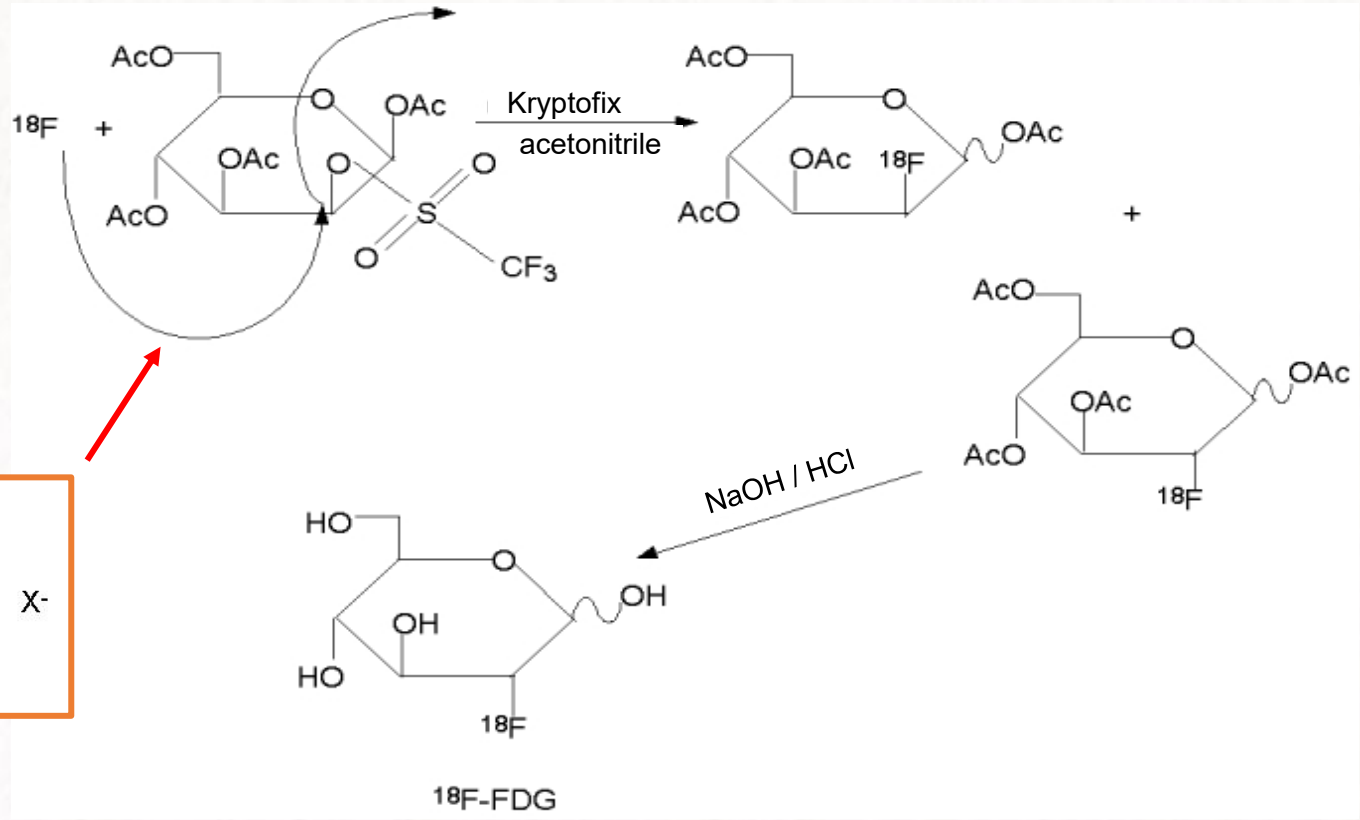


Yu S. Review of F-FDG Synthesis and Quality Control. Biomed Imaging Interv J. 2006 Oct;2(4):e57

