Role of Radiochemistry in Nuclear Data Research and the Cyclotron Production of Medical Radionuclides

Syed M. Qaim

Research Centre Jülich and University of Cologne, Germany

Becquerel Medal Lecture given at the “Seminar on Production, Use and Disposal of Radioisotopes in Medicine”, held in Loughborough on 11 November 2008 under the Auspices of the Radiochemistry Group of the Royal Society of Chemistry, London, UK.

Topics

- Introduction
- Radiochemical determination of nuclear data
- Nuclear data for medical applications
  - *radionuclide production*
  - *decay data of novel PET nuclides*
- Radiochemistry in cyclotron production of medical radionuclides
  - *target chemistry, radiochemical separations, quality assurance*
- Novel positron emitters
- Conclusions and perspectives
- Appreciation

Introduction

The term "nuclear data" includes all data which describe the characteristics of nuclei as well as their interactions

Nuclear Data

- **Nuclear Structure Data**
  (*e.g. nuclear level, spin, parity*)
- **Nuclear Decay Data**
  (*e.g. $T_{1/2}$, α-, β-, γ-ray energy*)
- **Nuclear Reaction Data**
  (*e.g. Q-value, energy / angular distribution, cross section, fission yield*)

Applications of Nuclear Data

Neutron Data

- Reactor dosimetry
- Activation products
- Materials damage
- Nuclear heating
- Nuclear transmutation
- Neutron activation analysis

Charged Particle Data

- Cyclotron production of medical radionuclides
- Charged particle therapy
- Thin layer activation analysis
- Ion beam analysis
- Astrophysics
- Cosmochemistry

Major applications of nuclear data are in energy research and medicine

Radiochemical Determination of Charged Particle Data

Principle

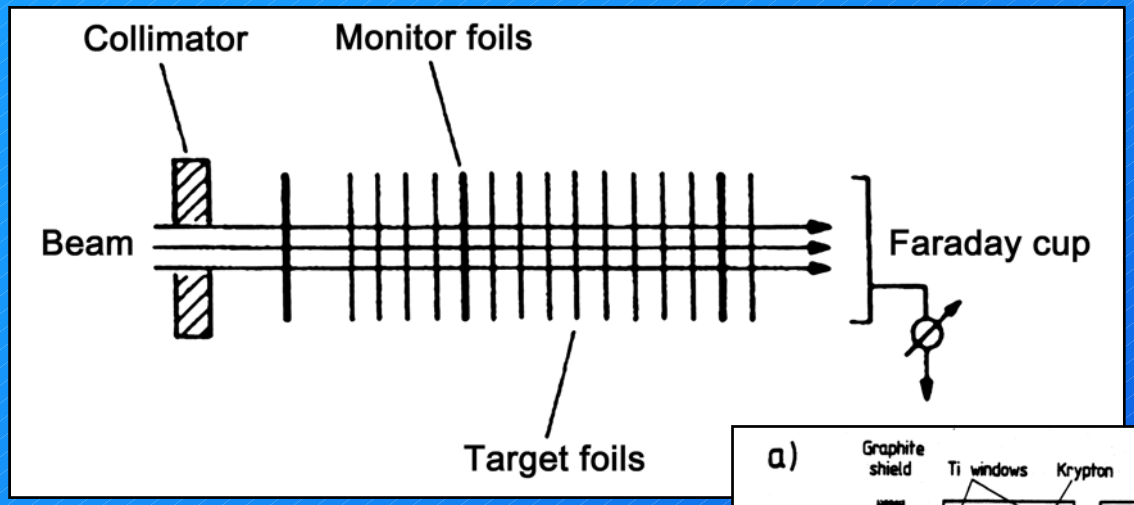
Activation of sample; chemical separation and identification of radioactive product

Steps

- Preparation of thin sample *(sedimentation, electrolysis, etc.)*
- Low current irradiation of several samples in a row *(stacked-foil technique)*
- Determination of beam current
- Calculation of projectile energy degradation in the stack
- Quantitative measurement of radioactivity using high-resolution detectors
- Calculation of cross section and its uncertainty

Irradiation Geometry

A. Solid samples

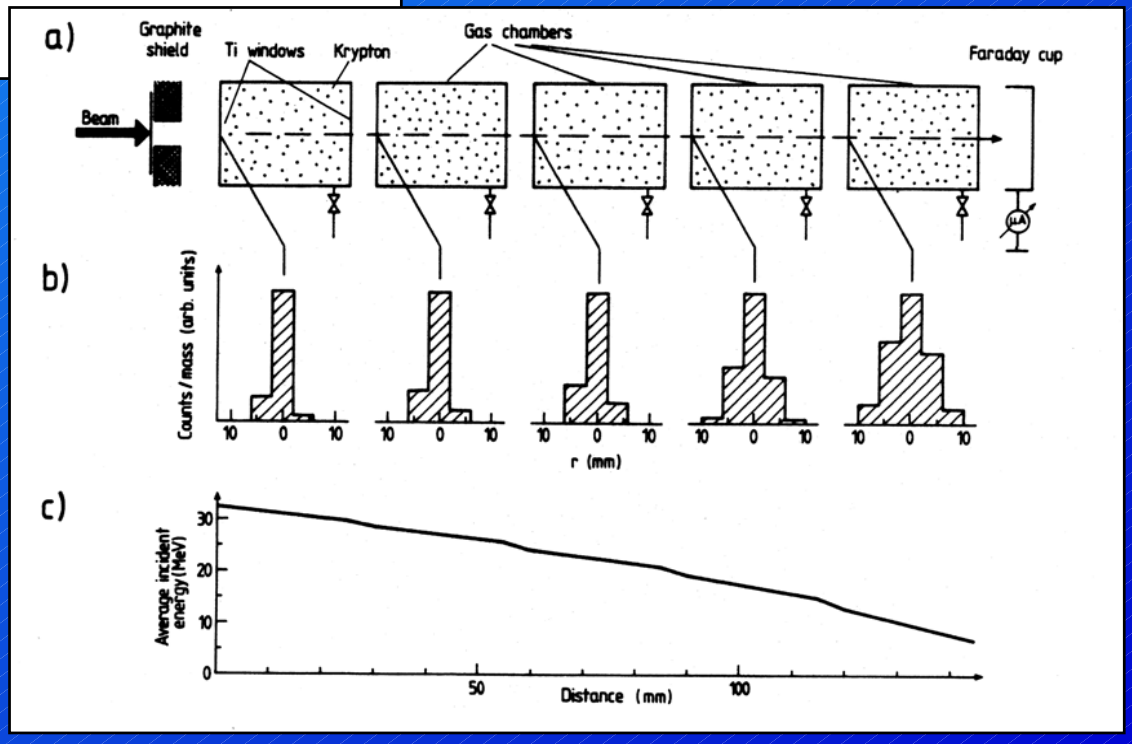


B. Gas cylinders

a) Gas cells in a row

b) Radial distribution of radioactivity

c) Energy degradation along the beam path



Radiochemical Separations

Aims

- To isolate desired product in a pure form
- To prepare thin samples for soft-radiation counting (β^-, X-rays)
- To recover the enriched target material

Commonly used methods

- Ion-exchange
- Solvent extraction
- Distillation
- Thermochromatography
- Co-precipitation, followed by further separation
- Steam-bath

Quantitative nature of work to be emphasized

Advantageous Use of Radiochemical Methods in Nuclear Data Research

- **Investigation of low-yield reactions**
  - Low cross section (nb – mb)
  - High matrix activity
- **Study of soft radiation emitters**
  - ß$^-$ emitters
  - Low-energy X-ray emitters
- **Characterisation of low-lying isomeric states**
- **Search for short-lived products**

High quality, well-optimised separations are mandatory

Nuclear Data for Medical Applications

- Radionuclide production
  - standard SPECT and PET radionuclides
  - novel positron emitters
  - therapeutic radionuclides
- Decay properties
  (selected positron emitters : ^{64}Cu, ^{76}Br, ^{120}I, etc.)
- Hadron therapy
  (short-lived activation products)

Nuclear Data for Radionuclide Production

- Choice of optimum energy range
  - maximise production yield
  - minimise radionuclidic impurities
- Constraints
  - availability of suitable cyclotron and enriched target material

Important considerations

- Search for alternative routes to achieve higher purity
- Isomeric states
- Use of X-ray spectrometry
- Role of nuclear theory
- Special case: light elements

