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Overview of Diagnostic and Therapeutic Radionuclides

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Overview of Common Diagnostic and Therapeutic Radionuclides (Nuclear Data and Production Technology)

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Lecture delivered during the Workshop on Nuclear Data for Science and Technology: Medical Applications, Abdus Salam ICTP, Trieste, Italy, 30 September to 4 October 2013

Topics

- General considerations about nuclear data related to production of radionuclides

  - in a nuclear reactor

  - at a cyclotron

- Production of diagnostic radionuclides

  - SPECT radionuclides

  - PET radionuclides

- Production of therapeutic radionuclides
- Summary

Nuclear Data for Radionuclide Production in a Nuclear Reactor

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Main Production Reaction: (n, γ) Process

Examples:

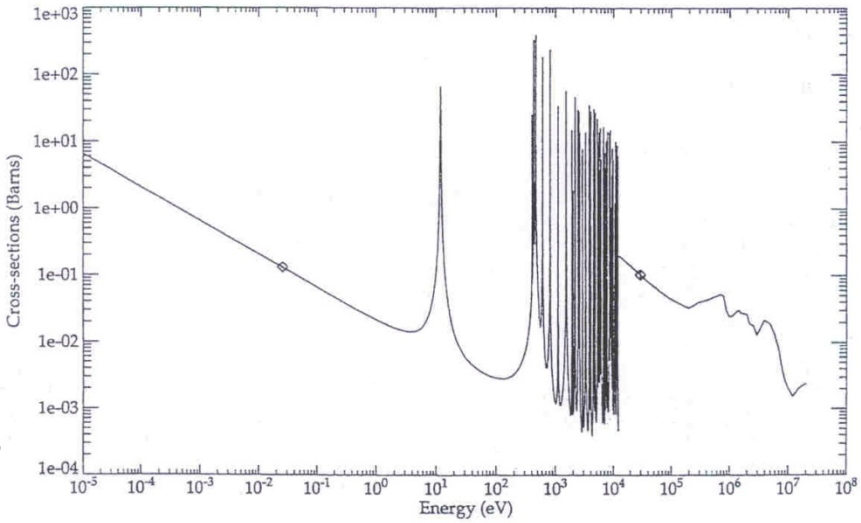
$^{31}P(n,\gamma)^{32}P$	(14.3 d)	σ = 0.18 b
$^{50}Cr(n,\gamma)^{51}Cr$	(27.7 d)	σ = 15.9 b
$^{59}Co(n,\gamma)^{60}Co$	(5.3 a)	σ = 37.0 b
$^{98}Mo(n,\gamma)^{99}Mo$	(66.0 h)	σ = 0.14 b
$^{197}Au(n,\gamma)^{198}Au$	(2.7 d)	σ = 98.8 b

Double neutron capture is also possible

Example: $^{186}W(n,\gamma)^{187}W(n,\gamma)^{188}W$ (69 d) (23.8 h)

- Process occurs in high flux reactors

Excitation function of $^{98}Mo(n,\gamma)$-Process



- ***Contribution of thermal neutrons to product formation is most important.***
- ***Radioactive product is of low specific activity.***

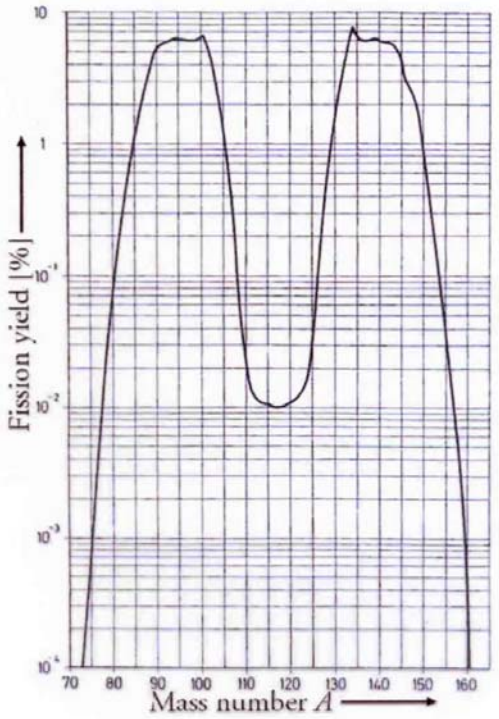
Other Production Reactions

Fission Process

Examples: $^{235}U(n,f)^{90}Sr$ (28.6 a) FY = 5.8 %
$^{235}U(n,f)^{99}Mo$ (66.0 h) FY = 6.2 %
$^{235}U(n,f)^{131}I$ (8.0 d) FY = 2.9 %

Fission yields

Mass distribution in fission of ^{235}U



(n,z) Process

Examples:

$^{6}Li(n,\alpha)^{3}H$	(12.3 a)	σ = 940 b
$^{14}N(n,p)^{14}C$	(5730 a)	σ = 1.8 b
$^{32}S(n,p)^{32}P$	(14.3 d)	σ = 31.0 mb
$^{67}Zn(n,p)^{67}Cu$	(61.9 h)	σ = 1.07 mb
$^{89}Y(n,p)^{89}Sr$	(50.5 d)	σ = 0.3 mb

- ***Production yield with reactor neutrons is high only for light mass target nuclei.***
- ***Process is applied only in special cases in the medium mass region.***
- ***Specific activity of product is high.***

- ***Extensive radiochemical work is involved.***
- ***Product is of high specific activity.***

Nuclear Data Relevant to Cyclotron Production of Radionuclides

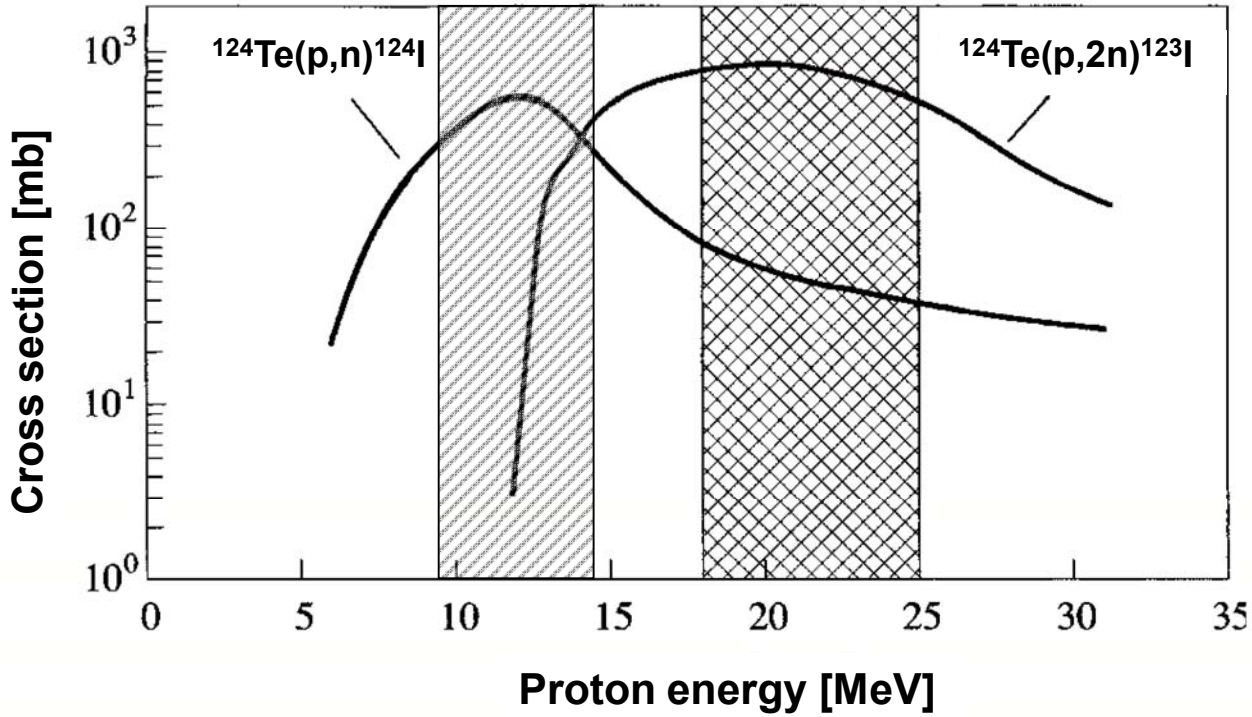
- Due to rapid energy loss of charged particles in target, knowledge of excitation function is essential
- Data needed for optimisation of production process
  - maximise yield of product
  - minimise impurity level
- The higher the projectile energy, the more are data needs
- Often many production routes are possible. However, major criteria for choice are yield and purity

Role of Nuclear Data in Optimisation of a Production Route using Charged Particles

Example:

Excitation functions of $^{124}Te(p,xn)^{123,124}I$ reactions

Scholten et al.,
ARI **46**, 255 (1995).