Prinsip Sintesis Radiokimia Radiofarmaka atau tracer ^{18}F

2. Nucleophilic fluorination

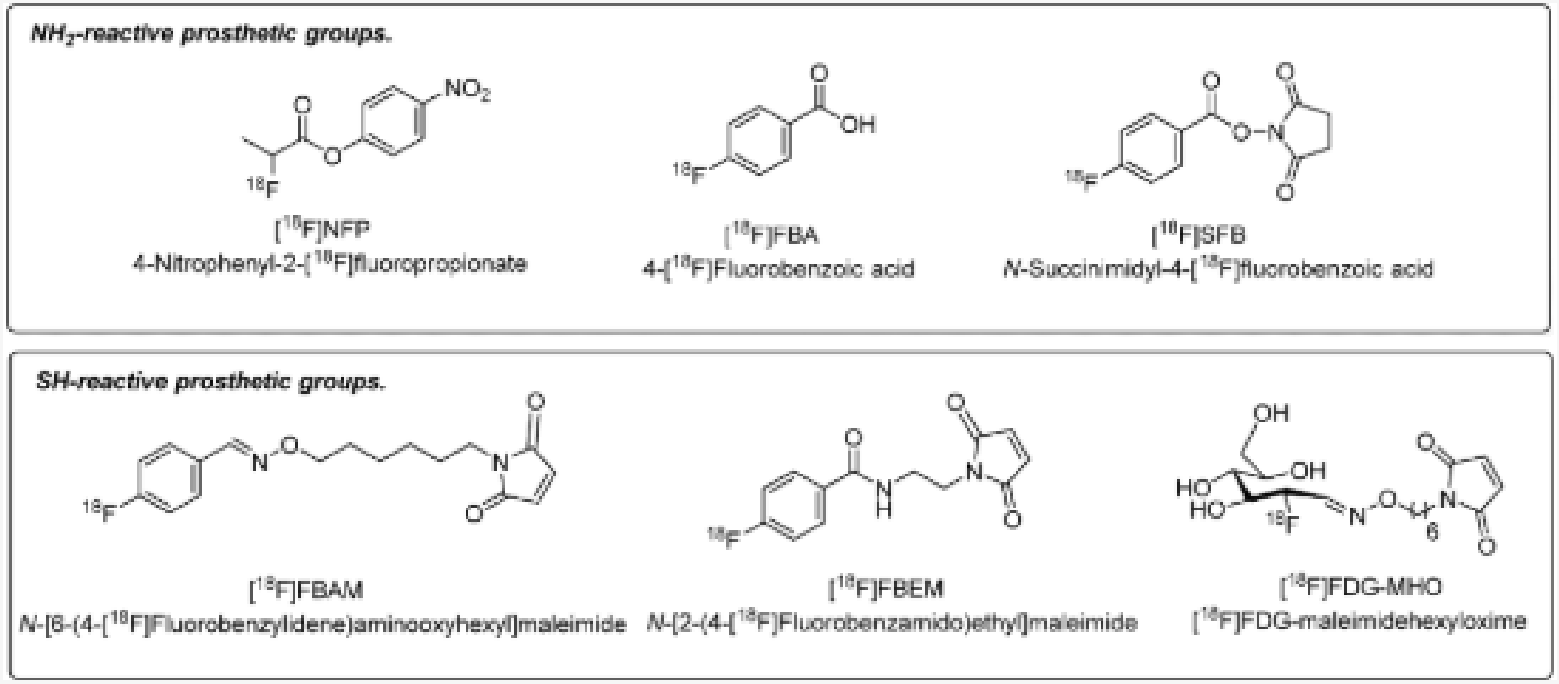




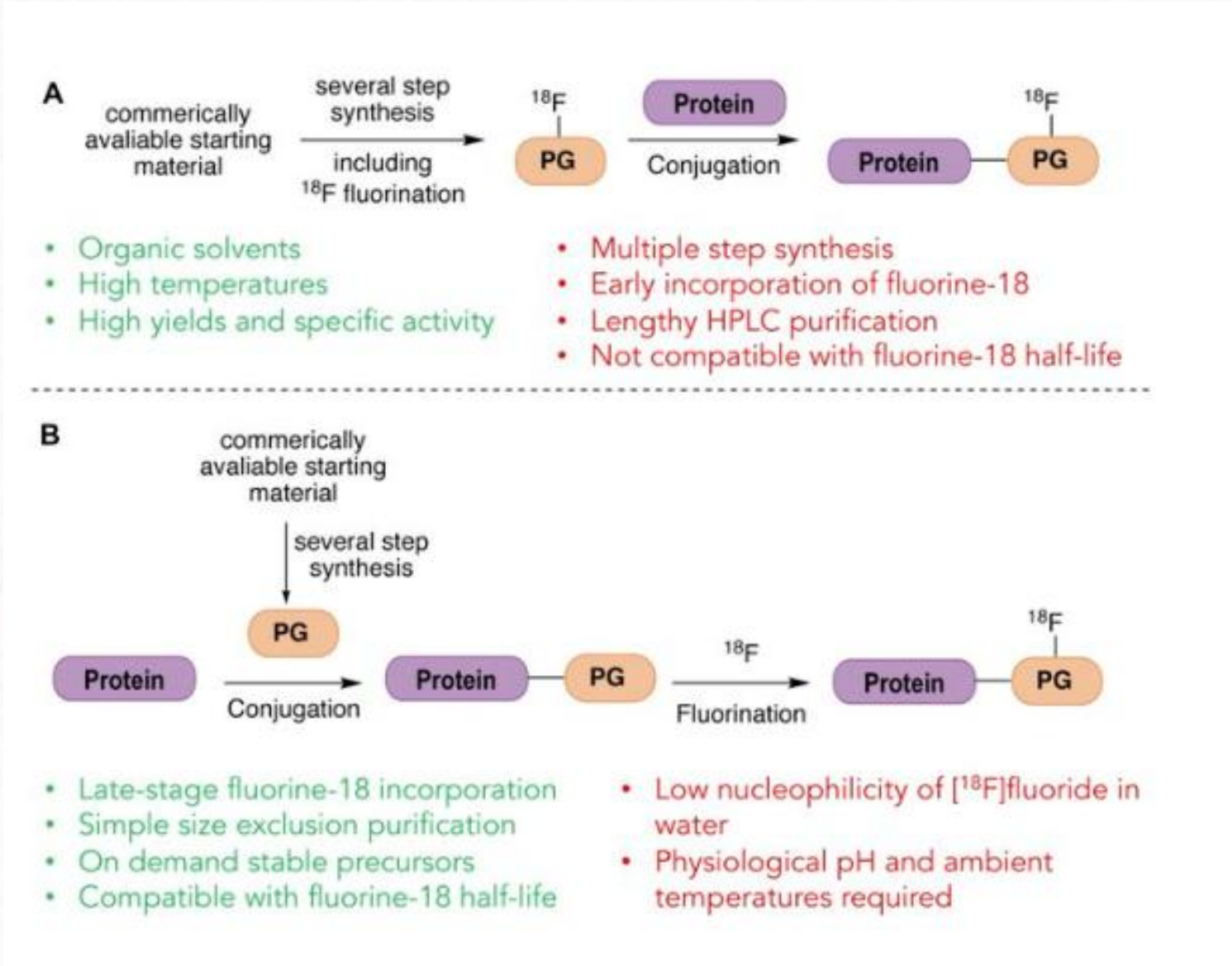
Prinsip Sintesis Radiokimia Radiofarmaka atau tracer ^{18}F

- In direct fluorination

  Prostetic groups → Penandaan biomolekul seperti peptida, antibodi monoklonal



Richter, S.; Wuest, F. Molecules 2014, 19, 20536-20556.



•DOI: 10.3389/fchem.2021.687678

Labeling tracer PET dengan ^{18}F

$$\text{Prekursor-LG} + [^{18}F]F^- \rightarrow [^{18}F]\text{Produk} + LG^-$$

Berlaku mekanisme reaksi substitusi nukleofilk:

- $[^{18}F]$fluoride sebagai nukleofil
- Prekursor mengandung LG (*Leaving Group*) atau gugus pergi seperti OTs, OTf, OMs, ONs, I, Br)
- Reaksi berlangsung pada solvent polar aprotik, solvent yang tidak mengandung air (DMSO, DMF, acetonitrile)
- Membutuhkan Phase Transfer Catalyst (Kryptofix-2.2.2, garam tetrabutylammonium)
- “Naked fluoride”
- Inversi stereokimia

Prekursor

monografi khusus di Farmakope Eropa:

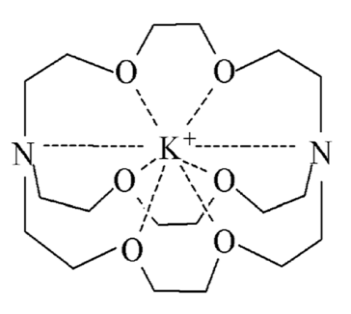
“prekursor kimia dari preparasi radiokimia bukanlah zat radioaktif yang diperoleh melalui sintesis kimia untuk dikombinasikan dengan suatu radionuklida”

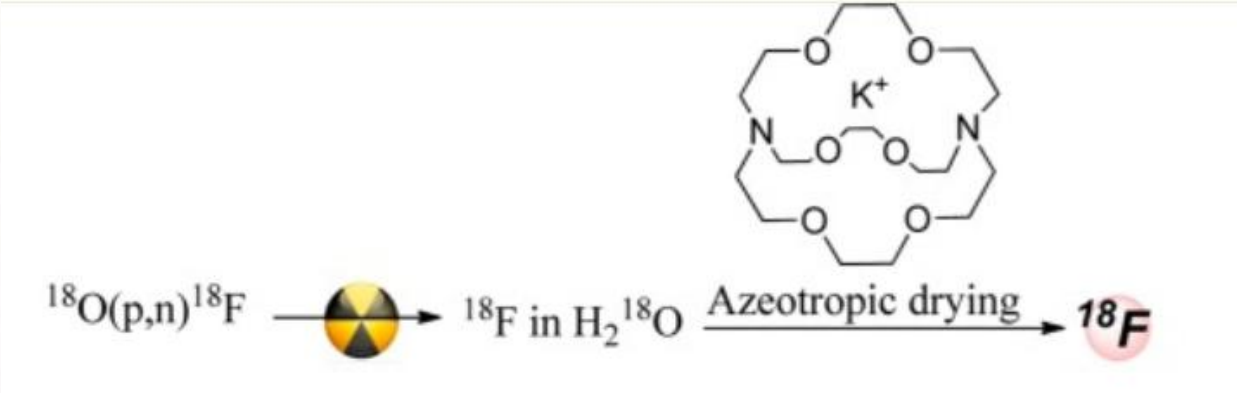
- Kelarutan dalam kondisi reaksi kimi
- Leaving group atau gugus pergi dan gugus pelindung yang baik
- Stabilitas suhu

Kenapa diperlukan Kryptofix

Kryptofix adalah nama dagang untuk sekelompok senyawa cryptand, yang merupakan ligan makrosiklik yang digunakan dalam kimia untuk mengikat ion logam tertentu.