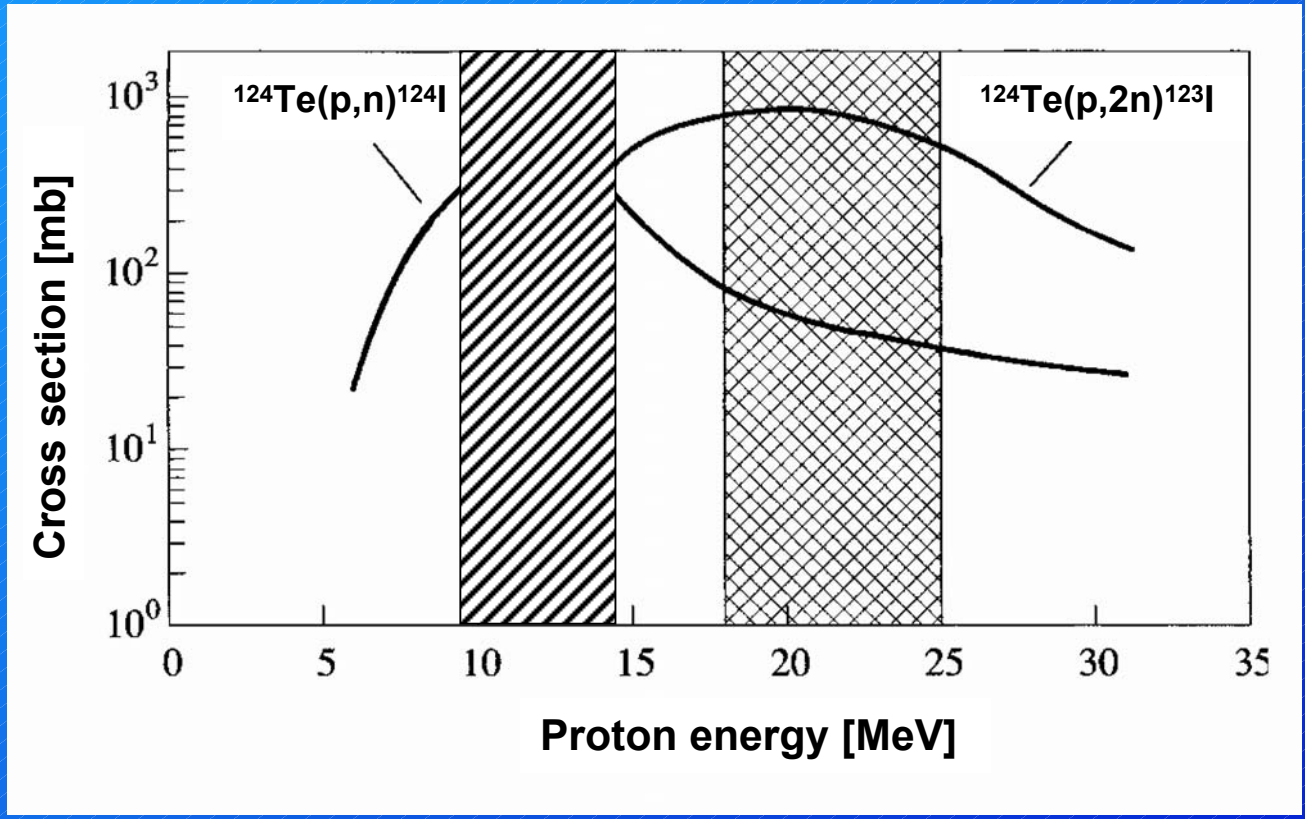
Role of Nuclear Data in Optimisation of a Production Route using Charged Particles

Example:

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

(Jülich – Debrecen)

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



Production of ^{124}I

E_p: 14 → 9 MeV

(^{125}I impurity < 0.1%)

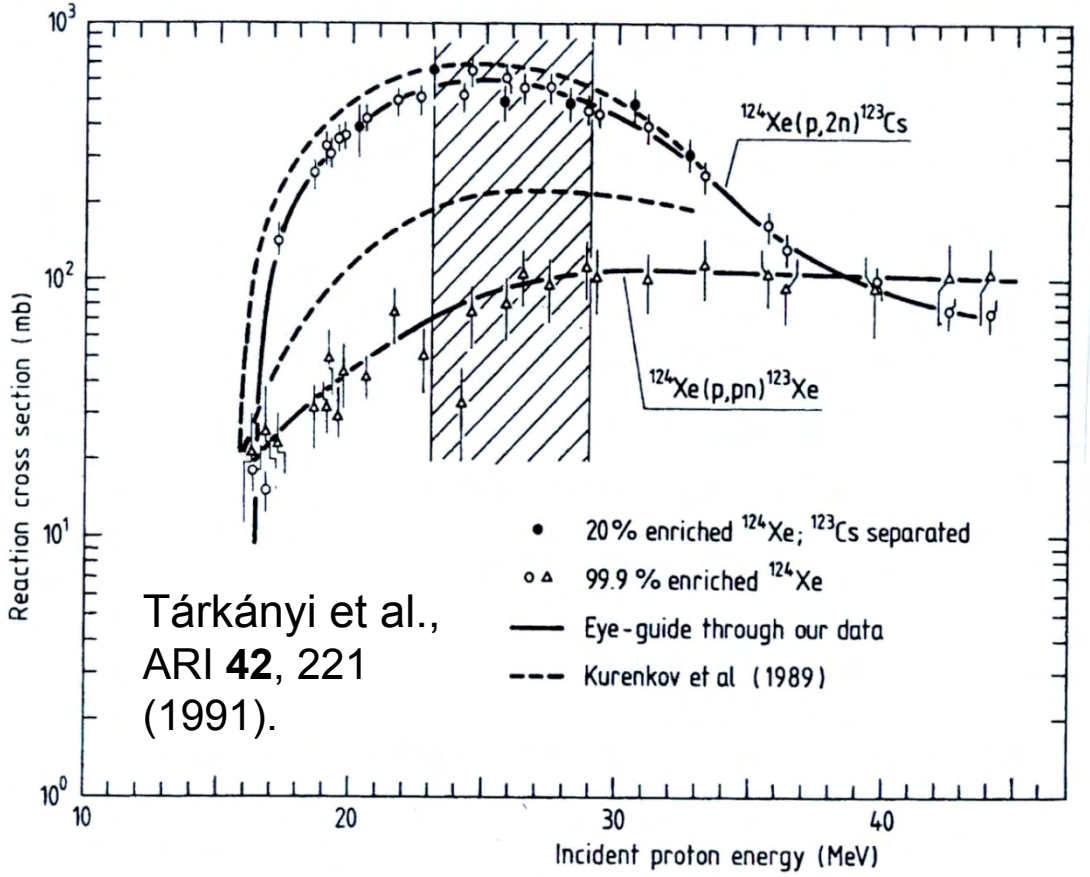
Production of ^{123}I

E_p: 25 → 18 MeV

(^{124}I impurity < 1%)

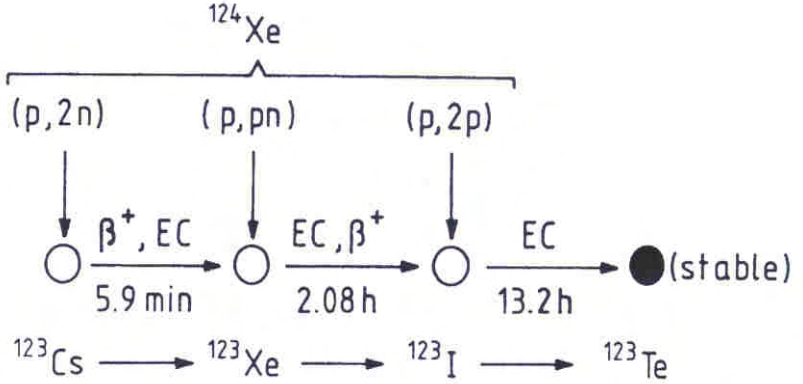
Production of ^{123}I via the ^{124}Xe(p,x)^{123}I-Process

Excitation Function



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

Routes



Optimum energy range: E_p = 29 → 23 MeV

^{123}I-yield: 414 MBq/μA·h

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

(Jülich-Karlsruhe)

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

Routes for Production of ^{124}I

(all values calculated from excitation functions measured at Jülich)

Nuclear reaction	Energy range [MeV]	Thick target yield of ^{124}I [MBq/μA·h]	Impurity [%] ^{123}I	^{125}I	^{126}I
^{124}Te(d,2n)	14 → 10	17.5	-	1.7	-
^{124}Te(p,n)	12 → 8	16	1.0	< 0.1	-
^{125}Te(p,2n)	21 → 15	81	7.4	0.9	-
^{126}Te(p,3n)	38 → 28	222	148	1.0	1.0
^{nat}Sb(α,xn)	22 → 13	1.02	890	13	16
^{121}Sb(α,n)	22 → 13	2.1	895	< 0.2	< 0.2
^{nat}Sb(^{3}He,xn)	35 → 13	0.95	3877	0.6	0.6

^{124}Te(p,n) reaction gives the purest form of ^{124}I

Routes for Production of ^{64}Cu

Production route	Suitable energy range [MeV]	Integral yield [MBq/μA·h]
^{64}Zn(n,p)^{64}Cu (*ORNL*)	**Fission spectrum**	**14.5***
^{64}Ni(d,2n)^{64}Cu (*Manchester, Debrecen/Brussels*)	**19 → 15**	**389**
^{64}Ni(p,n)^{64}Cu (*Jülich*)	**12 → 9**	**241**
^{nat}Zn(d,x)^{64}Cu (*Jülich, Debrecen, Milan*)	**25 → 10**	**50**
^{66}Zn(d,α)^{64}Cu (*Jülich*)	**13 → 7**	**6.6**
^{68}Zn(p,αn)^{64}Cu (*Jülich, Debrecen/Cape Town*)	**35 → 20**	**~100**