Production of ^{124}I

E_p: 14 → 9 MeV

(^{125}I impurity < 0.1%)

Production of ^{123}I

E_p: 25 → 18 MeV

(^{124}I impurity < 1%)

Radionuclides for Modern Nuclear Medicine

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Diagnostic Radionuclides

- **For SPECT**

  γ-emitters (100 – 250 keV)

  ^{99m}Tc, ^{123}I, ^{201}Tl

- **For PET**

  β^+ emitters

  ^{11}C, ^{13}N, ^{15}O, ^{18}F,

  ^{68}Ge (^{68}Ga), ^{82}Sr (^{82}Rb)

Therapeutic Radionuclides (in-vivo)

- β^--emitters (^{67}Cu, ^{90}Y, ^{131}I, ^{153}Sm)
- α-emitters (^{211}At, ^{225}Ac, etc.)
- Auger electron emitters (^{51}Cr, ^{75}Se, ^{77}Br, ^{125}I, ^{193m}Pt)
- X-ray emitters (^{103}Pd, ^{131}Cs, etc.)

Routine Methods of Production of Some Commonly Used Photon Emitters

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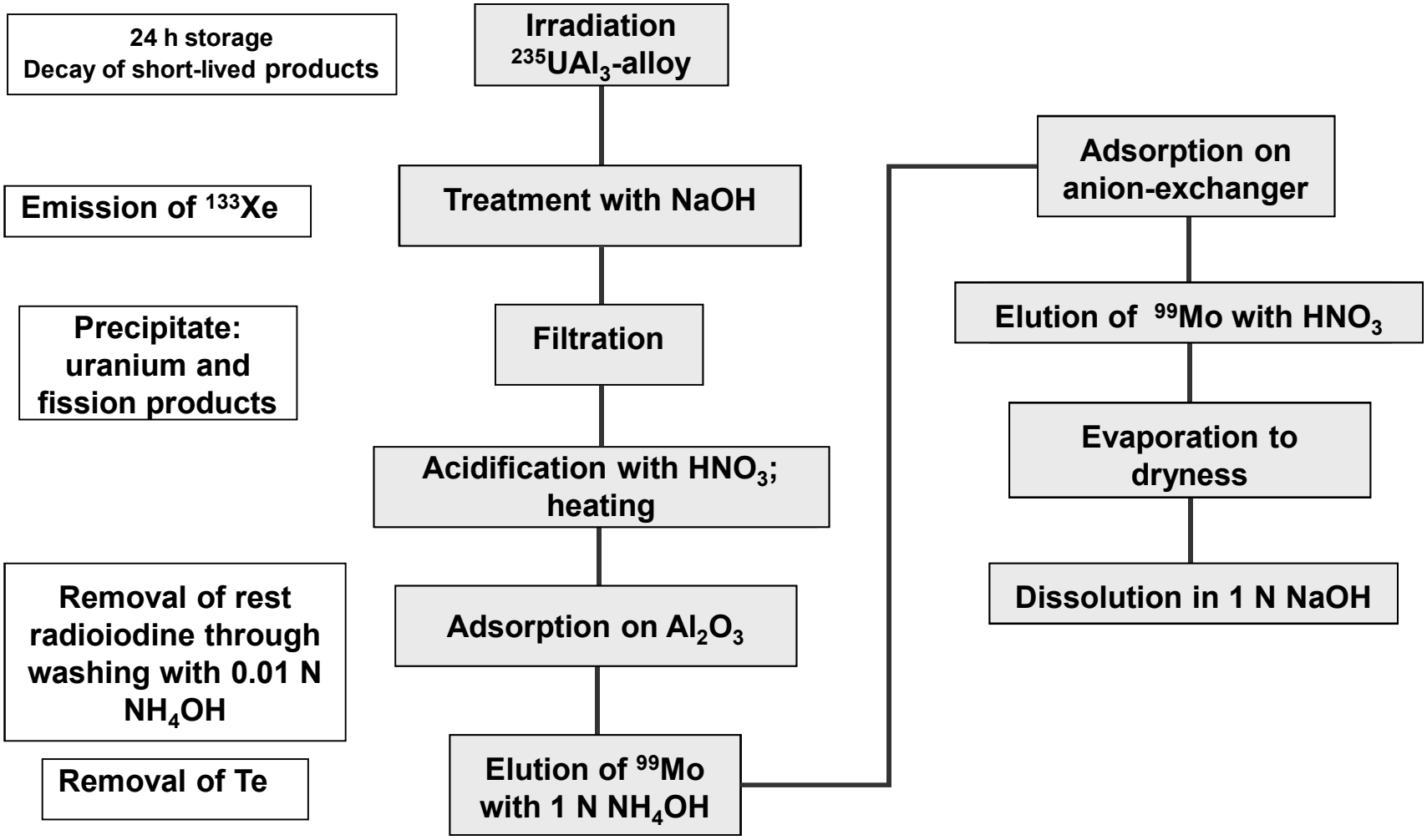
Radionuclide	$T_{1/2}$	Main γ-ray energy in keV (%)	Production route	Energy range (MeV)
^{67}Ga	3.26 d	93 (37) 185 (20)	^{68}Zn(p,2n)	26 → 18
^{99}Mo ↓ (generator)	2.75 d	181 (6) 740 (12)	^{235}U(n,f) ^{98}Mo(n,γ)	
^{99m}Tc	6.0 h	141 (87)		
^{111}In	2.8 d	173 (91) 247 (94)	^{112}Cd(p,2n)	25 → 18
^{123}I	13.2 h	159 (83)	^{123}Te(p,n) ^{124}Te(p,2n) ^{127}I(p,5n)^{123}Xe[a)] ^{124}Xe(p,x)^{123}Xe[a)]	14 → 10 26 → 23 65 → 45 29 → 23
^{201}Tl	3.06 d	69 – 82 (X-rays) 166 (10.2)	^{203}Tl(p,3n)^{201}Pb[b)]	28 → 20

a) ^{123}Xe decays by EC (87%) and β^+ emission (13%) to ^{123}I
b) ^{201}Pb decays by EC to ^{201}Tl

