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Novel Medical Radionuclides and Related Nuclear Data

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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

- Introduction
- Non-standard positron emitters

  - production using low-energy reactions

    (Examples: ^{64}Cu, ^{94m}Tc, ^{124}I, etc.)

  - production via intermediate energy reactions

    (Examples: ^{52}Fe, ^{73}Se, ^{124}I, etc.)
- Novel therapeutic radionuclides

  (Examples: ^{67}Cu, ^{186}Re, ^{225}Ac, ^{193m}Pt, etc.)
- Conclusions

New Directions in Development of Radiotracers for Nuclear Medicine

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- Enhancing the yield, purity and specific activity of presently used radiotracers
- Development of new organ specific radiopharmaceuticals, especially using
  - ^{99m}Tc and ^{123}I for SPECT
  - ^{18}F and ^{68}Ga for PET
- Development of novel longer-lived positron emitters for
  - study of slow metabolic processes
  - improvement of radiation dosimetry
- Development of novel low-energy highly ionising radiation emitters for internal radiotherapy

This lecture deals with development of novel radionuclides

Radionuclide Development

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- Nuclear data
  - excitation functions and yield measurements
  - occasionally decay scheme investigations
- High current targetry
- Radiochemical separations
  - dry and wet methods of separation
  - enriched target recovery
- Quality control
- Imaging suitability
  - phantom measurements (PET, SPECT) to determine resolution, background correction, etc.

This lecture concentrates on nuclear data and some production aspects.

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

Problems

- Constraints on production yield and purity
- Imaging difficulties due to high energy positrons and γ-rays
- Demanding metal-chelate chemistry

Production Routes of ^{64}Cu

Nuclear process	Optimum energy range [MeV]	Thick target yield [MBq/μA·h]
^{64}Ni(p,n)^{64}Cu [a]	12 → 8	304
^{64}Ni(d,2n)^{64}Cu [a]	17 → 11	430
^{68}Zn(p,αn)^{64}Cu [a]	30 → 21 [b]	116
^{66}Zn(p,2pn)^{64}Cu [a]	52 → 37	316
^{64}Zn(d,2p)^{64}Cu [a]	20 → 10	27.1
^{66}Zn(d,α)^{64}Cu [a]	13 → 5	13.8
^{nat}Zn(d,x)^{64}Cu	25 → 10 [c]	57.0

a) Using highly enriched target material. Low enrichment leads to impurities

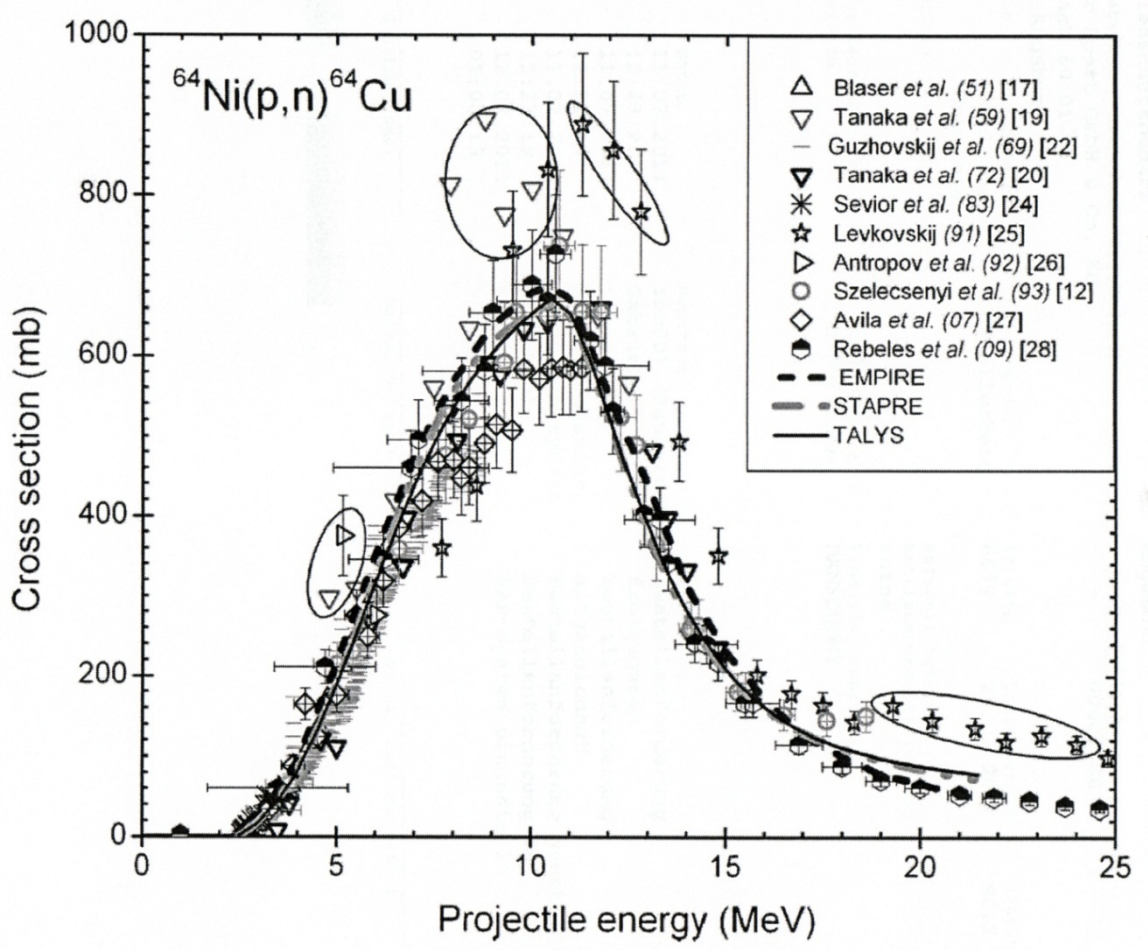
b) Below threshold of ^{67}Cu impurity via the ^{68}Zn(p,2p)^{67}Cu reaction

c) Below thresholds of ^{61}Cu and ^{67}Cu impurities via the ^{64}Zn(d,αn)^{61}Cu and ^{68}Zn(d,2pn)^{67}Cu reaction, respectively