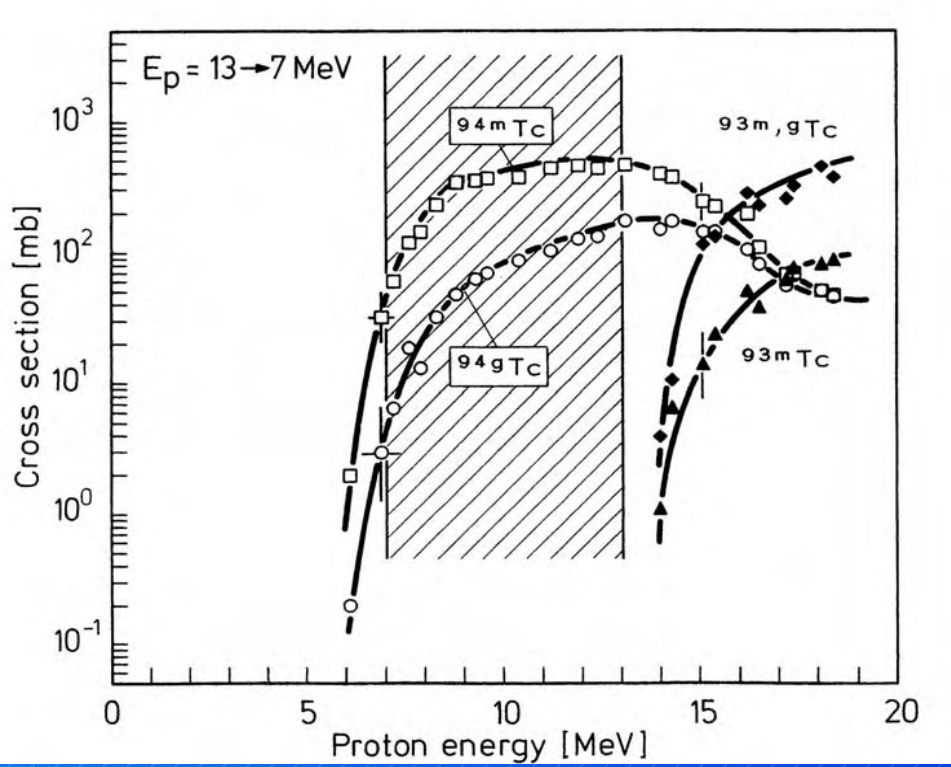
•Activity/mg Zn at Φ_n = 8.7 x 10^{13} n cm^{-2} s^{-1} for 150 h

^{64}Ni(p,n)^{64}Cu reaction is the method of choice

Formation of Isomeric States

- Occasionally unavoidable isomeric impurity
- Level depends mainly on type of reaction

Example : $^{94}Mo(p,n)^{94m,g}Tc$



Rösch, Qaim, RCA **62**, 115 (1993)

^{94g}Tc impurity in ^{94m}Tc

$^{94}Mo(p,n)$: 6%
$^{93}Nb(^{3}He,2n)$: 25%
$^{92}Mo(\alpha,pn)$: 30%

Fundamental investigations mandatory

Palladium-103

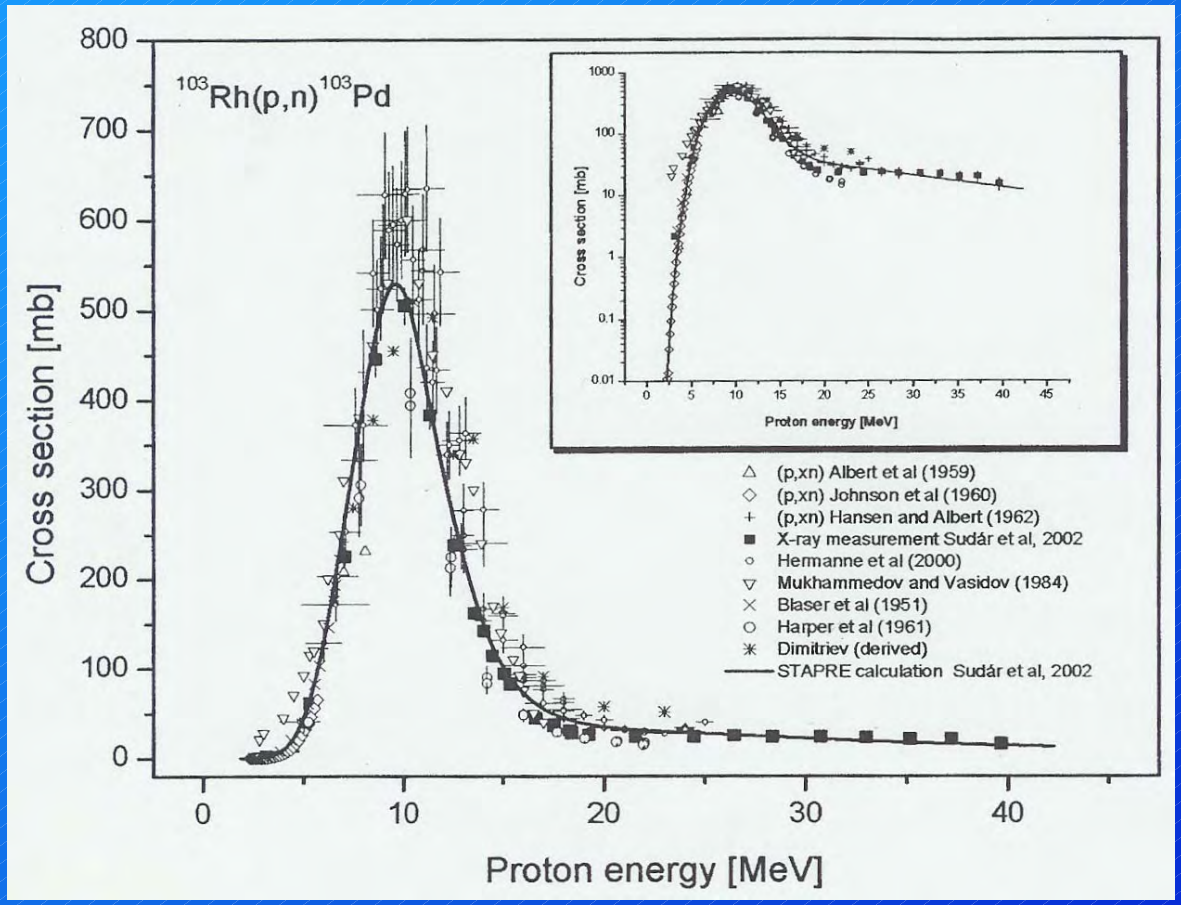
$T_{1/2}$ = 16.96 d; EC = 100 %; X-rays; Auger electrons

Nuclear reaction : $^{103}Rh(p,n)^{103}Pd$

Measurements : Stacked-foil technique; X-ray spectroscopy

Nuclear model calculation : Hauser-Feshbach + Precompound (STAPRE)

Excitation Function



Sudár et al.,
ARI **56**, 821 (2002).

^{103}Pd Production

E_p = 14 → 7 MeV

Yield = 6.6 MBq/μA·h

Novel Therapeutic Radionuclides

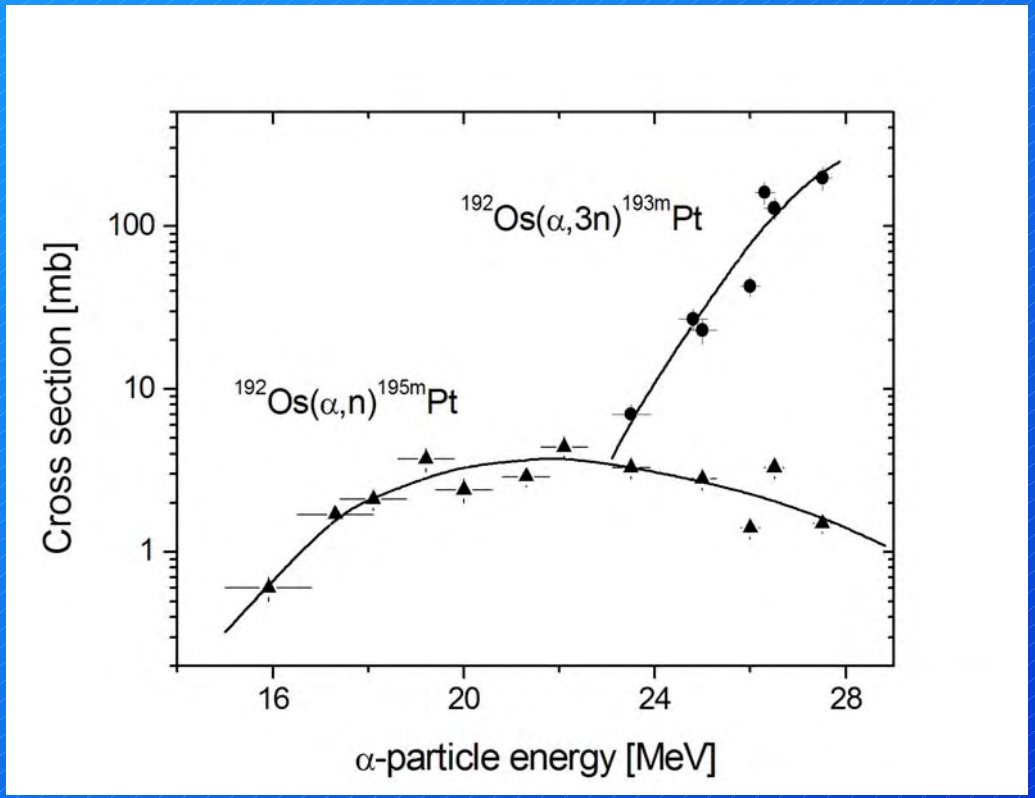
Examples: ^{193m}Pt ($T_{½}$ = 4.33 d; Auger electrons ~ 33 per decay)

^{195m}Pt ($T_{½}$ = 4.03 d; Auger electrons ~ 26 per decay)