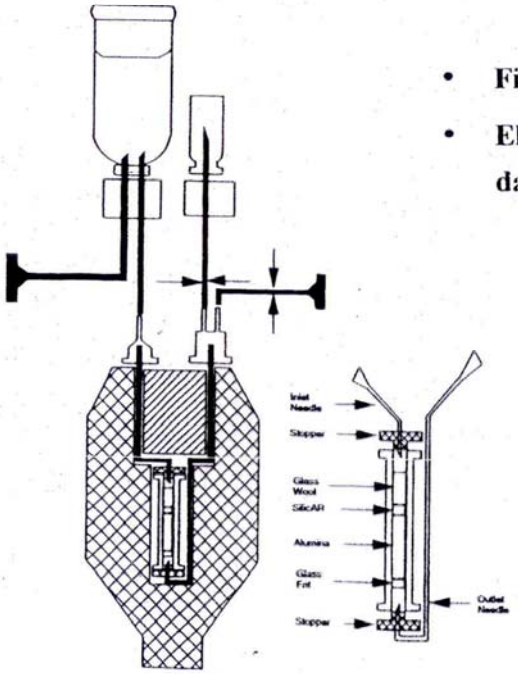
Wet Chemical Process for Separation of ^{99}Mo from Neutron Irradiated ($^{235}UAl_3$)-Alloy



Preparation of Generator

- Selection of the adsorbent that will
  - bind the long-lived parent
  - allow removal of the short-lived daughter in an easy and reproducible manner
- Factors requiring systematic evaluation include
  - nature of the adsorbent
  - oxidation state of parent
  - chemical form of parent
  - pH
  - chemical nature and complexing character of the elution solution

Example: ^{99}Mo (66 h) / ^{99m}Tc (6 h) Generator



- Fission ^{99}Mo adsorbed on Al_2O_3
- Elution with normal saline removes daughter as $Na^{99m}TcO_4$

Structure of some Tc-complexes

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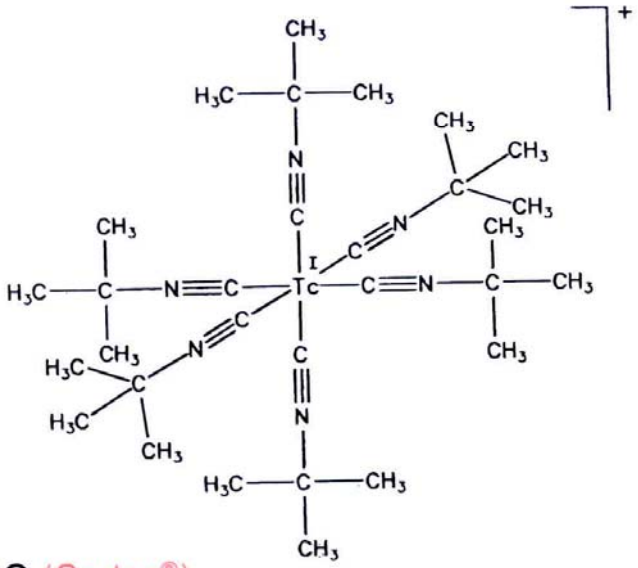
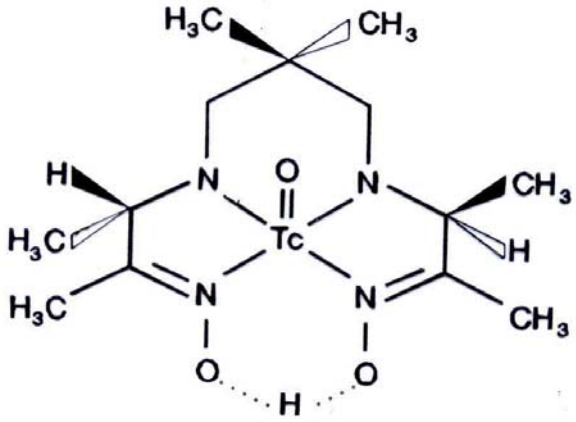
Hexakis(t-butylisonitrile)technetium (I), $[Tc(CN\text{-}t\text{-}Bu)_6]^+$

(MIBI)



L-HMPAO (Certec®)



Important Nuclear Processes for the Production of ^{123}I

Indirect Methods

$^{127}I(p,5n)^{123}Xe$	$E_p = 70 \rightarrow 50$ MeV
$^{127}I(d,6n)^{123}Xe$	$E_d = 78 \rightarrow 64$ MeV
Cs, La(p,spall)^{123}Xe	$E_p = 590 \rightarrow 200$ MeV
$^{124}Xe(p,x)^{123}Xe^*$	$E_p = 30 \rightarrow 25$ MeV

$$^{123}Xe \xrightarrow[2.0\ h]{EC,\beta^+} {}^{123}I$$

Major impurity ^{125}I

Direct Methods*

$^{124}Te(p,2n)^{123}I$	$E_p = 30 \rightarrow 20$ MeV
$^{123}Te(p,n)^{123}I$	$E_p = 15 \rightarrow 10$ MeV
$^{122}Te(d,n)^{123}I$	$E_d = 16 \rightarrow 8$ MeV

Several impurities

* These methods demand highly enriched isotopes as target materials.

The major criteria for choice of a production process are ***yield and purity***.

Production of ^{123}I via the ^{124}Xe(p,x)^{123}I-Process

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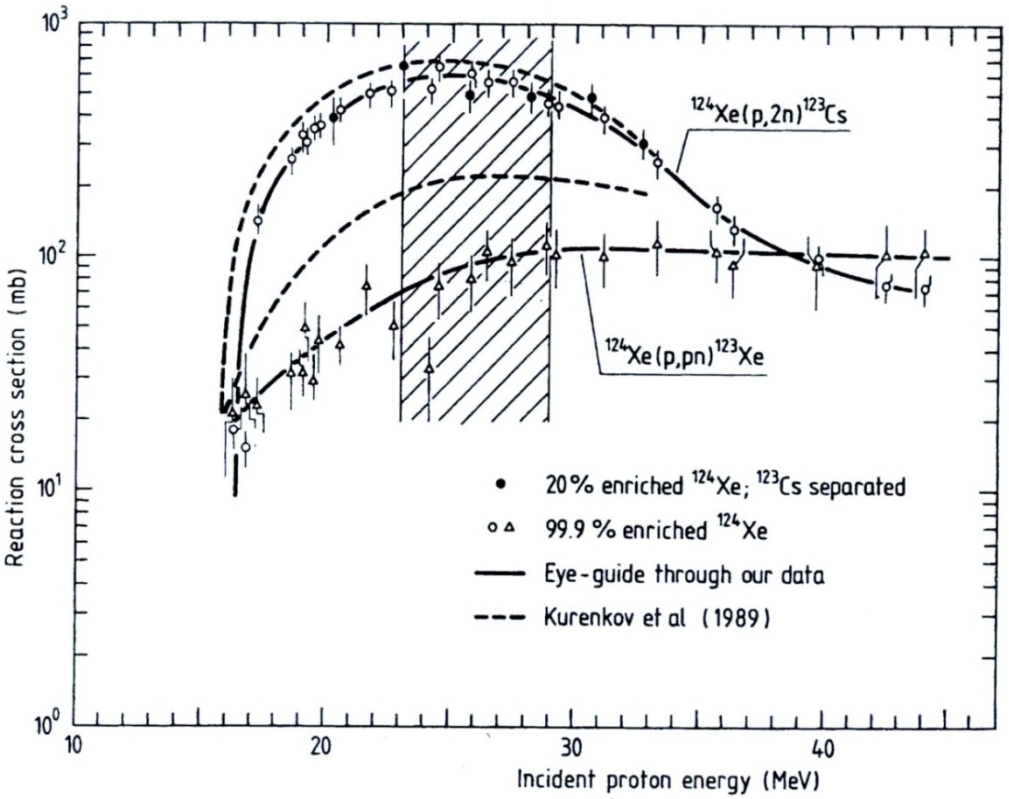
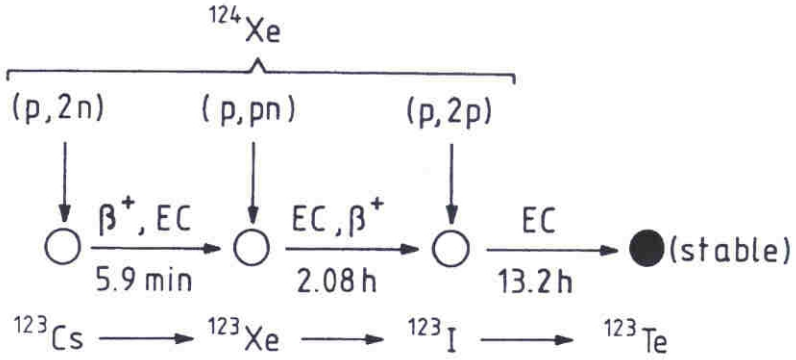
Excitation Function