Kryptofix 2.2.2., misalnya, adalah *cryptand* yang sering digunakan dalam sintesis kimia dan aplikasi analitik. Senyawa ini memiliki struktur tiga dimensi yang memungkinkan pengikatan kuat terhadap ion logam tertentu, seperti kalium.





Naked Fluoride reaktif untuk reaksi penandaan

Solvent atau pelarut

Penggunaan pelarut dapat menjadi tahap pembatas dalam suatu reaksi radiokimia; oleh karena itu, dua aspek berbeda perlu dievaluasi.

- Sifat nukleofilik dari [^{18}F]fluorida meningkat dalam pelarut organik polar aprotik yang stabil terhadap panas, dan karena aplikasi radiofarmasi, toksisitas pelarut perlu dievaluasi serta jumlah pelarut residu diatur secara ketat oleh otoritas regulatori.
- Dimetil sulfoksida (DMSO), asetonitril, dimetilformamida (DMF), dan tetrahidrofuran (THF) merupakan pelarut yang paling umum digunakan dalam preparasi radiofarmasi untuk aplikasi medis rutin.

Penandaan ^{18}F ke Peptida

- **Direct Radiolabeling**

Dengan Pendekatan Alumunium Fluoride atau [^{18}F]AlF

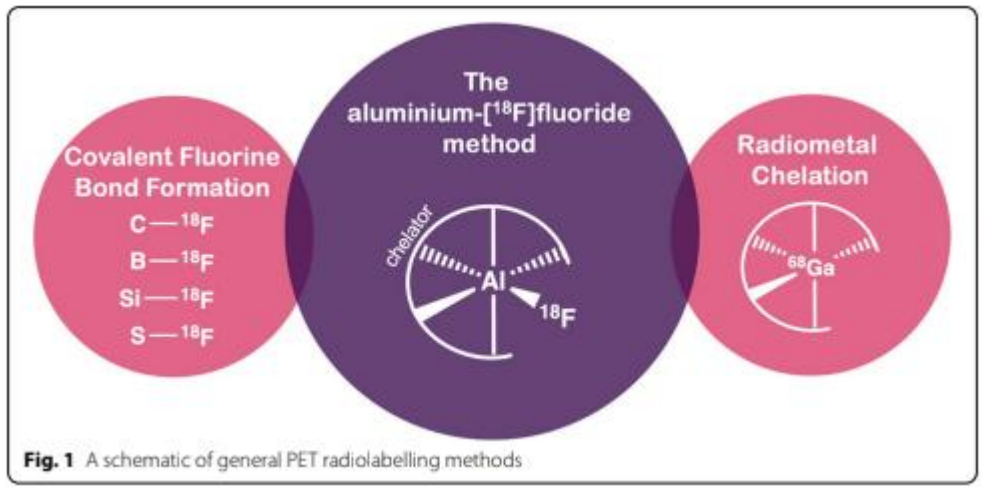
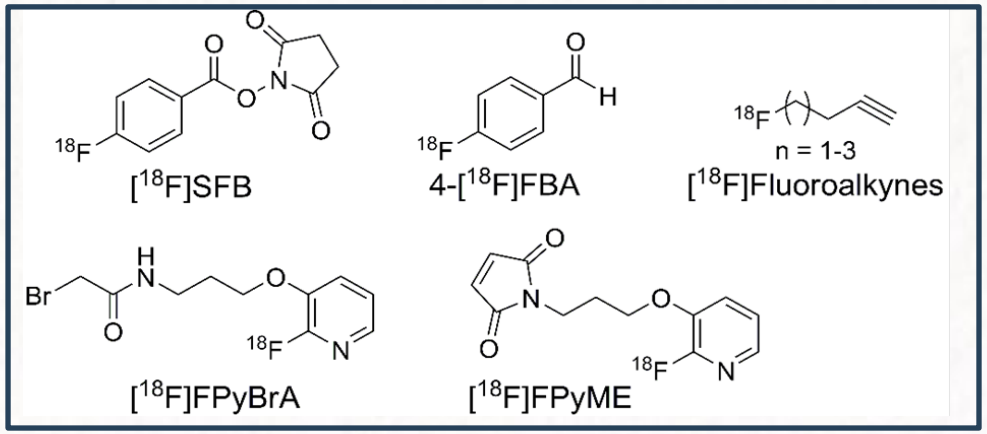


Fig. 1 A schematic of general PET radiolabelling methods

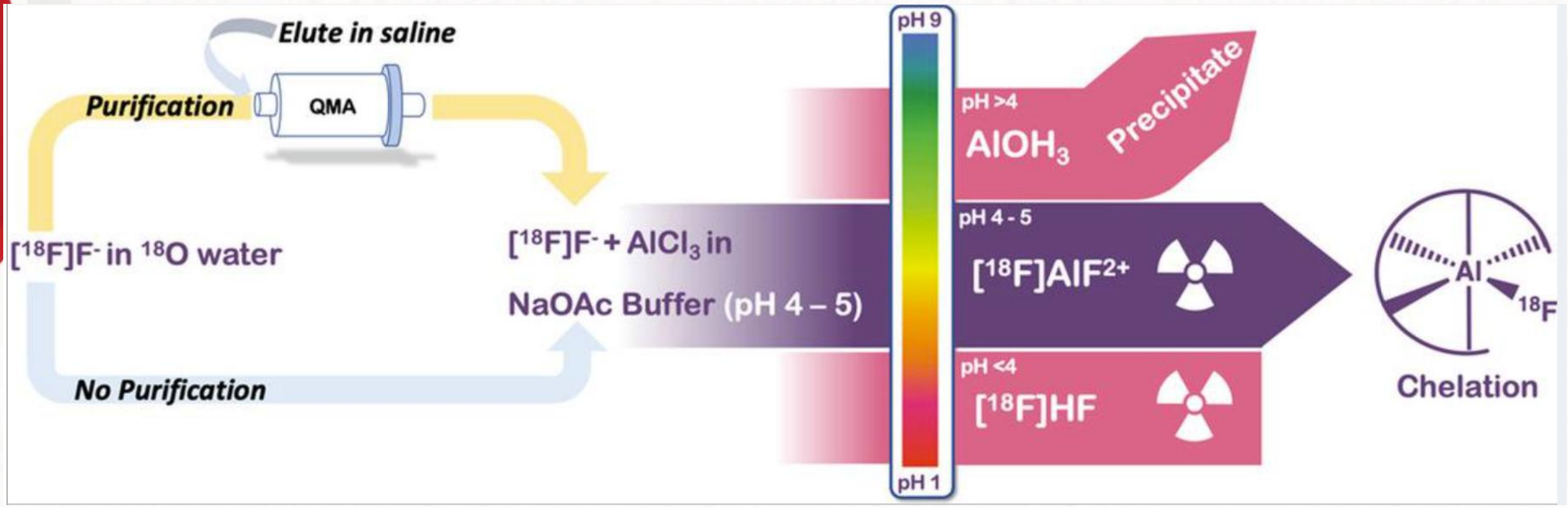
Radiokimia yang *simple* dan sesuai dengan waktu paruh ^{18}F yang pendek dan chemistry radiometal (chelation) dengan agen pengkelat