High-spin isomers

Measurements: Stacked-foil technique; X-ray spectroscopy

Production Method: α-particles on enriched ^{192}Os



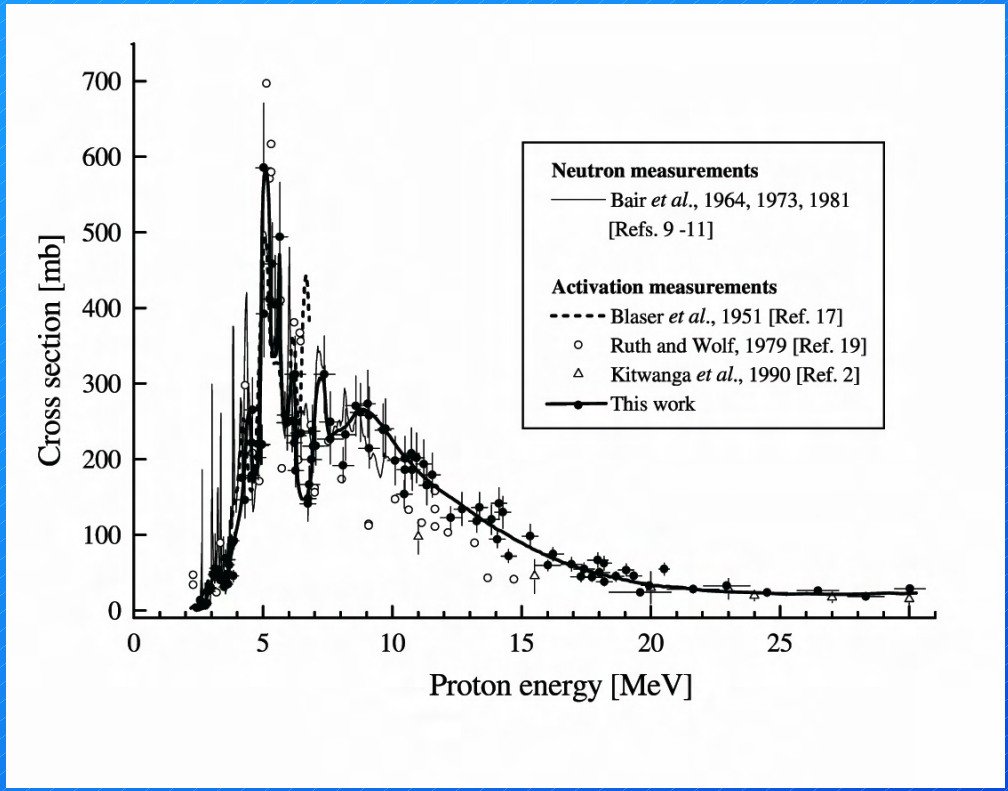
Hilgers et al. , ARI **66**, 545 (2008).

^{195m}Pt-yield E_α = 24 → 18 MeV:
0.013 MBq/μA·h

^{193m}Pt-yield E_α = 28 → 24 MeV:
0.25 MBq/μA·h

Production of high-specific activity ^{193m}Pt in sufficient quantity feasible

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



Optimum energy range:

$E_P = 16 \rightarrow 3$ MeV

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

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

Recent Progress in Availability of Charged Particle Data for Radionuclide Production

Experimental studies at

Brussels, Cape Town, Debrecen, Jülich, Los Alamos, Milan, Sendai

Standardisation Work at

Nuclear Data Section, IAEA, Vienna

- Compilation (EXFOR)
- Evaluation
  - diagnostic radionuclides — TECDOC-1211 (2001)
  - therapeutic radionuclides — TECDOC- *reaching finalisation*
  - emerging positron emitters — CRP *in preparation*

Worldwide efforts underway to provide reliable data

Decay Data of Novel PET Nuclides

Status of Data

- Decay data generally well known
- Occasionally I_{β^+} rather uncertain due to
  - use of impure samples
  - lack of high-precision β-ray spectroscopy

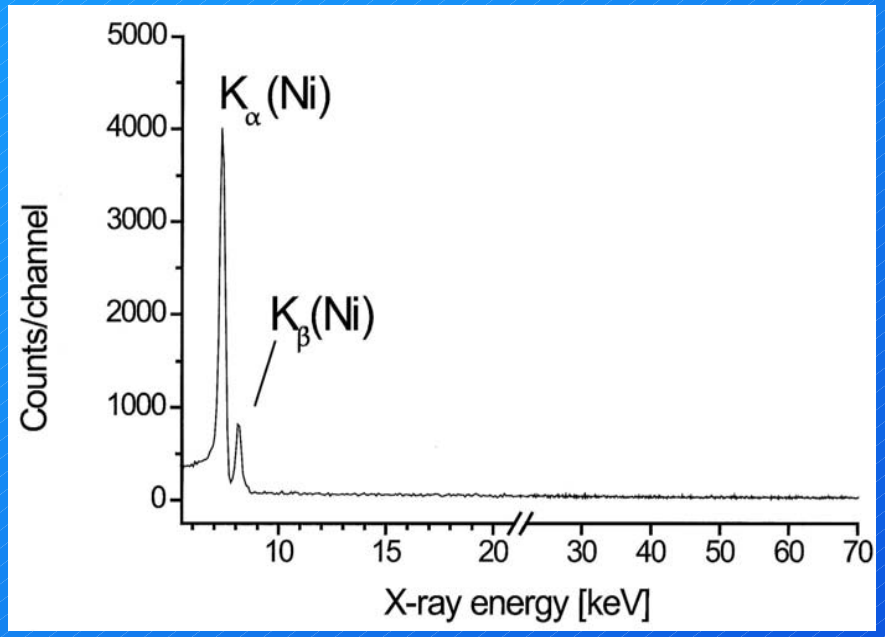
Modern Experimental Approach

- Preparation of very clean thin samples
- Accurate measurement of annihilation radiation (HPGe detector γ-ray spectrometry and γγ-coincidence counting)
- X-ray spectrometry using a thin Ge or a Si(Li) detector

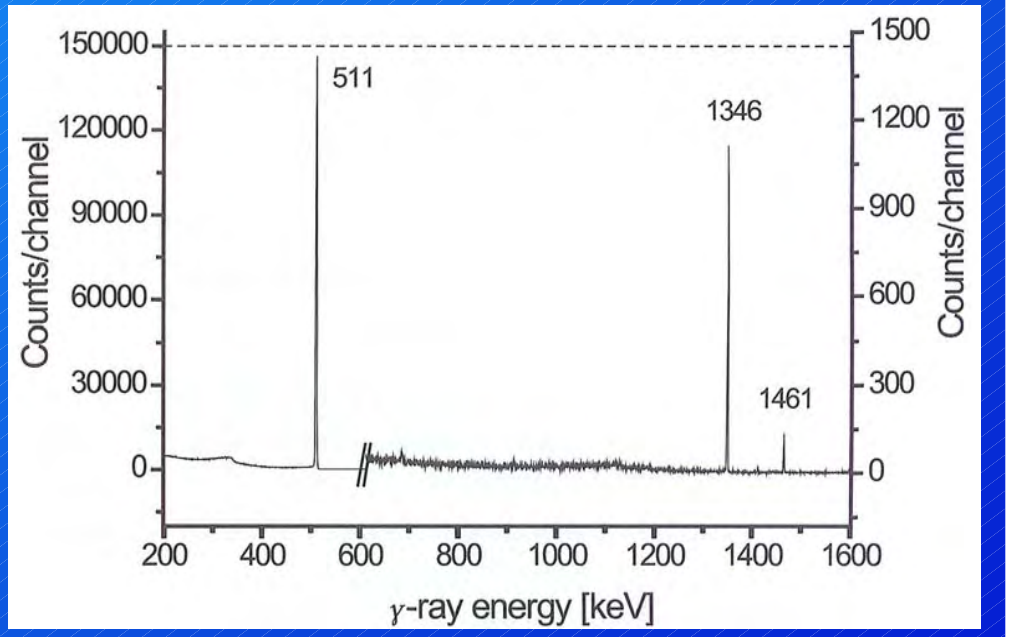
Determination of $I_{\beta+}$ of ^{64}Cu ($T_{1/2}$ = 12.7 h)

Sample preparation: $^{64}Ni(p,n)^{64}Cu$ or $^{66}Zn(d,\alpha)^{64}Cu$ reaction;
in each case chemical separation

X-ray spectrum



γ-ray spectrum



Precise determination of $I_{\beta+}$ performed

Recently Determined $I_{\beta+}$ Values of some Radionuclides

Radionuclide	$T_{½}$	Positron emission intensity (%)	
		Literature values [a]	Precise values
^{64}Cu	12.7 h	17.4 – 19.0	17.8 ± 0.4 [b]
^{76}Br	16.2 h	56.0 – 62.5	58.2 ± 1.9 [b]
^{120}I	1.35 h	39 – 81	56.1 ± 3.2 [c]
^{124}I	4.18 d	21.6 – 26.0	22.0 ± 0.5 [b,d] 21.6 ± 0.4 [e]

a) ENSDF (2006)
b) Qaim et al., RCA **95**, 67 (2007)
c) Hohn et al., RCA **88**, 139 (2000)
d) Qaim et al., ARI **58,** 69 (2003)
e) Woods et al., ARI **43**, 551 (1992)

Radiochemistry in Cyclotron Production of Medical Radionuclides

Special features

- Chemistry starts already in the target during irradiation
- High level of radioactivity
- Generally short-lived products
- Stringent purity control
- Demand of high specific activity

Factors related to target chemistry

- Nuclear recoil effects
- Radiation induced chemical reactions

The two effects need considerable attention when liquid and geaseous targets are used

Target Chemistry in Production of Short-lived Organic Positron Emitters

Radionuclide	$T_{½}$	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.