Routes



Optimum energy range: E_p = 29 → 23 MeV

^{123}I-yield: 414 MBq/μA·h

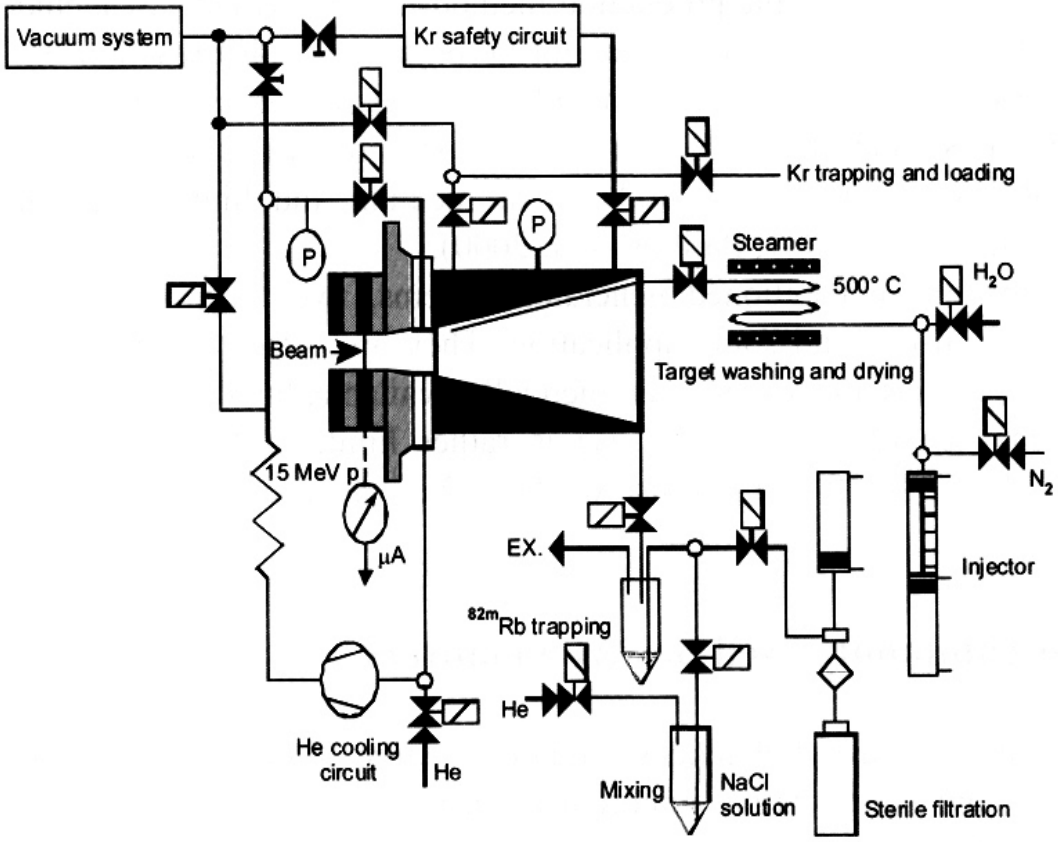
^{121}I(^{121}Te)-impurity: 10^{-7} %

Tárkányi et al.,
ARI **42**, 221 (1991).

This is the method of choice;
leads to the highest purity product.

Gas Targetry

Example: Production of alkali metal or radiohalogen via irradiation of an enriched rare gas



- Removal of radio-activity (e.g. ^{82m}Rb, ^{123}I) by rinsing the inner walls of the target
- Batch yield ≤ 100 GBq

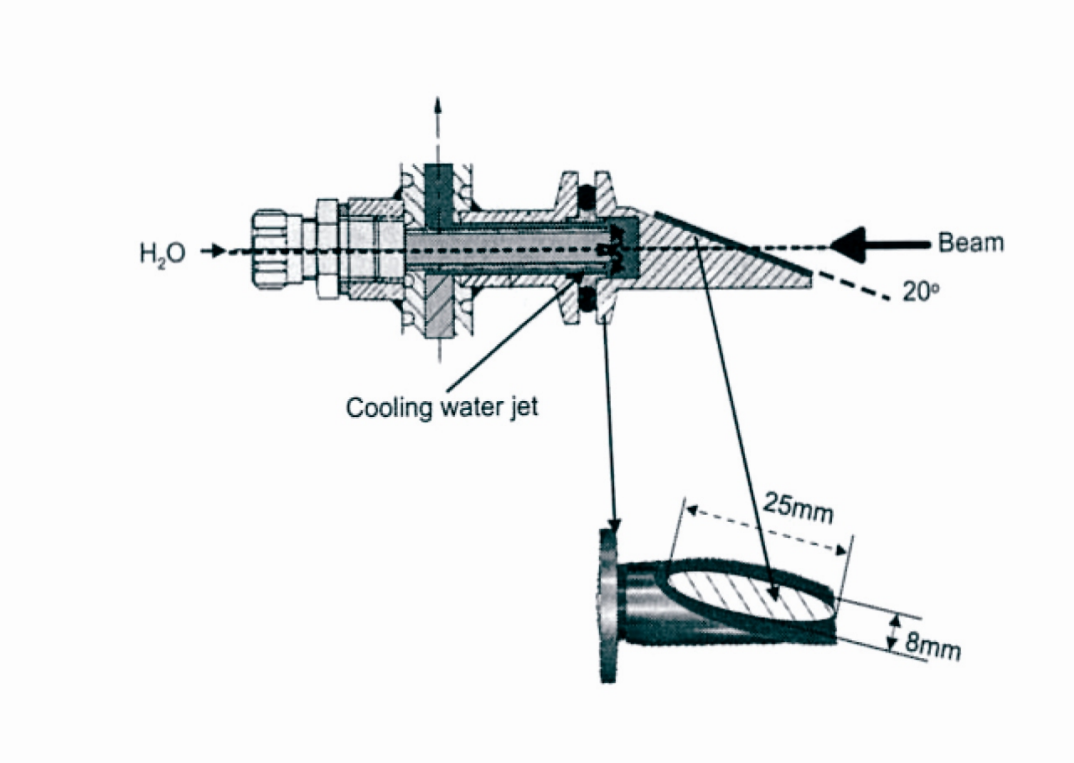
Blessing et al.,
ARI **48**, 37 (1997).

Solid Targetry

Sample preparation: electrolysis, alloy formation, pellet

Heat dissipation: 2π or 4π cooling, slanting beam

Example: Use of slanting beam

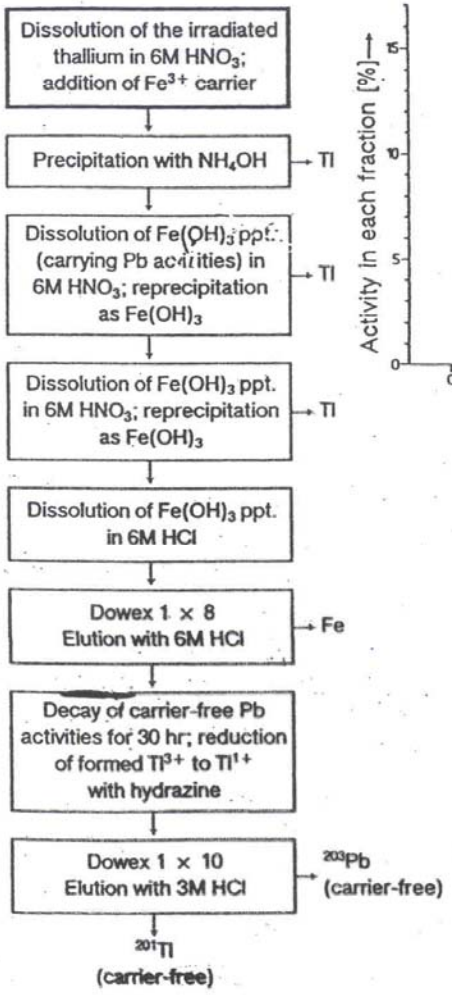


- Standard technology used in large scale production of several radionuclides (^{67}Ga, ^{111}In, ^{201}Tl, etc.)