- **In- Direct Radiolabeling**

Dengan Prostetik groups→ reaksi cukup kompleks



Archibald and Allott EJNMMI radiopharm. chem. (2021) 6:30



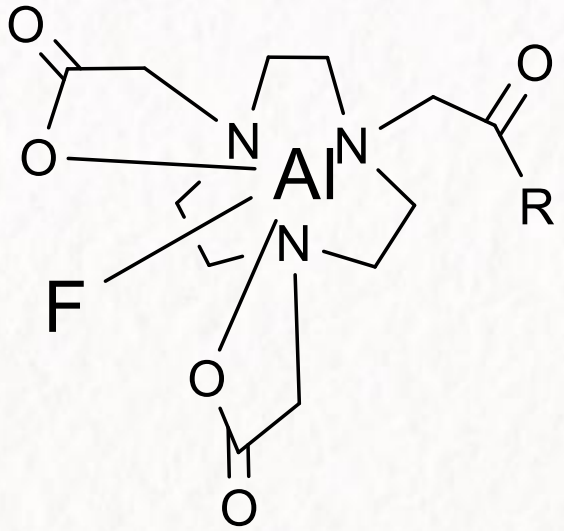
Archibald and Allott EJNMMI radiopharm. chem. (2021) 6:30

simple

Time saving

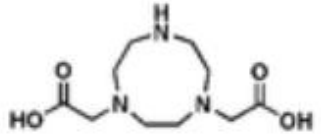
Efficient

stable

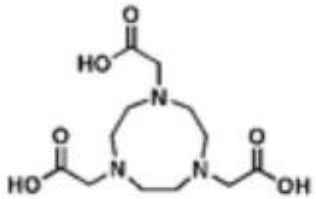


- The aluminium-[^{18}F]fluoride (**Al-^{18}F**) complex is a **"pseudo-radiometal"**
- The **bond strength** of **AlF bond** is ca. **670 kJ/mol**
- **Al-^{18}F** forms thermodynamically stable and kinetically inert chelates