Novel Positron Emitters in Medicine

Needs

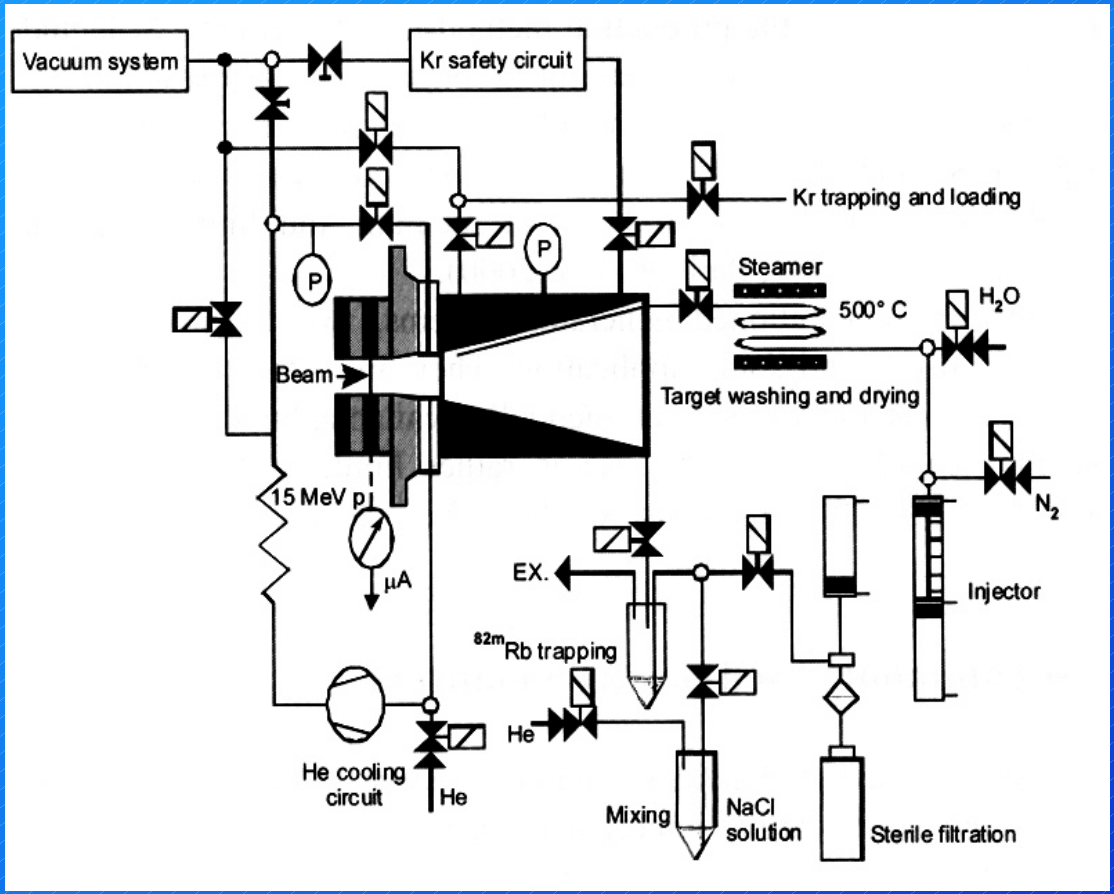
- Study of slow metabolic process, e.g. protein synthesis, cell proliferation, etc.
  (satellite concept)
- Analogue approach
  - Quantification of SPECT-radiopharmaceuticals
  - Therapy planning, exact dosimetry

Problems

- Constraints on yield and purity
- Imaging difficulties due to high energy positrons and γ-rays

Gas Targetry

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



- Removal of radio-activity (e.g. ^{76}Br, ^{82m}Rb) by rinsing the inner walls of the target
- Separation yield > 95 %

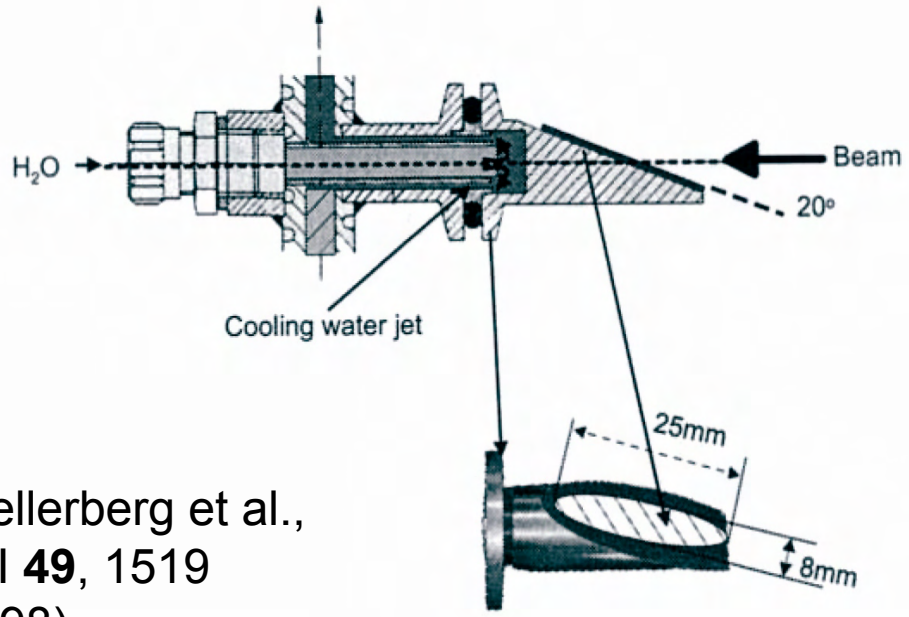
Blessing et al.,
ARI **48**, 37 (1997).

Solid Targetry

Sample preparation: electrolysis, thin layer formation

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

Example: Use of slanting beam



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

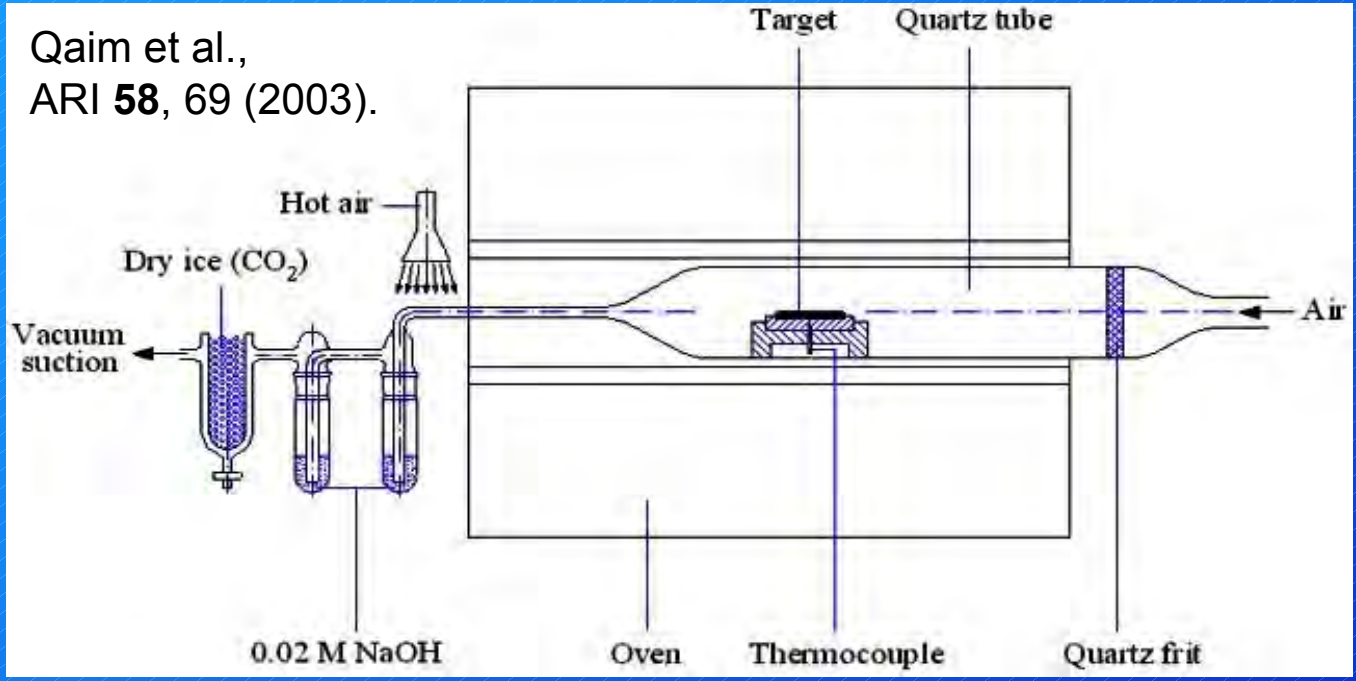
- Standard technology used in medium to large scale production of radionuclides (^{55}Co, ^{124}I, etc.)

Beam current: 30 – 300 μA

Separation of Radioiodine from a Solid Target

Example: Dry distillation technique for removal of ^{124}I from a $^{124}TeO_2$ target irradiated with protons

Qaim et al.,
ARI **58**, 69 (2003).