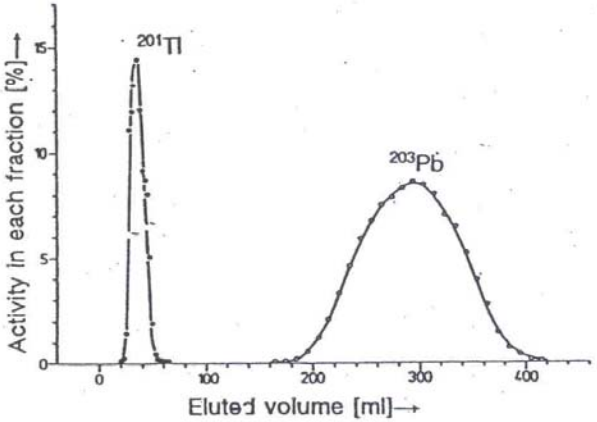
Spellerberg et al.,
ARI **49**, 1519 (1998).

Radiochemical Separation of ^{201}Tl ($T_{1/2}$ = 73 h) via the $^{203}Tl(p,3n)^{201}Pb \xrightarrow[9.4\,h]{EC,\beta^+} {}^{201}Tl$-Process

Flow sheet of separation procedure



Final purification via anion-exchange chromatography



Qaim et al.,
ARI **30**, 85 (1979).

Commonly Used SPECT Radiopharmaceuticals

Radiopharmaceutical	Function
^{99m}Tc – HMPAO	Brain blood flow
^{99m}Tc – ECD	Brain blood flow
^{99m}Tc – sestamibi	Heart blood flow
^{99m}Tc – tetrofosmin	Heart blood flow
^{99m}Tc – DMSA	Renal function
^{99m}Tc – TRODAT	Dopamin–transporter
^{111}In – DTPA-D-Phe-1-octreotide	Somatostatin receptor ligand
^{111}In – pentetreotide	Somatostatin receptor ligand
^{123}I – IMP	Brain blood flow
^{123}I – IBZM	Dopamin2–receptor–ligand
^{123}I – iomazenil	Benzodiazepine receptor ligand
^{123}I – epidepride	Dopamin2–receptor–ligand
^{123}I – β – CIT	Dopamin–transporter
^{201}TlCl	Heart blood flow

Common Methods of Production of Short-lived Organic Positron Emitters

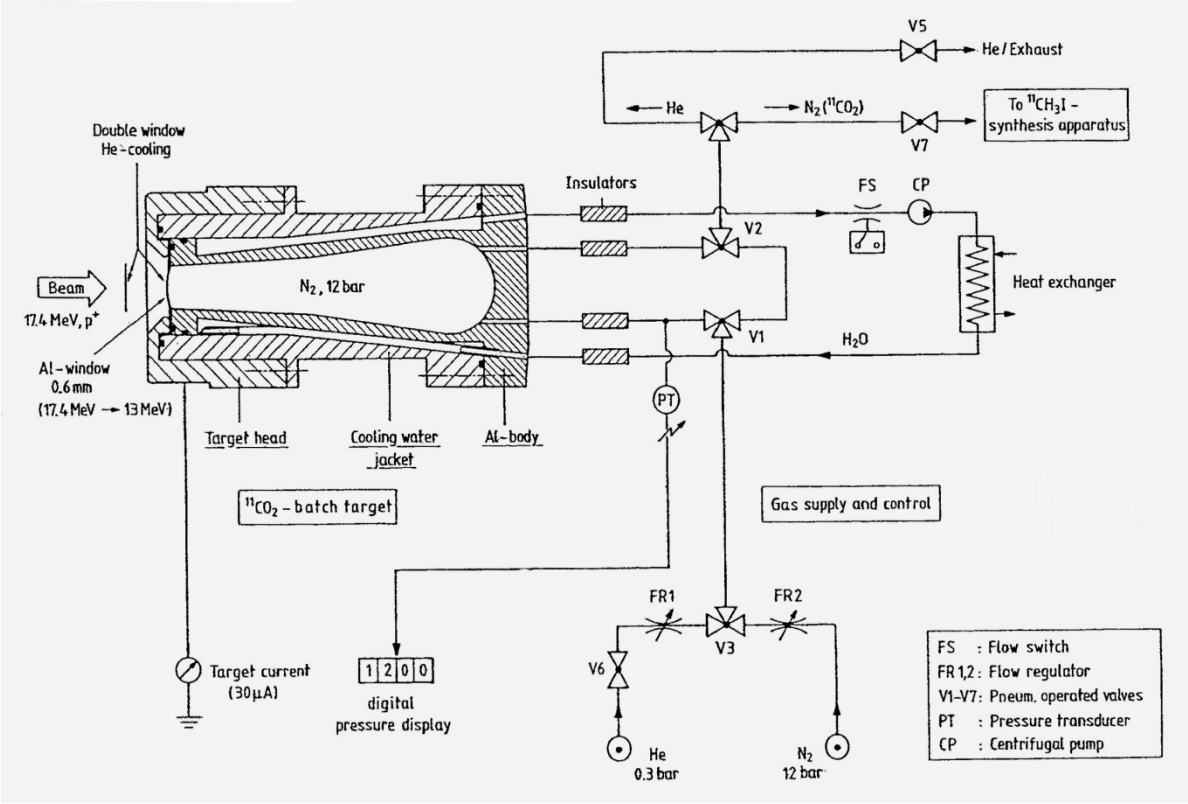
Radionuclide	$T_{1/2}$	Mode of decay	Production data				
			Nuclear reaction	Energy range	Calculated yield MBq/μA·h	Target	In-target product
^{11}C	20 min	β^+ (99.8) EC (0.2)	$^{14}N(p,\alpha)$	13 → 3	3820	$N_2(O_2)$	^{11}CO, $^{11}CO_2$
^{13}N	10 min	β^+ (100)	$^{16}O(p,\alpha)$	16 → 7	1665	$H_2{}^{16}O$	$^{13}NO_2^-$, $^{13}NO_3^-$
^{15}O	2 min	β^+ (99.9) EC (0.1)	$^{14}N(d,n)$ $^{15}N(p,n)$	8 → 0 10 → 0	2368 2220	$N_2(O_2)$ $^{15}N_2(O_2)$	^{15}OO ^{15}OO
^{18}F	110 min	β^+ (97) EC (3)	$^{18}O(p,n)$ $^{20}Ne(d,\alpha)$	16 → 3 14 → 0	2960 1110	$H_2{}^{18}O$ $^{18}O_2/(F_2)$ $Ne(F_2)$	$^{18}F_{aq}^-$ $[^{18}F]F_2$ $[^{18}F]F_2$

- All radionuclides are almost pure β^+ emitters.
- Large quantities can be produced at a small-sized two particle cyclotron.
- Chemical form of radioactive product depends on target filling.