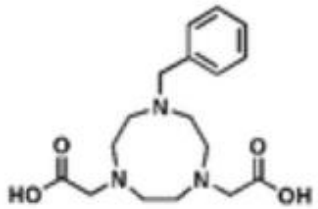
Al-^{18}F



NODA



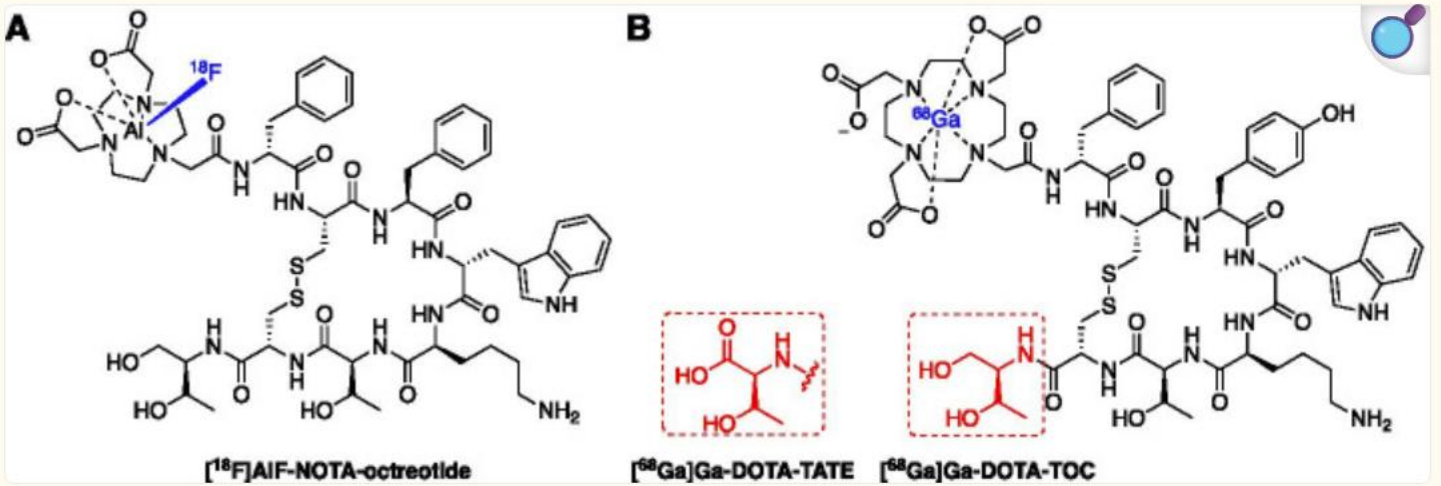
NOTA

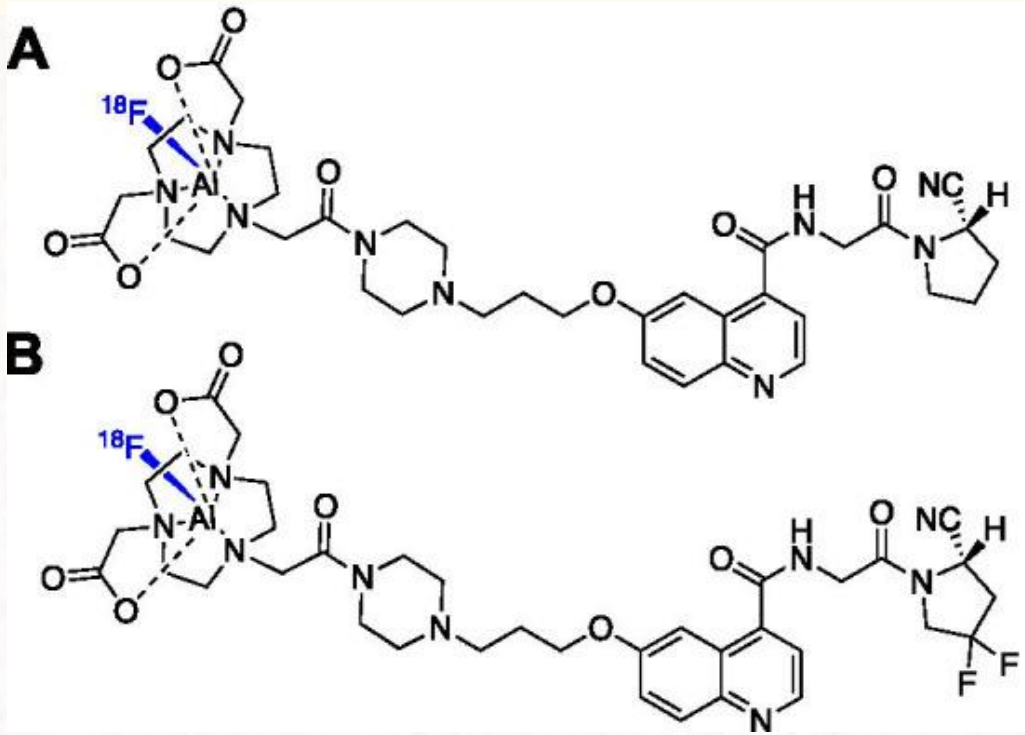


N-Benzyl-NODA

Bioconjugate Chem. 2016, 27, 3, 790−798

Radiofarmaka Berbasis ^{18}F-AlF





[18F]AlF-NOTA-FAPI-74

[18F]AlF-NOTA-FAPI-04

Archibald and Allott EJNMMI radiopharm. chem. (2021) 6:30

Tahapan Penyiapan Radiofarmaka Berbasis ^{18}F

1 **Produksi ^{18}F**

Iradiasi air berlabel ^{18}O pada siklotron.

2 **Isolasi $^{18}F^-$**

Pemisahan [^{18}F]fluoride dari target irradiated water.

3 **Sintesis (Penandaan)**

$^{18}F^-$ bereaksi dengan prekursor membentuk radiofarmaka.

4 **Pemurnian**

Pemurnian produk dari prekursor sisa dan pengotor kimia.

5 **Kontrol Mutu**

Uji identitas, radiokimia, kimia, sterilitas, pirogen, dll.

6 **Filtrasi Steril**

Penyaringan menggunakan filter 0,22 µm (steril).

7 **Dispensing Aseptik**

Pengisian ke dalam vial steril secara aseptik di dalam hot cell.

8 **Produk Akhir**

Radiofarmaka ^{18}F siap untuk digunakan.

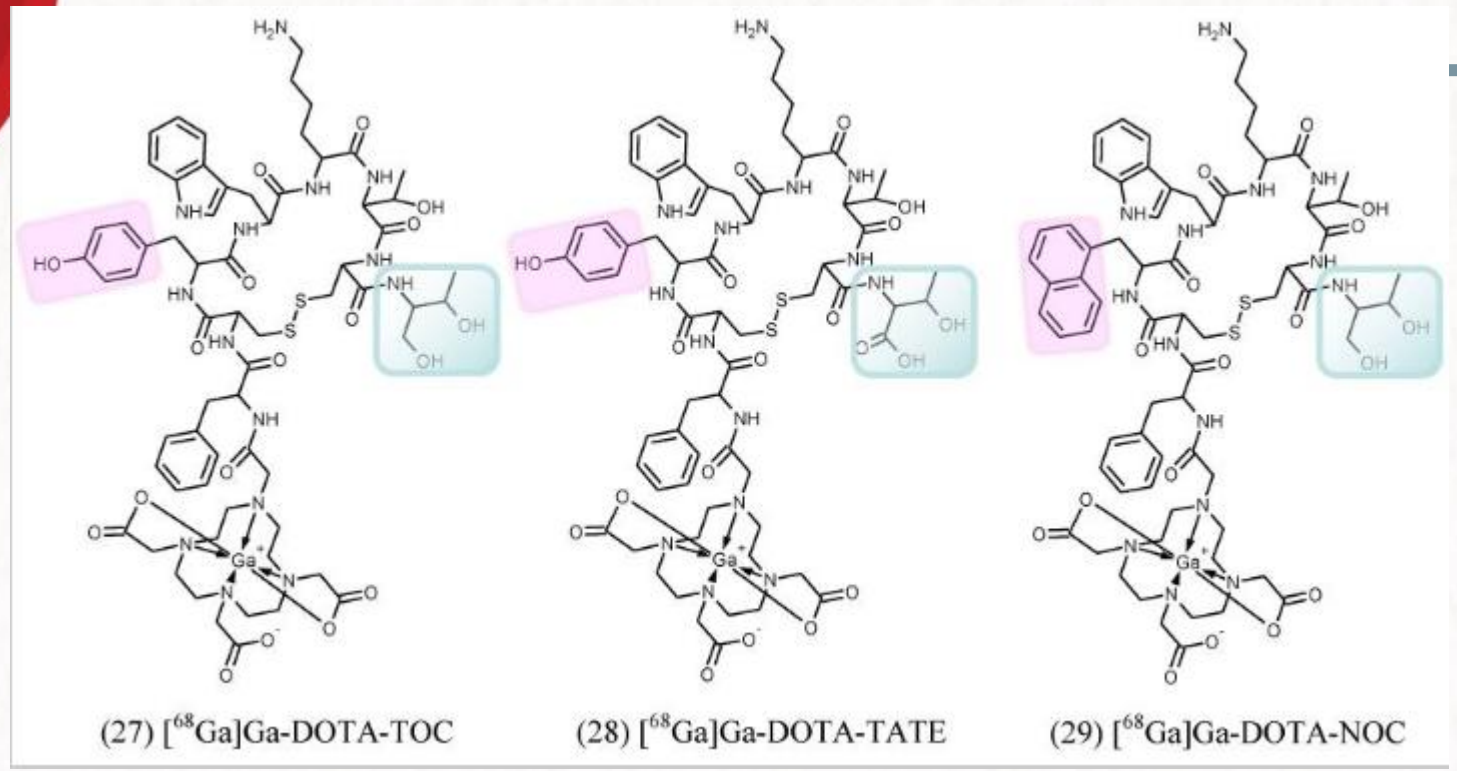
9 **Distribusi**

Pengemasan dalam wadah berperisai dan dikirim ke fasilitas nuklir kedokteran.