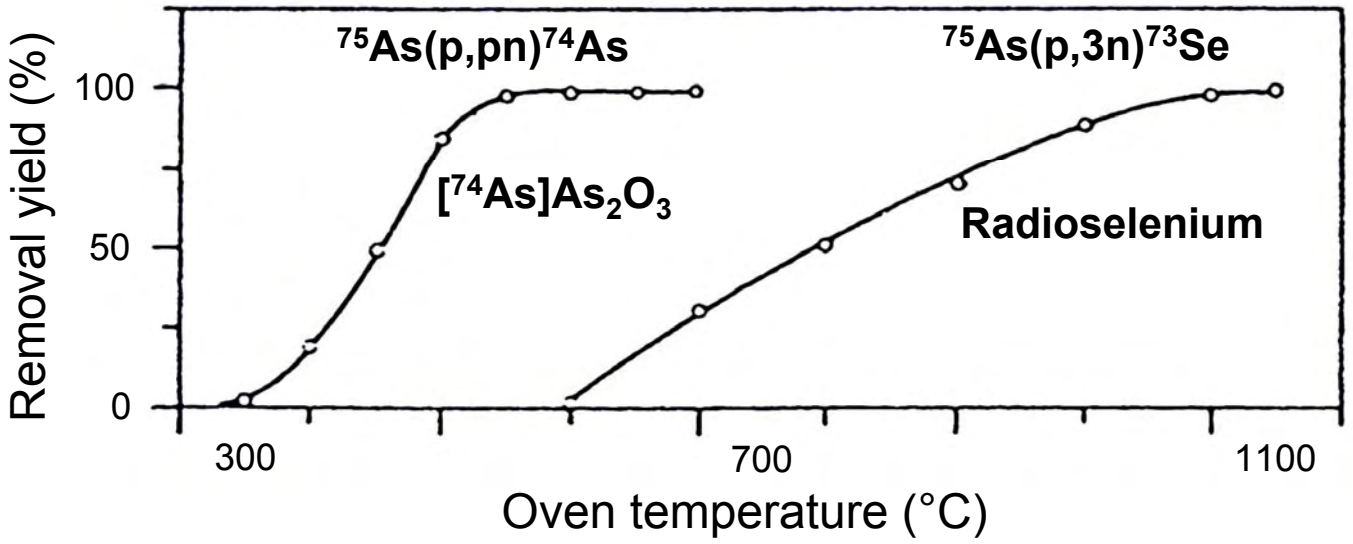


Distillation at 750 °C for 15 min

Batch yield :	480 MBq (≈13mCi) ^{124}I
Radionuclidic purity (%):	^{124}I (99), ^{123}I (<1), ^{125}I (0.1)
Radiochemical purity:	> 98 % iodide
Chemical impurity:	Te (<1µg)

Separation of ^{73}Se ($T_{1/2}$ = 7.1 h) via Thermochromatography

- Irradiated Cu_3As target heated in O_2 stream
- Fractionated removal of As and radioselenium



Blessing et al., RCA **65**, 93 (1994).

➡ **Two step thermochromatography essential**

➡ **Purification of ^{73}Se via extraction in benzene**

Batch yield: 6 GBq (≈160 mCi) ^{73}Se (2 h, 20 μA)

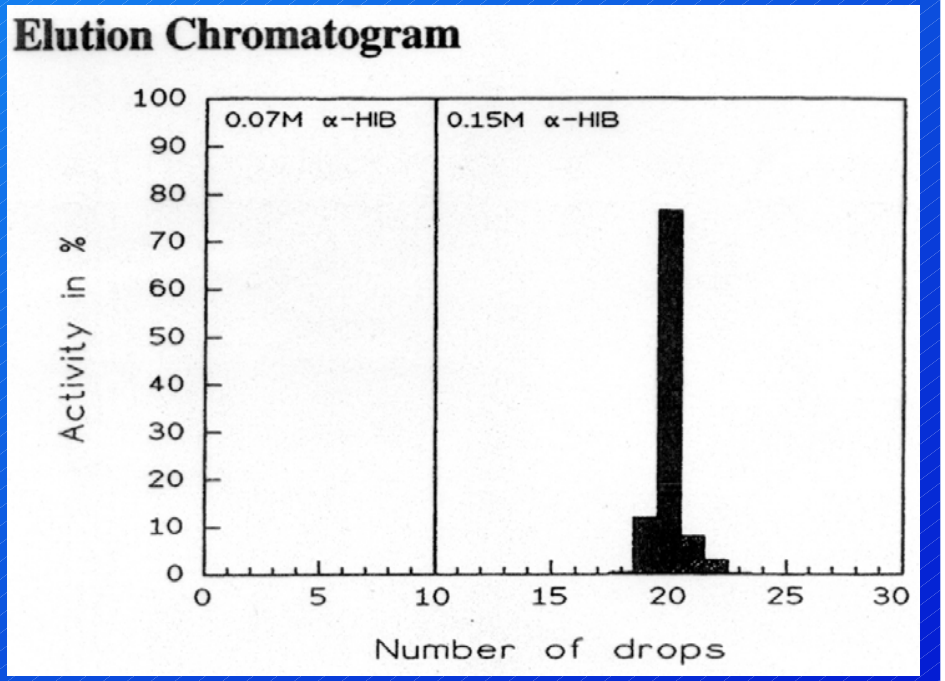
$^{72,75}Se$ impurity: < 0.05 %

Radiochemical Separation of ^{86}Y ($T_{1/2}$ = 14.7 h) Produced via $^{86}Sr(p,n)$-Process

Target : 96.3 % $^{86}SrCO_3$ pellet

Irradiation : 16 MeV p, 4μA, 5h

Separation :
Coprecipitation and ion-exchange chromatography
- Dissolution of $^{86}SrCO_3$ in conc. HCl
- Addition of 2 mg La^{3+} carrier
- Precipitation as $La(OH)_3$ (carrying ^{86}Y)
- Dissolution of ppt. in HCl
- Transfer to Aminex A5
- Elution with α-HIB
  (separation of ^{86}Y from La)



Rösch et al., ARI **44**, 677 (1993).

- **^{86}Y activity (3 GBq) collected in 3 drops**

Quality Assurance of the Product

Radionuclidic purity

- High resolution γ-ray spectrometry (^{64}Cu, ^{86}Y, ^{94m}Tc, ^{124}I, etc.)
- X-ray spectrometry (^{82}Sr, ^{125}I, etc.)

Radiochemical purity

- TLC, HPLC ($^{94m}TcO_4^-$, $^{124}I^-$, $^{124}IO_3^-$)

Chemical purity

- UV-spectrophotometry
- ICP-OES

Specific activity

- Determination of radioactivity via radiation detector
- Determination of mass via UV, refractive index or thermal conductivity detector

(Increasing demand on high specific activity)

Novel Positron Emitters for Medical Applications

Nuclide	Major production route	Energy range [MeV]	Application
^{38}K (7.6 min)	^{35}Cl(α,n)	22 → 10	Cardiology
^{55}Co (17.6 h)	^{58}Ni(p,α) ^{54}Fe(d,n)	15 → 7 10 → 5	Tumor imaging; neuronal Ca marker
^{64}Cu (12.7 h)	^{64}Ni(p,n)	14 → 9	Radioimmunotherapy
^{73}Se (7.1 h)	^{75}As(p,3n)	40 → 30	Selenopharmaceuticals
^{75}Br (1.6 h)	^{75}As(^{3}He,3n)	35 → 25	Bromopharmaceuticals
^{76}Br (16.0 h)	^{76}Se(p,n)	15 → 8	Radioimmunotherapy
^{86}Y (14.7 h)	^{86}Sr(p,n)	14 → 10	Therapy planning
^{94m}Tc (52 min)	^{94}Mo(p,n)	13 → 8	Quantification of SPECT-pharmaceuticals
^{120}I (1.3 h)	^{120}Te(p,n)	13.5 → 12	Iodopharmaceuticals
^{124}I (4.2 d)	^{124}Te(p,n)	12 → 8	Tumor targeting; dosimetry

Conclusions and Perspectives

- Radiochemical method of nuclear data measurement is well established; it is especially suitable for studying soft-radiation emitting radionuclides
- Nuclear data are of basic significance in cyclotron production of medical radionuclides
- Radionuclide production technology well established. Yet there is constant need of development of other radionuclides.
- Demands on quality assurance are stringent
- Novel PET-radionuclides ^{64}Cu, ^{86}Y, ^{124}I, etc. in great demand.
- Radiotracer research is opening new perspectives
- Interdisciplinary approaches absolutely necessary

Combination of interesting science and useful technology

Appreciation

- Educational Institutions
- Governments (Pakistan, UK, Germany)
- Research Centre Juelich, University of Cologne
- Department Heads, Administrators
- Co-workers, Guest Scientists, Ph.D. Students
- Co-operation Partners
- Funding Agencies
- Family and Friends
- Radiochemistry Group of RSC for Honour and Felicitation