Gas Target

Target: suitable construction material; conical shape; target dimensions and gas pressure dependent on excitation function

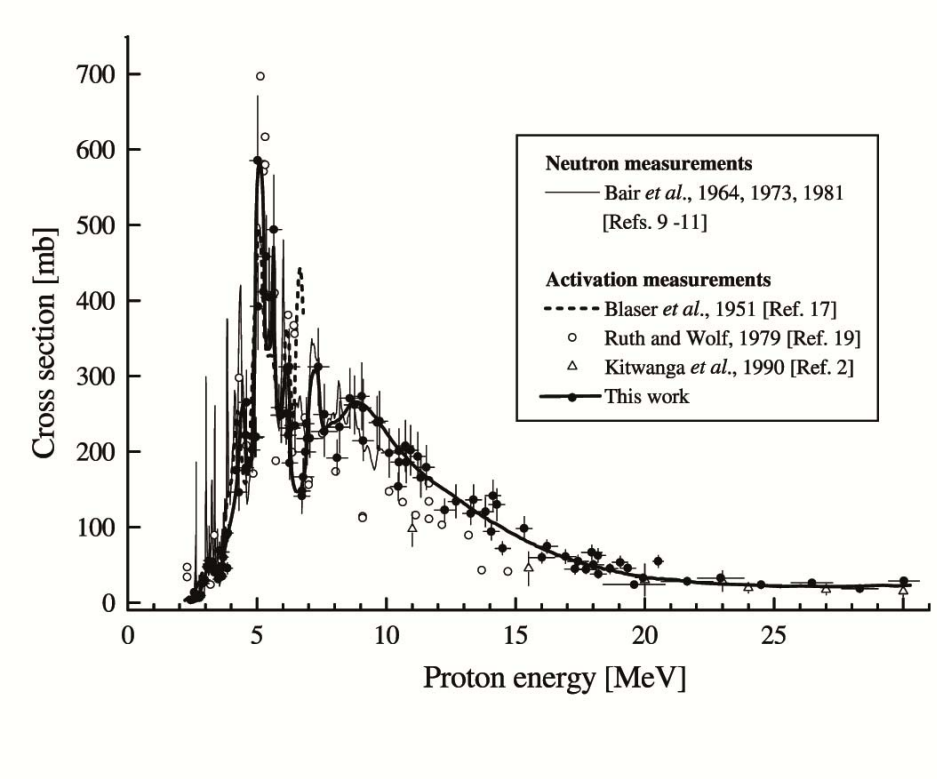
Example: Production of $^{11}CO_2$ via $^{14}N(p,\alpha)^{11}C$ reaction



- Removal of radioactivity by expansion
- Batch yield (13 MeV p, 30 µA, 40min) ≈ 100 GBq

Qaim et al., in
PET Radiopharmaceuticals,
Kluwer, 1993, 1 - 42.

Excitation Function of $^{18}O(p,n)^{18}F$ Reaction



Hess et al.,
RCA **89**, 357 (2001).

- Optimum energy range: $E_P = 16 \rightarrow 3$ MeV

- Excitation function rather unique and shows strong fluctuations
- For a (p,n) reaction, both neutron counting and activation measurement possible; the latter is more relevant
- Theory cannot reproduce the excitation function

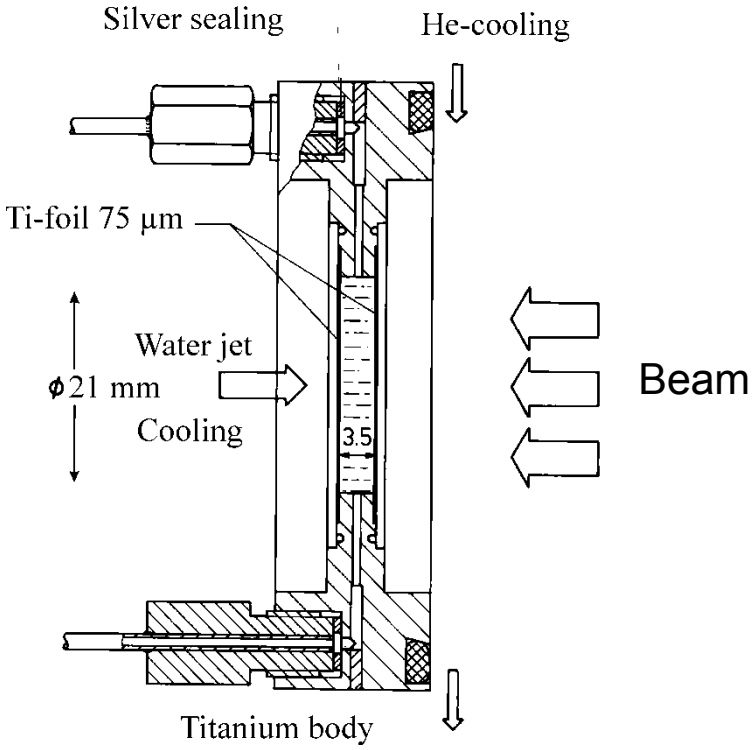
Liquid Targetry

Example: Production of ^{18}F from liquid $H_2{}^{18}O$

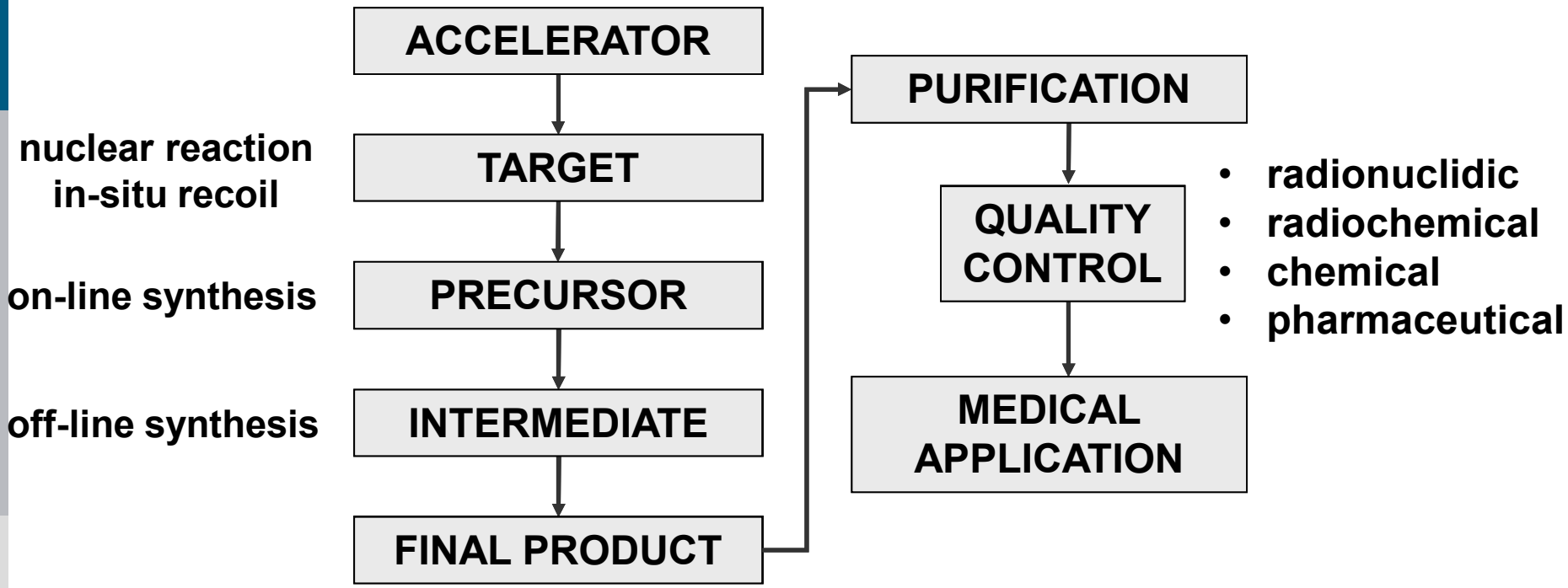
- 4 π cooling, simple and remote controlled recovery of product
- Product ready for use without further processing

Water target at the BC 1710, Jülich

Qaim et al., in
PET Radiopharmaceuticals,
Kluwer, 1993, 1 - 42.