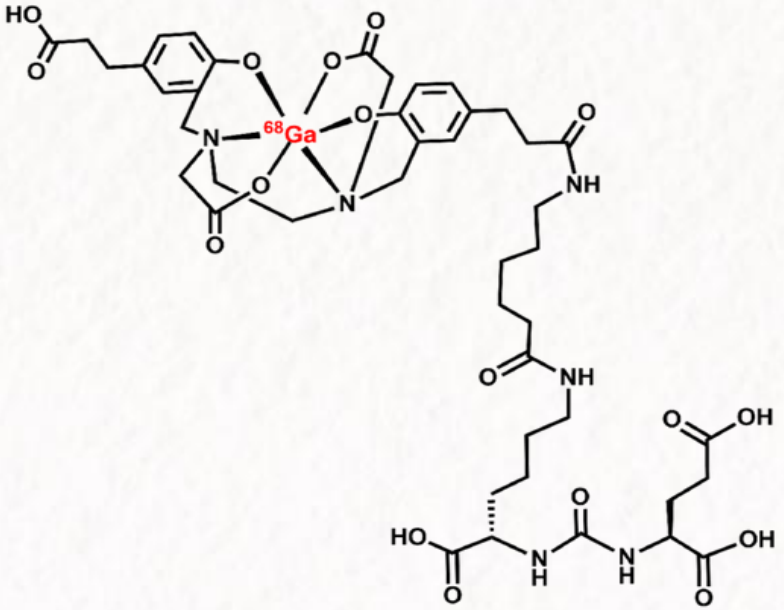
5 Radiofarmaka ^{68}Ga

Radiofarmaka ^{68}Ga

Due to the nearly ideal nuclear properties of radiometals (68Ga $t_{1/2}$ 68 minutes; 1.899 MeV of max positron energy,14 mm of tissue penetration) for positron emission tomography (PET) and chelation chemistry using a bifunctional chelating approach (BFCA), various classes of ^{68}Ga-labeled tracers have been developed including ^{68}Ga[Ga]-DOTA-Bombesin, ^{68}Ga[Ga]-NOTA-RGD, ^{68}Ga[Ga]-albumin, and ^{68}Ga[Ga]-DOTAhEGF (human epidermal growth factor)



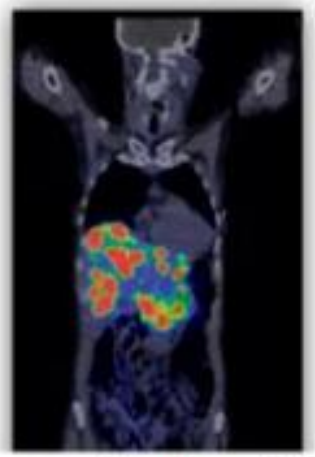
(27) [^{68}Ga]Ga-DOTA-TOC (28) [^{68}Ga]Ga-DOTA-TATE (29) [^{68}Ga]Ga-DOTA-NOC



^{68}Ga[Ga]-PSMA

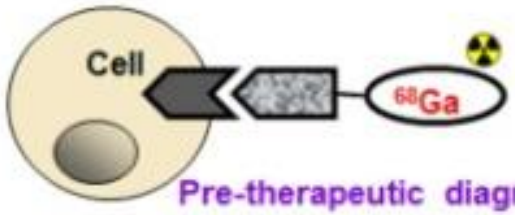
Velikyan I. Prospective of ^{68}Ga-radiopharmaceutical development. Theranostics. 2013 Dec 10;4(1):47-80.

- Tumour-type specificity
- Precise localisation of lesions
- Pre-therapeutic quantification
  - Receptor status
  - Uptake kinetics
  - Dosimetry
- Staging, Selection, Planning,
- Monitoring the response to the therapy
- Detection of recurrent disease

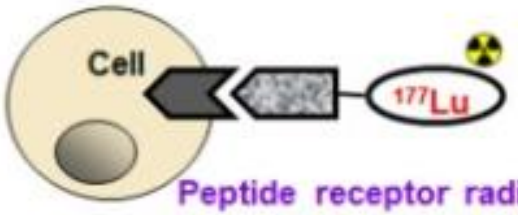


Personalized medicine

RADIOTHERANOSTICS



Pre-therapeutic diagnostics



Peptide receptor radiotherapy

Velikyan I. 68Ga-Based radiopharmaceuticals: production and application relationship. Molecules. 2015 Jul 16;20(7):12913-43.

6 ^{68}Ga Production

^{68}Ga Production

^{68}Ga can be produced in an ionic form of the chemically active $^{68}GaCl_3$ by two methods

via a medium-energy cyclotron

Ga is obtained via $^{68}Zn(p,n)^{68}Ga$ activation using either a target foil or plate in a solid target solution in a liquid target

- ✓ This reaction has a high cross-section in the energy range of 11–14 MeV
- ✓ It is easily accessible in small medical cyclotrons (< 20 MeV).
- ✓ Solid or liquid targets can be used, both having their advantages and limitations.

a $^{68}Ge/^{68}Ga$ generator

A typical generator consists of a small chromatographic column, where ^{68}Ge is immobilized with selected absorbents, such as TiO_2, SnO_2, pyrogallol-derivatized SiO_2, and a mixed matrix, situated in a shielding lead container.

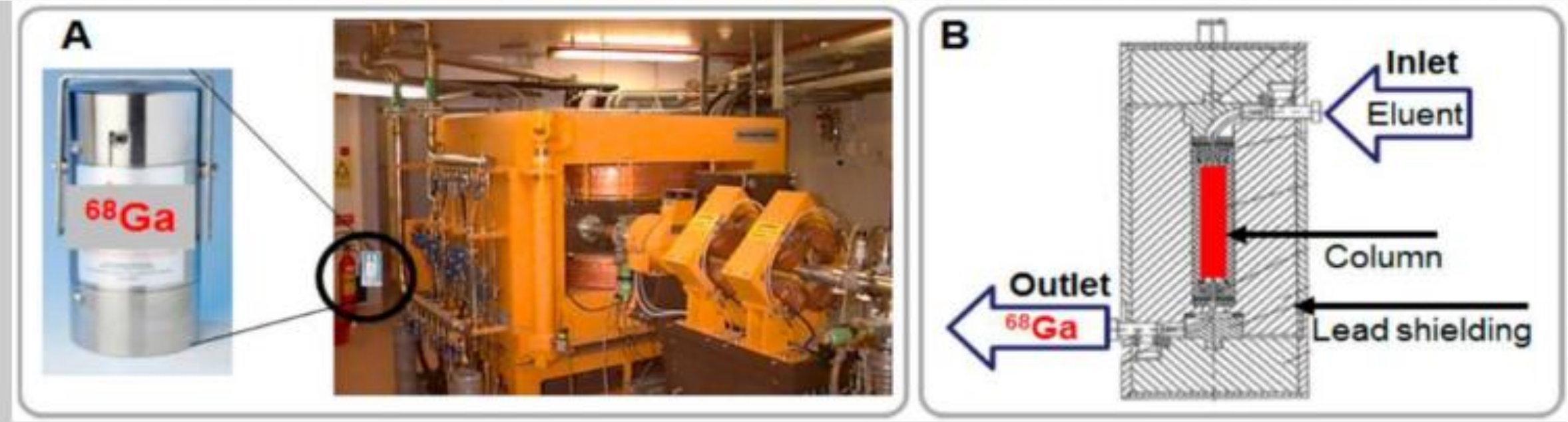
Generator $^{68}Ge/^{68}Ga$

^{68}Ge , a parent radionuclide, spontaneously decays in the column to give ^{68}Ga, with typical yields of 70%–80% in the elution.

Secular equilibrium, where both ^{68}Ge and ^{68}Ga have equal radioactivity, in the $^{68}Ge/^{68}Ga$ generator occurs due to the half-life of ^{68}Ge (270 d) being over 100 times longer than that of ^{68}Ga (68 min).

Most manufacturers suggest that the ^{68}Ga production cycle for clinical use can be repeated up to 2–3 times a day depending on the generator-loaded radioactivity and the age of the generator.