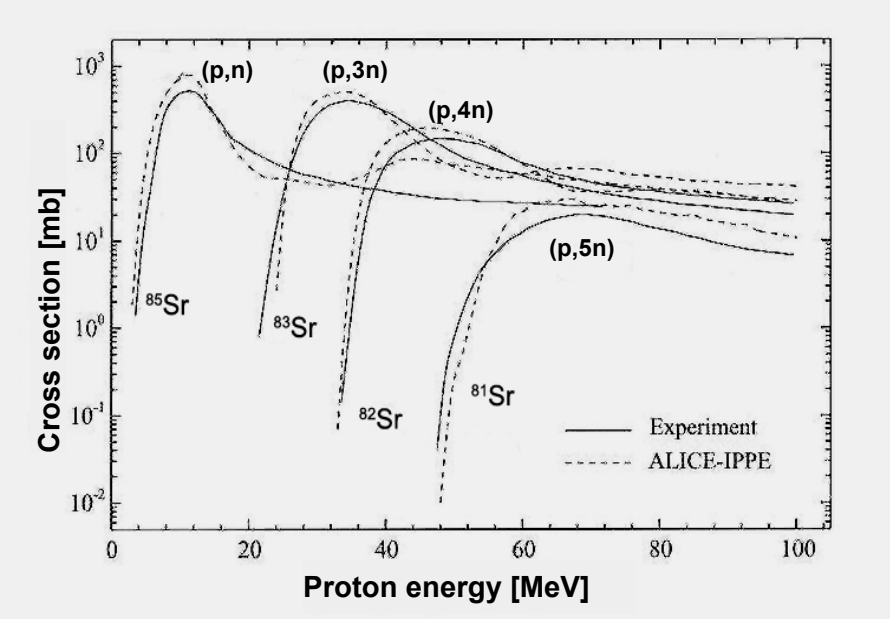
Examples of Thin Sample Preparation

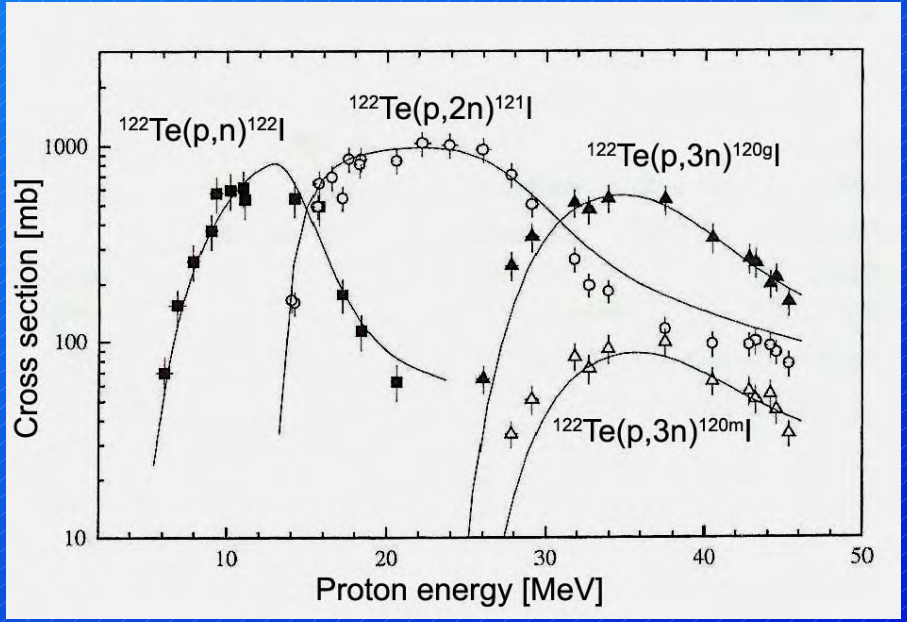
Technique	Sample	Nuclear process studied
Sedimentation	$Si^{18}O_2$ on Al	$^{18}O(p,n)^{18}F$
	$^{85}RbCl$ on Cu	$^{85}Rb(p,xn)^{82,83}Sr$
	$^{94}MoO_3$ on Ni	$^{94}Mo(p,n)^{94m,g}Tc$
Electrolytic deposition	^{50}Cr on Au	$^{50}Cr(d,n)^{51}Mn$
	^{58}Ni on Au	$^{58}Ni(p,\alpha)^{55}Co$
	^{64}Ni on Au	$^{64}Ni(p,n)^{64}Cu$
	^{68}Zn on Au	$^{68}Zn(p,2p)^{67}Cu$
	^{70}Ge on Cu	$^{70}Ge(\alpha,n)^{73}Se$
	^{120}Te on Ti	$^{120}Te(p,n)^{120m,g}I$
Electrochemical oxidation	^{18}O on Al (as $Al_2{}^{18}O_3$)	$^{18}O(p,n)^{18}F$
Cryogenic handling	^{38}Ar	$^{38}Ar(p,n)^{38}K$
	^{82}Kr	$^{82}Kr(p,n)^{82m}Rb$
	^{124}Xe	$^{124}Xe(p,x)^{123}I$

Comparison of Experimental Data with Nuclear Model Calculations

^{85}Rb(p,xn)-reactions
Calculation: ALICE-IPPE
Kastleiner et al., RCA **92**, 449 (2004).
(Jülich – Cape Town – Obninsk)

^{122}Te(p,xn)-reactions
Calculation: STAPRE
Hohn et al., ARI **49**, 93 (1998).
(Jülich – Debrecen)





- (p,xn)-reactions are described well by statistical/precompound model as well as by exciton model
- Isomeric cross section is estimated well by STAPRE

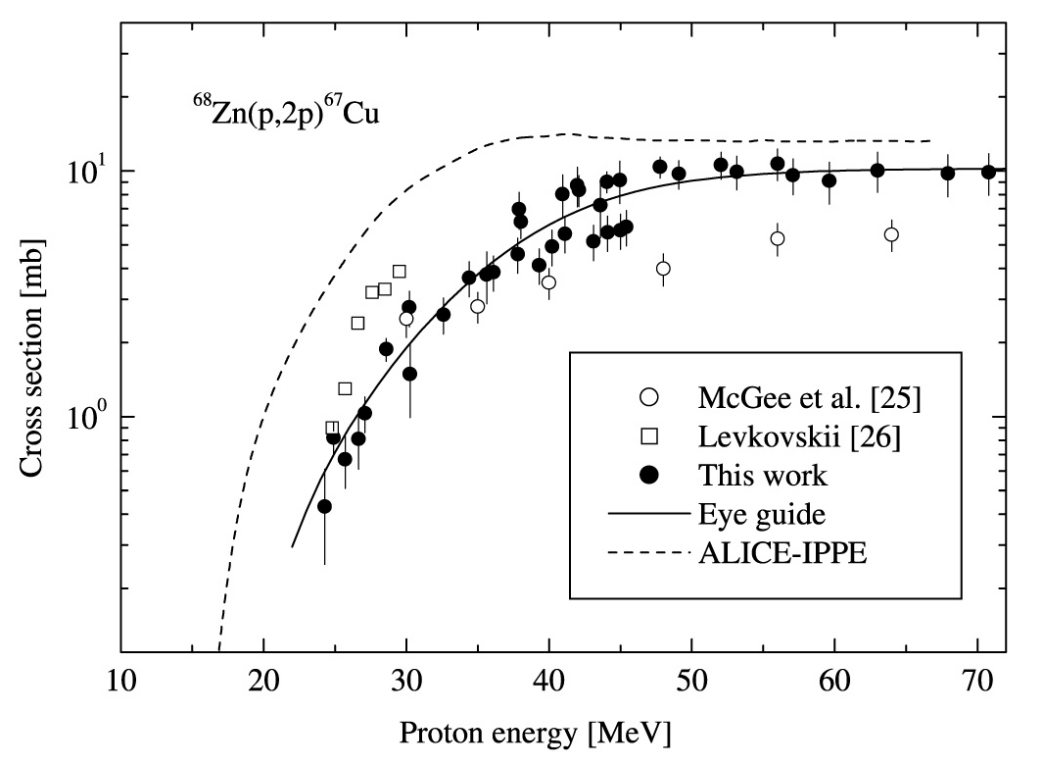
Copper-67

$T_{1/2}$ = 2.58 d; β^- = 100%; E_{β^-} = 0.58 MeV; E_γ = 184.6 keV (48.6 %)

Nuclear reaction: $^{68}Zn(p,2p)^{67}Cu$

Measurements: Interference from ^{67}Ga; chemical separation and γ-ray spectrometry mandatory.

Nuclear model calculation: ALICIE-IPPE

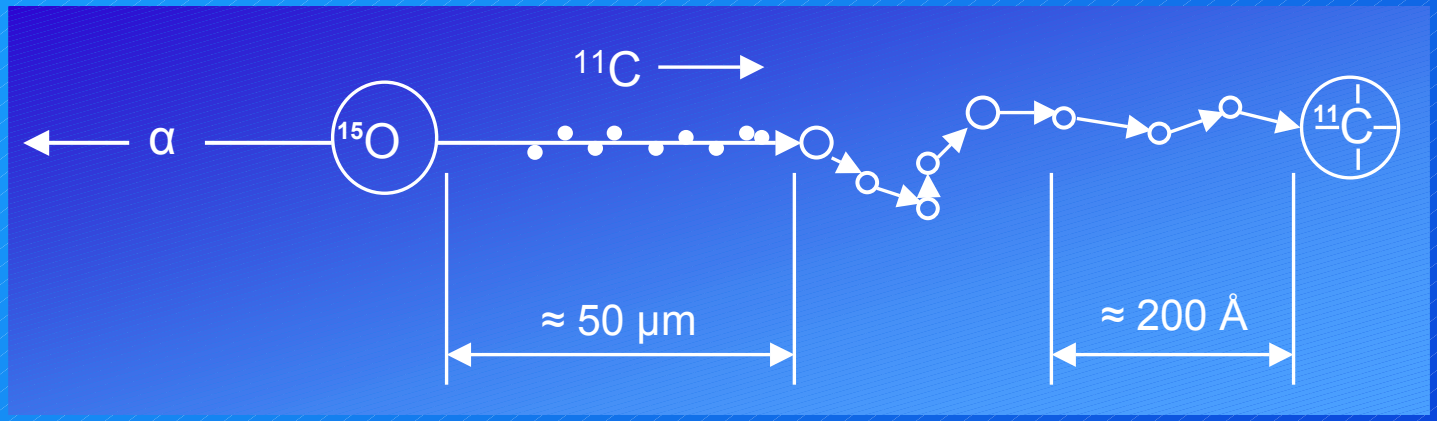


Stoll et al., RCA **90**, 309 (2002)

Predictive power of theory for rather complex reactions is limited

Hot Chemical Reactions in a Gas Target

Example: $^{14}N(p,\alpha)^{11}C$ reaction in N_2 gas target



Kinetic energy	Energy loss
2 MeV	excitation, ionisation
10 keV	inelastic and elastic collisions
50 eV	chemical reactions
0.025 eV	