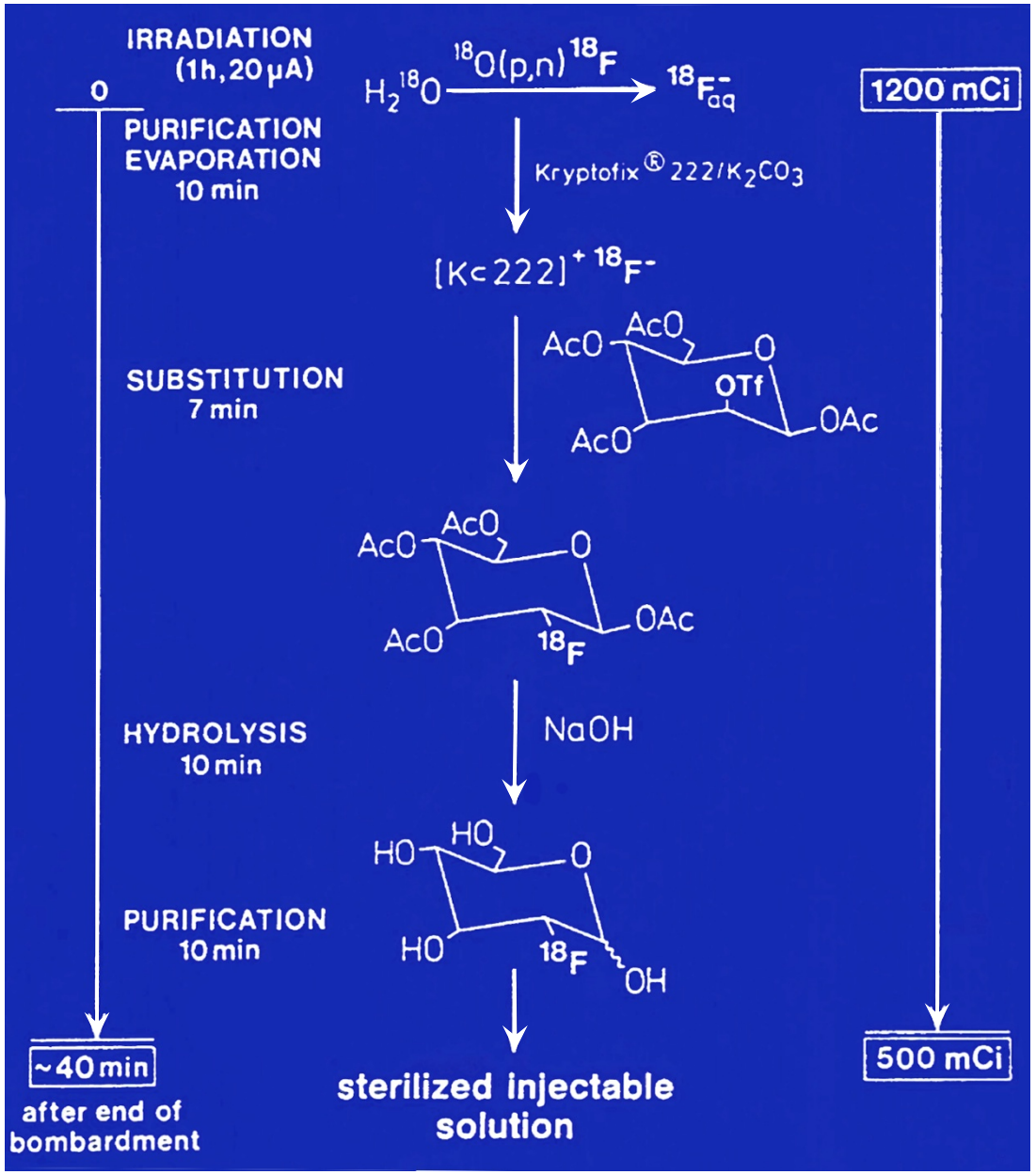


Flow Sheet of Production of Short-lived PET Radiopharmaceuticals



Fast, automated methods of production are absolutely necessary

Synthesis of 2-[^{18}F]FDG



Hamacher et al., JNM **27**, 235 (1986).

Major PET Radiodiagnostics

Radiopharmaceutical	Application	
Neurology		
$[^{15}O]O_2$	Oxygen consumption	dementia, ischemia, stroke
$[^{15}O]H_2O$	Blood flow	
$[^{15}O]$Butanol	Blood flow	
2-$[^{18}F]$FDG	Glucose metabolism	
L-6-$[^{18}F]$FDOPA	Presynaptic dopaminergic function	parkinsonism
$[^{18}F]$N-Methylspiperone	D_2-receptor density or occupancy	schizophrenia, therapy control
Cardiology		
$[^{13}N]NH_3$	Blood flow	
2-$[^{18}F]$FDG	Glucose metabolism	
$[^{11}C]$Acetate	Oxidative metabolism (Oxygen consumption)	
$[^{11}C]$ or $[^{18}F]$Fatty acids	β-Oxidation	
Oncology		
$[^{15}O]H_2O$	Blood flow	
2-$[^{18}F]$FDG	Glucose metabolism	
$[^{11}C]$Methionine	Amino acid metabolism and transport	

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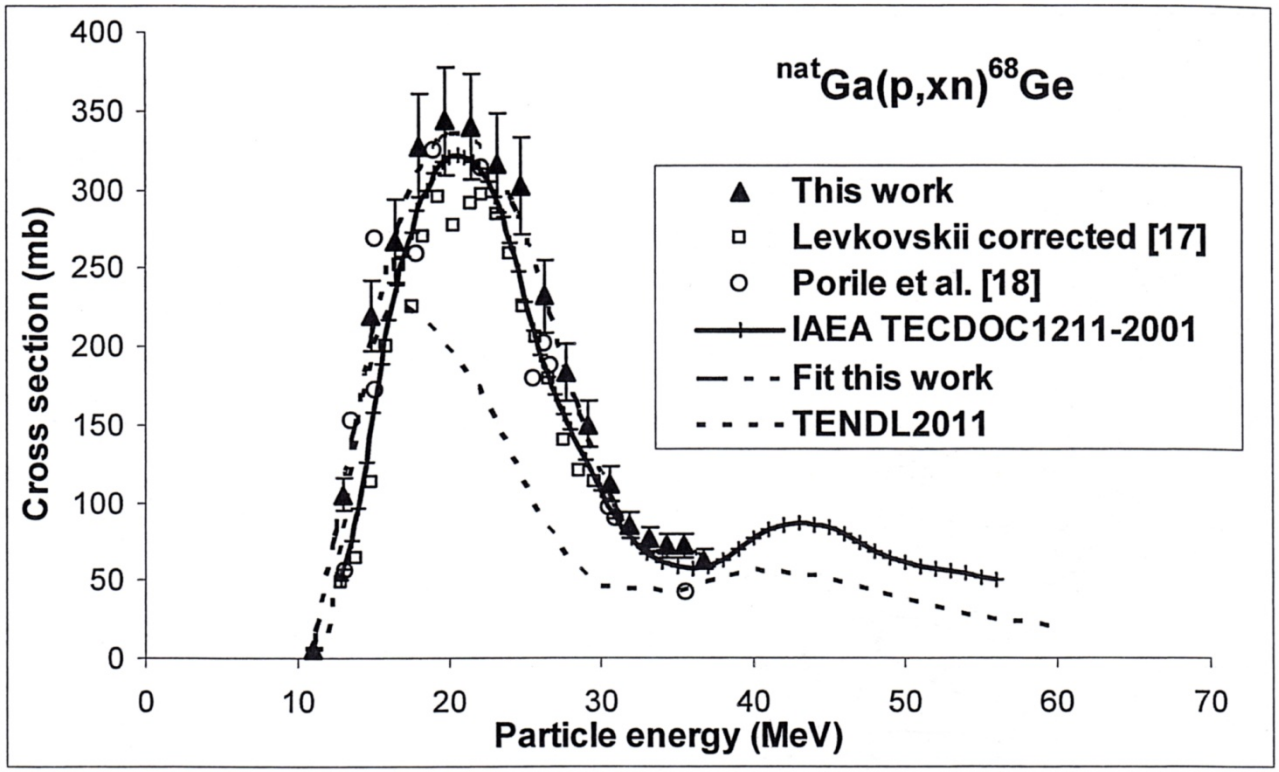
Production of Positron Emitters via Generator Systems