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



Velikyan I. 68Ga-Based radiopharmaceuticals: production and application relationship. Molecules. 2015 Jul 16;20(7):12913-43

The advantages of generator $^{68}Ge/^{68}Ga$:

- the stable column matrices,
- easy elution,
- long shelf-life of 1–2 years,
- effective shielding container
- compact size.

Consideration for choosing generator $^{68}Ge/^{68}Ga$:

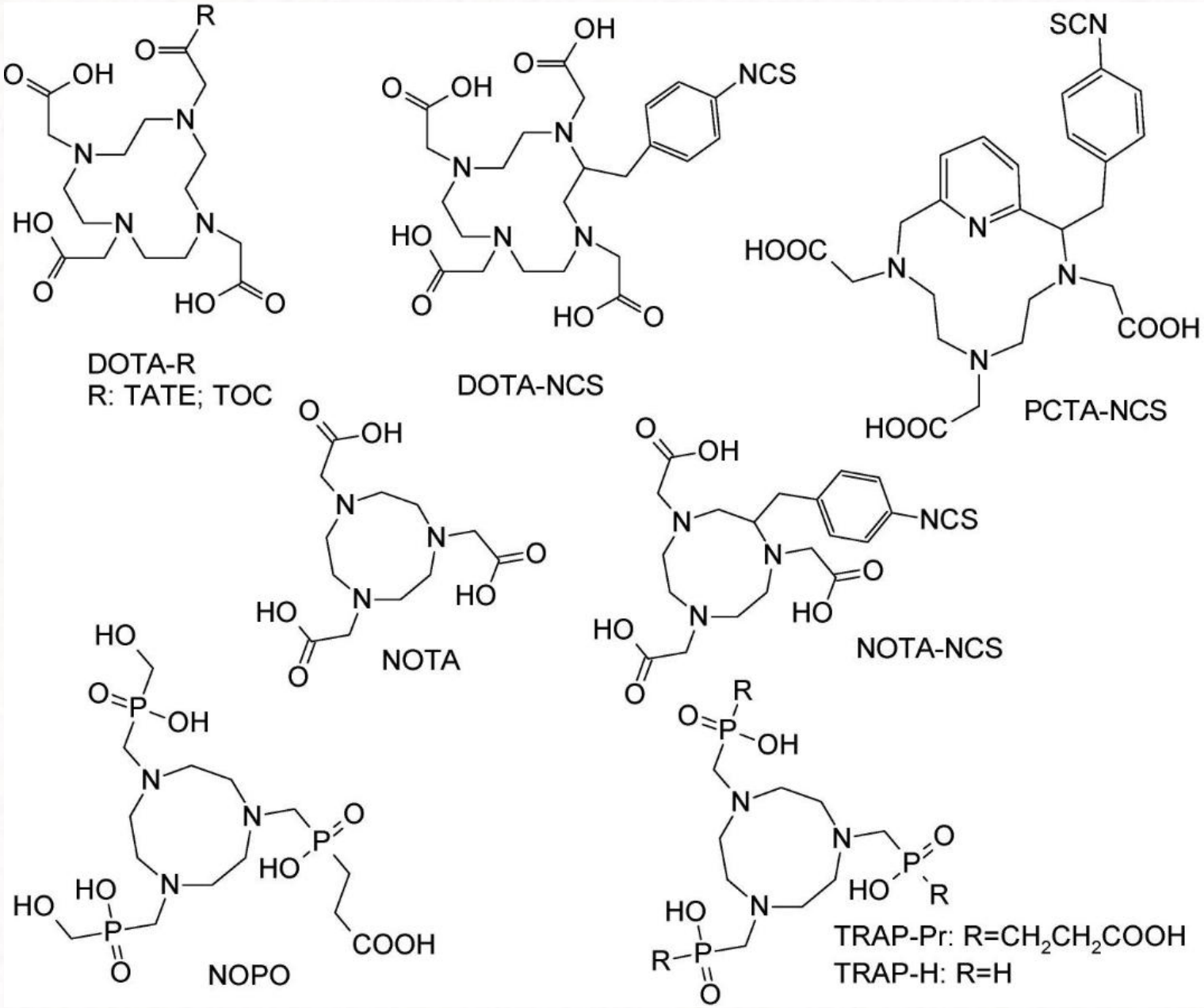
- Material of the column
- Concentration of HCl
- Elution Factor

Company	Generator specifications					
	Column material	Eluent	^{68}Ge breakthrough	Elution volume	Metallic impurities	Weight of generator
Eckert & Ziegler Cyclotron Co. Ltd. (Obninsk)[23]	TiO_2	0.1 M HCl	< 0.005%	5 ml	Ga < 1 µg/mCi Ni < 1 µg/mCi	11.7 kg
Eckert & Ziegler IGG100 and IGG101 GMP (Gallia Pharm)[23]	TiO_2	0.1 M HCl	< 0.001%	5 ml	Fe < 10 µg/mCi Zn < 10 µg/mCi	IGG100 = 10 kg IGG101 = 14 kg
iThemba LABS, South Africa[23]	SnO_2	0.6 M HCl	< 0.002%	5 ml	1–20 ppm for Sn, Fe, Cu, Mn, and Al	
Pars Isotope (PARS-GalluGEN®), Tehran, Iran[23]	SnO_2	0.6 M HCl	< 0.00002%		>1 ppm for Fe, Sn and Zn	
IRE EliT (Galli Eo®), Fleurus, Belgium[23]	Unspecified	0.1 M HCl	< 0.001%		< 10 µg/GBq of ^{68}Ga for Fe, Cu, Ni, Zn, Pb, and Al	
Isotope Technologies Garching, GmbH, Germany[23]	Silica gel modified with dodecayl gallate	Sterile 0.05 M HCl	< 0.005%	3–4 ml	< µg/GBq of ^{68}Ga for (Ni, Zn, Nb, Pb, Fe, and Cu)	
Isotope ROSATOM[24]	TiO_2	0.1 M HCl	< 0.005%	5 ml		11.7 kg
I.D.B. Holland B.V.[25]	SnO_2	0.6 M HCl	< 0.002%	6 ml	< 10 ppm (Ga, Ge, Zn, Ti, Sn, Fe, Al, and Cu)	26 kg