Formation of precursors

$^{11}C + N_2 \rightarrow {}^{11}CN + N$

$^{11}CN + O_2 \rightarrow {}^{11}CO_2 + NO$

$^{11}C + O_2 \rightarrow {}^{11}CO + NO$

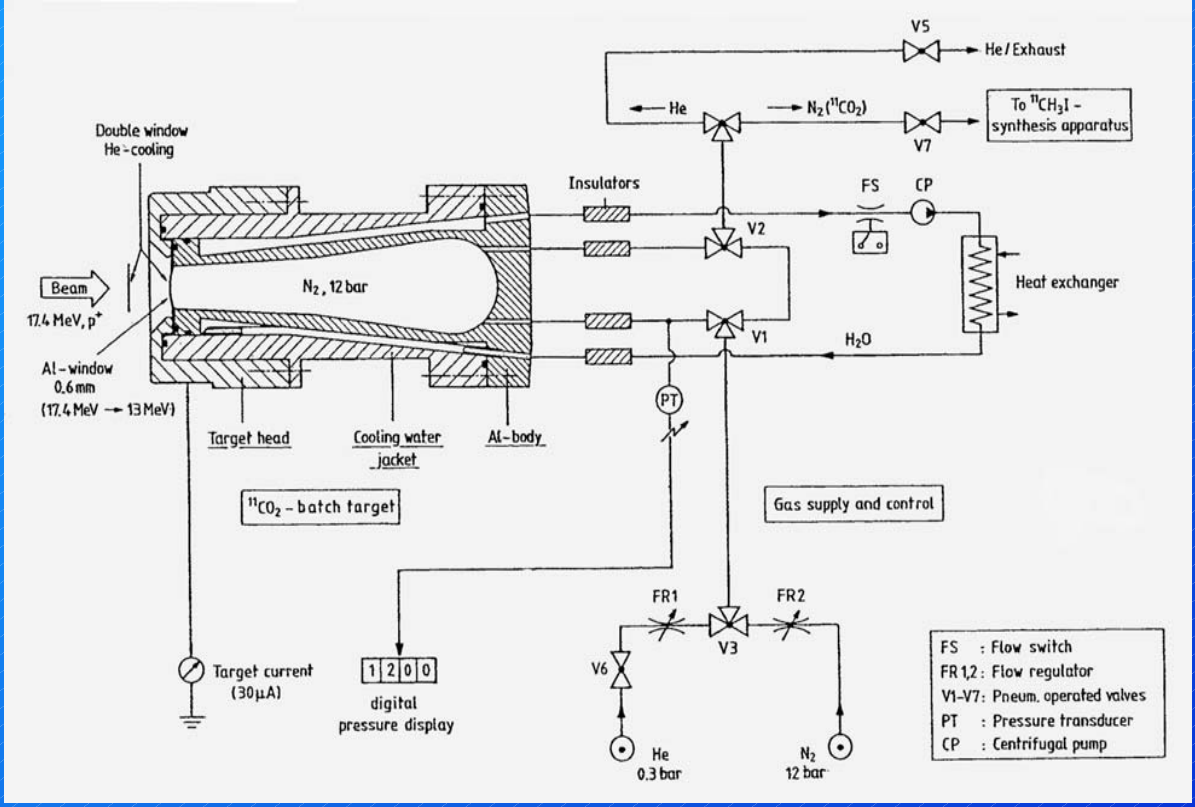
$^{11}CO + O_2 \rightsquigarrow {}^{11}CO_2 + O$

- A high current irradiation for 45 min leads mainly to $^{11}CO_2$

Gas Targetry

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

Production of ^{18}F using a Water Target

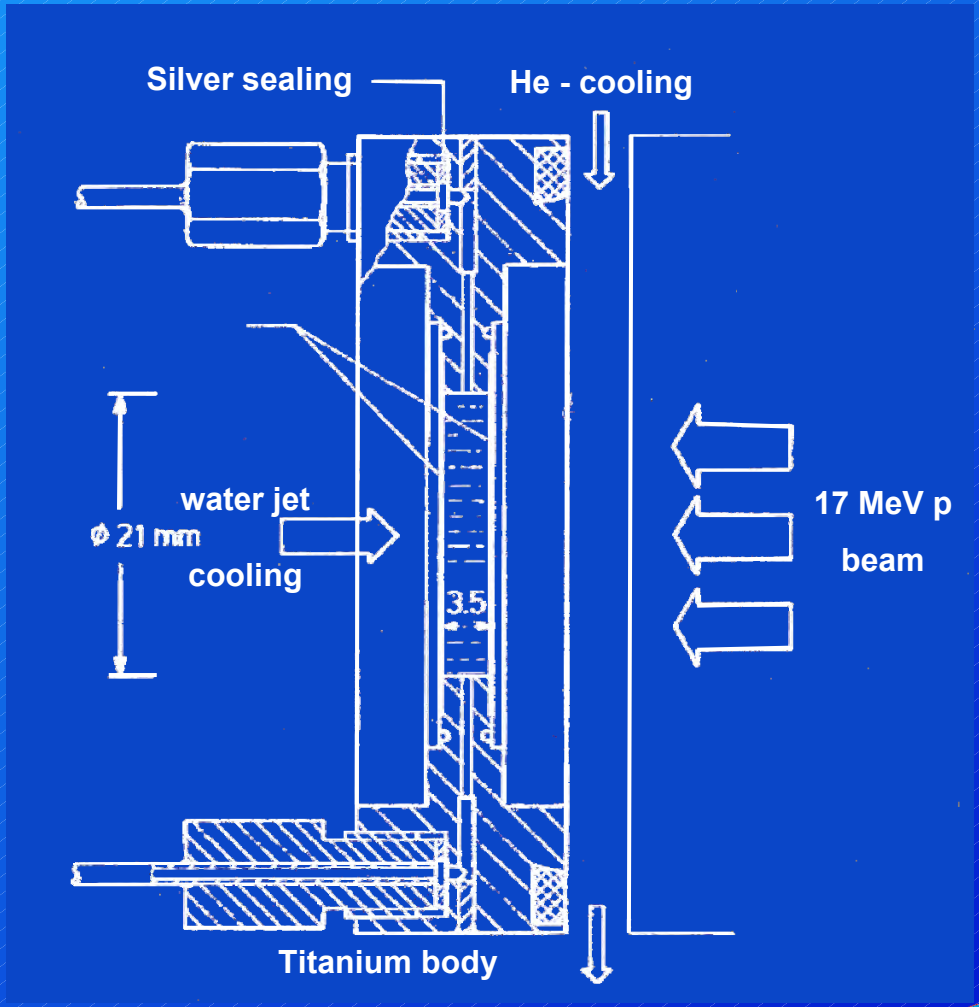
Nuclear process: $^{18}O(p,n)^{18}F$

Batch yield of $^{18}F^-_{aq}$

$E_P = 16 \rightarrow 3$ MeV

15 µA, 2 h

74 GBq (2 Ci)



Target volume: 1.3 ml

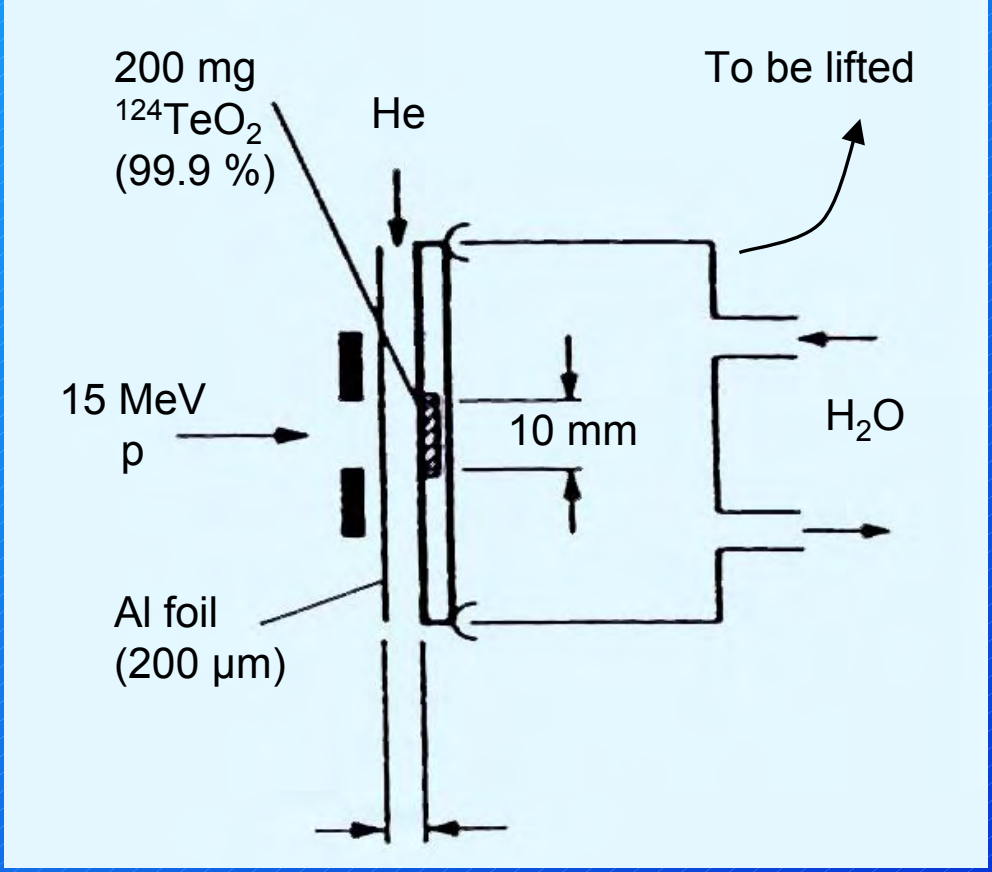
Purification of $^{18}F^-$ and Recovery of $H_2{}^{18}O$

- Transfer of irradiated water to an anion-exchange column (AG 1x8)
- Adsorption of $^{18}F^-$ on the column
- $H_2{}^{18}O$ flows through and is recovered for reuse
- Desorption of $^{18}F^-$ from the column using K_2CO_3

Solid Targetry:

Example: Production of ^{124}I via the $^{124}Te(p,n)$-Process

Irradiation Arrangement for Medium Scale Production



E_p = 13 → 9 MeV

Irradiation: 6 h, 10 µA