- Two standard positron emitters, namely ^{68}Ga ($T_{½}$ = 68 min) and ^{82}Rb ($T_{½}$ = 1.3 min) are routinely obtained via the generator systems ^{68}Ge (271 d) / ^{68}Ga and ^{82}Sr (25.3 d) / ^{82}Rb.
- For production of the two parent radionuclides, high intensity intermediate energy cyclotrons are needed.
- Presently, supply of ^{82}Sr appears to be adequate.
- Due to enhancing interest in ^{68}Ga-radiopharmaceuticals, more efforts related to ^{68}Ge production and efficient generator column preparation are called for. Some discrepancy in data recently removed.

Excitation Function of $^{nat}Ga(p,xn)^{68}Ge$ Process



Adam-Rebeles et al.,
RCA 101, 481 (2013).

- Discrepancy in data removed
- Optimum energy range for production

  $E_p = 30 \rightarrow 15$ MeV
- Due to low m.p. of Ga, use of alloy as target material is preferable

Novel Positron emitters in Medicine

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Needs

- Study of slow metabolic processes, e.g. protein synthesis, cell proliferation, etc.
  (satellite concept)
- Analogue approach
  - Quantification of SPECT-radiopharmaceuticals
  - Therapy planning, exact dosimetry

Detailed treatment in lecture on novel medical radionuclides

Production Methods of Important Therapeutic Radionuclides

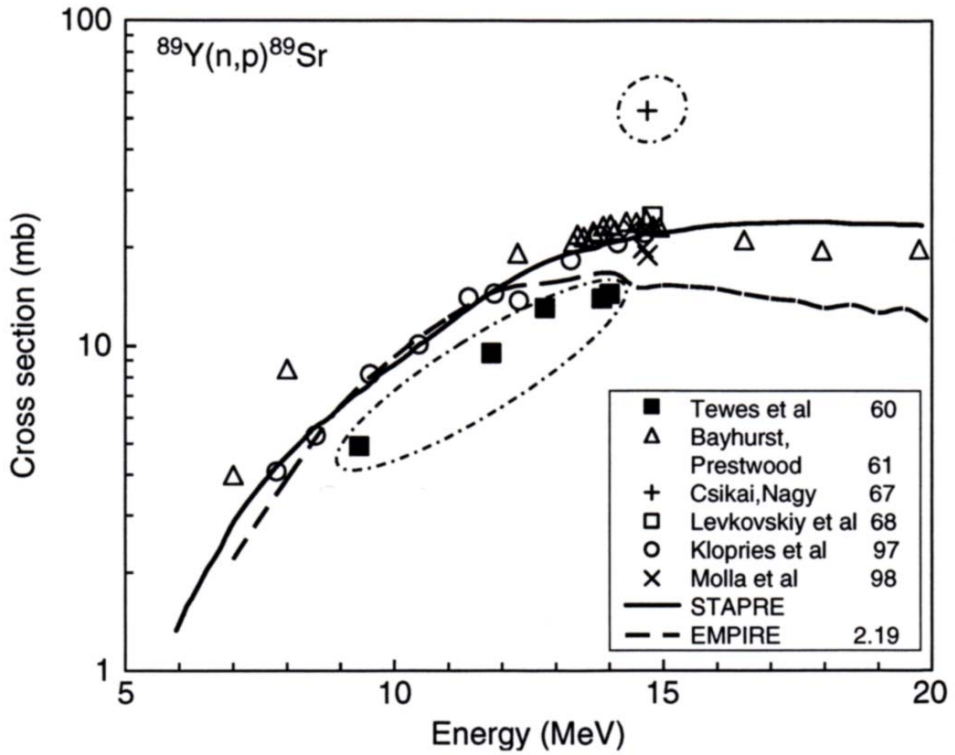
(β^- Emitters)

Nuclide	$T_{1/2}$	Production route	Nuclide	$T_{1/2}$	Production route
^{32}P	14.3 d	^{32}S(n,p)	**^{153}Sm**	1.9 d	^{152}Sm(n,γ)
^{64}Cu	12.7 h	^{64}Zn(n,p) ^{64}Ni(p,n)	**^{169}Er**	9.4 d	^{168}Er(n,γ)
^{67}Cu	2.6 d	^{67}Zn(n,p) ^{68}Zn(p,2p)	**^{177}Lu**	6.7 d	^{176}Lu(n,γ) ^{176}Yb(n,γ)^{177}Yb $\beta^-\rightarrow$
^{89}Sr	50.5 d	^{89}Y(n,p)	**^{186}Re**	3.8 d	^{186}W(p,n)
^{90}Y	2.7 d	^{90}Sr/^{90}Y (Generator)	**^{188}Re**	17.0 h	^{188}W/^{188}Re (Generator)
^{131}I	8.0 d	^{130}Te(n,γ)^{131m,g}Te $\beta^-\rightarrow$ ^{235}U(n,f)	**^{192}Ir**	73.8 d	^{191}Ir(n,γ)

Production is done using both nuclear reactors and cyclotrons

Radionuclide Production via (n,p)-Process

Example: $^{89}Y(n,p)^{89}Sr$



Al-Abyad et al., ARI **64**, 717 (2006).

- Statistical model incorporation precompound effects reproduces (n,p) excitation function well (codes STAPRE and EMPIRE)
- Fission neutron spectrum averaged cross section is low (0.3 mb); nonetheless, the reaction is used for production of no-carrier-added ^{89}Sr.

Production Methods of Important Therapeutic Radionuclides (cont´d)

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Nuclide	$T_{1/2}$	Production route
	β^+ Emitters	
^{64}Cu	12.7 h	^{64}Ni(p,n)
^{76}Br	16.0 h	^{76}Se(p,n)
^{124}I	4.2 d	^{124}Te(p,n)
	α Emitters	
^{211}At	7.2 h	^{209}Bi(α,2n)
^{213}Bi	46 min	^{225}Ac/^{213}Bi (Generator)
^{225}Ac	10.0 d	from nuclear waste ^{226}Ra(p,2n)

Nuclide	$T_{1/2}$	Production route
	X-Ray/Auger Electron Emitters	
^{77}Br	2.4 d	^{75}As(α,2n)
^{103}Pd	17.0 d	^{103}Rh(p,n)
^{111}In	2.8 d	^{112}Cd(p,2n)
^{125}I	60.0 d	^{124}Xe(n,γ)^{125}Xe $\xrightarrow{EC}$

Increasing use of cyclotrons in production of therapeutic radionuclides

Summary

- Technology for production of standard radionuclides using reactors and cyclotrons is well established. Status of data is fairly good.Yet some standardization and development work is constantly needed.
- Development work calls for interdisciplinary approach.
- Demand on quality assurance is stringent.