Sriprapa, Volume 75, No.10: 2023 Siriraj Medical Journal

6 Aspek Radiokimia dan Prinsip Penandaan dengan ^{68}Ga

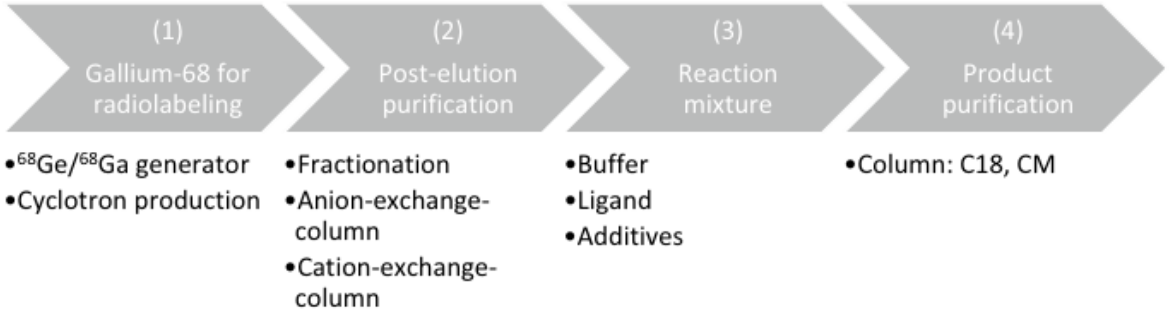
Chelating Agent atau Agen Pengkelat



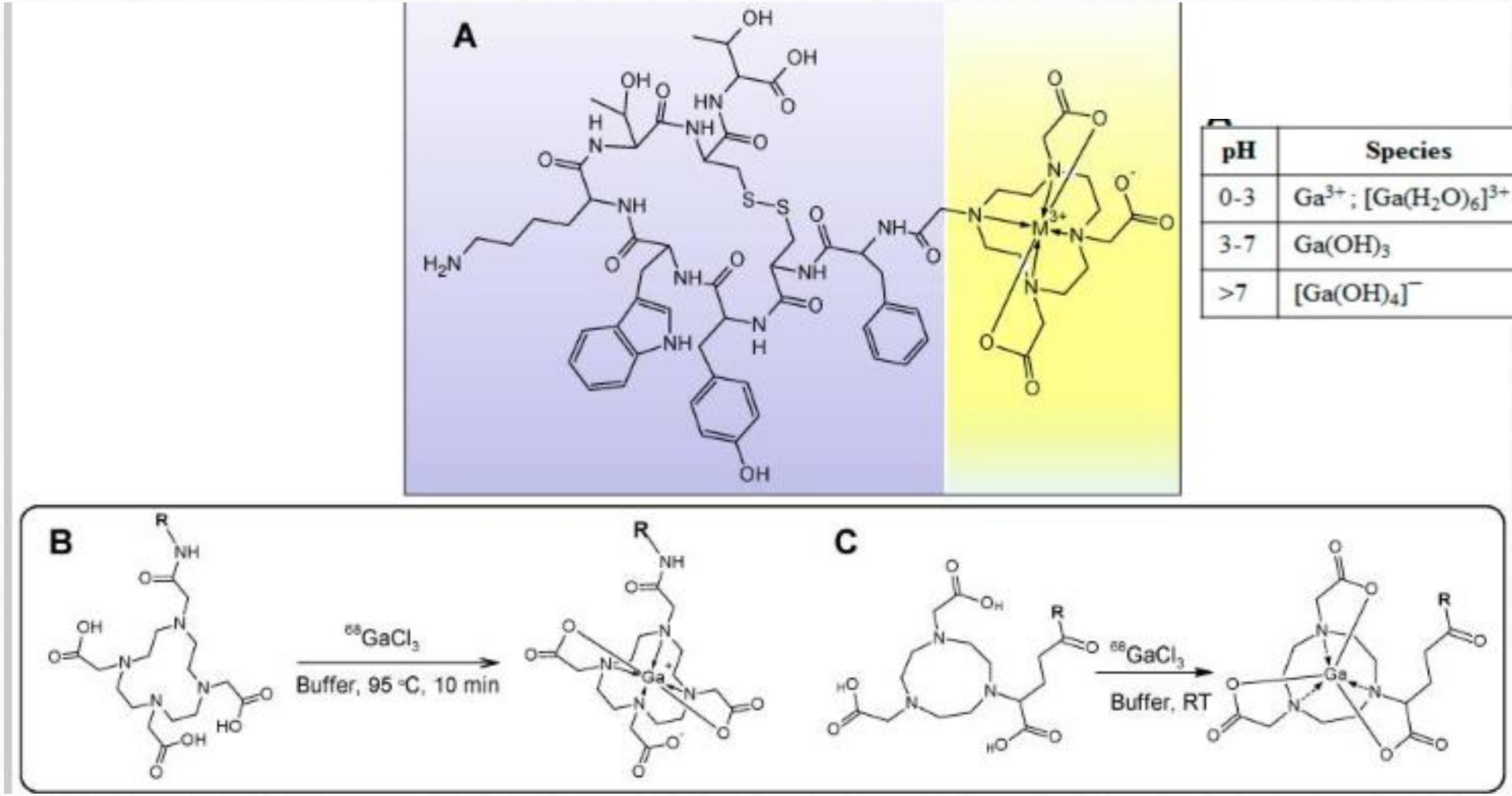
Velikyan I. 68Ga-Based radiopharmaceuticals: production and application relationship. Molecules. 2015 Jul 16;20(7):12913-43.

Produksi Radiofarmaka ^{68}Ga

1. Manual: cocok pada pengembangan radiofarmaka skala riset, namun dosis paparan radiasi tinggi ke operator, dan hasil yang tidak reprodusibel (*radiochemical yield*)
2. Proses (semi)automatis: reliable, reprodusibel, aman, praktis dan memenuhi persyaratan GMP karena terdokumentasi proses produksinya.



3. Menggunakan cold kit: tidak perlu proses pemurnian,, dan membutuhkan keahlian proses radiolabeling. Contoh *cold kit:* PSMA-11 (Illumet), DOTA-TATE (Netspot) dan DOTA-TOC (Somakit-TOC)



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

Velikyan I. Molecules. 2015 Jul 16;20(7):12913-43.

Rangkuman

Dasar Radiofarmaka PET dan ^{18}FDG

Positron Emission Tomography (**PET**) adalah teknik pencitraan medis yang menggunakan radiofarmaka pemancar positron untuk mendeteksi aktivitas metabolik dalam tubuh. **^{18}FDG (Fluorodeoxyglucose)** adalah radiofarmaka PET yang paling umum digunakan, karena menyerupai glukosa dan dapat menunjukkan aktivitas metabolik sel, terutama dalam diagnosis kanker.

Kelebihan ^{18}F sebagai Radioisotop

- **Waktu paruh optimal** (~110 menit), cukup lama untuk sintesis dan distribusi tetapi cukup pendek untuk mengurangi paparan radiasi.
- **Energi positron rendah** (~0,635 MeV), menghasilkan gambar PET dengan resolusi tinggi.
- **Reaktivitas kimia yang baik**, memungkinkan pelabelan berbagai molekul biologis.

Perkembangan personalized medicine dengan radiofarmaka teranostik yang memungkinkan diagnostic agent ditandai dengan radioisotope terapi sedang sangat meningkat kebutuhannya.

Radiofarmaka ^{68}Ga memungkinkan fasilitas radiofarmasi yang tidak memiliki siklotron untuk menyiapkan radiofarmaka ini dengan menggunakan ^{68}Ga yang diproduksi dari sistem generator ^{68}Ge/^{68}Ga.

Radiofarmaka berbasis ^{18}F dan ^{68}Ga ini sangat penting dalam kedokteran nuklir, terutama untuk mendeteksi kanker dan gangguan metabolik lainnya.

Terima Kasih

Atas Perhatian Anda

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