Extensive studies performed at Brussels, Cape Town, Debrecen, Jülich and Segrate

For review cf. Aslam et al., RCA **97**, 669 (2009)

Excitation Function of $^{64}Ni(p,n)^{64}Cu$ Reaction



Production method developed at Jülich; Szelecsényi et al., ARI **44**, 557 (1993).

Data evaluated by Aslam et al, RCA **97**, 669 (2009)

Optimum energy range for production of ^{64}Cu

E_p: 12 → 8 MeV

Yield: 304 MBq/μAh

Radiochemical Separation of ^{64}Cu Produced via ^{64}Ni(p,n)-Process

(Szelecsenyi et al., ARI **44**, 557 (1993).)

Target: 95% enriched ^{64}Ni electroplated on Au (thin target)

Irradiation: 16 MeV p, 4 μA, 5 h

Separation:

- Irradiated target dissolved in conc. HCl
- Anion-exchange chromatography (Dowex 1x8)
- ^{64}Ni eluted with 10 M HCl, collected in 1 ml, and reused for electroplating
- Radiocopper separated from radiocobalt by elution with HCl of lower concentration

Yield of ^{64}Cu: 1 GBq Purity: > 98%

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

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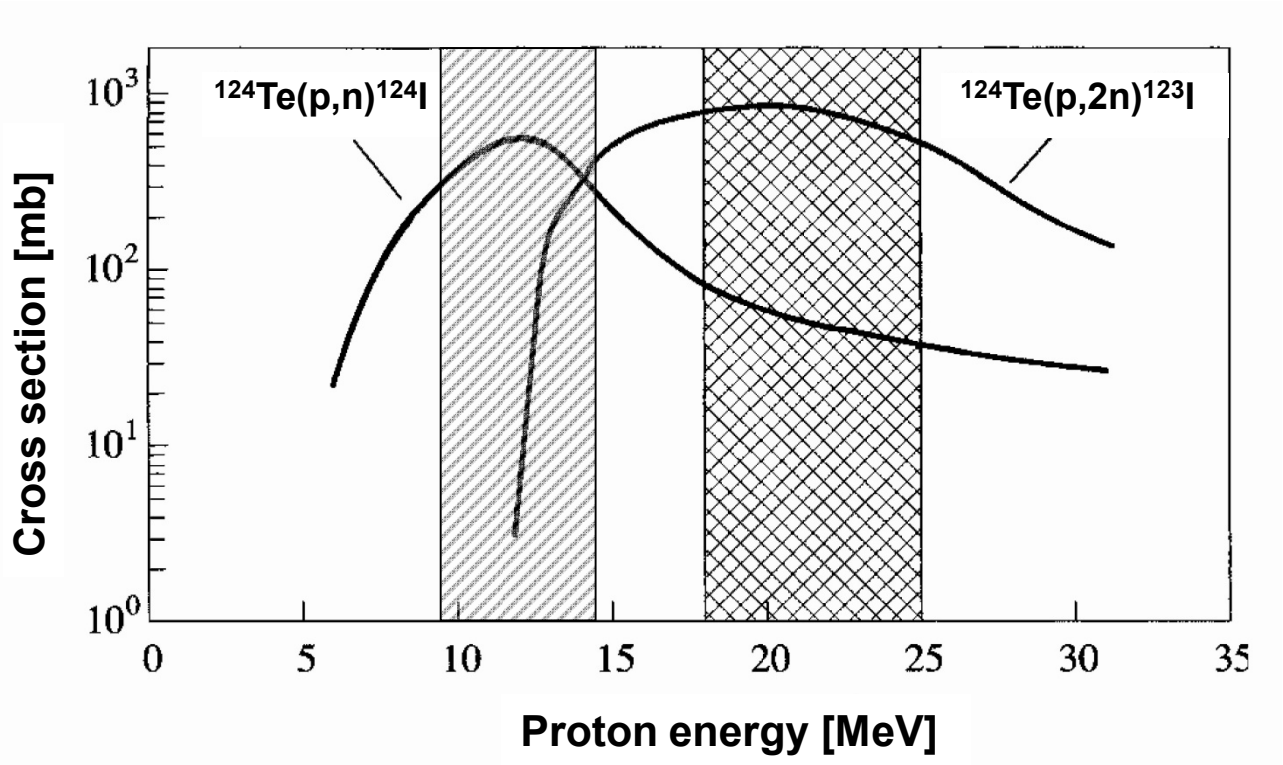
Example:

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

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



Production of ^{124}I	**Production of ^{123}I**
E_p: 14 → 9 MeV	E_p: 25 → 18 MeV
(^{125}I impurity < 0.1%)	(^{124}I impurity < 1%)

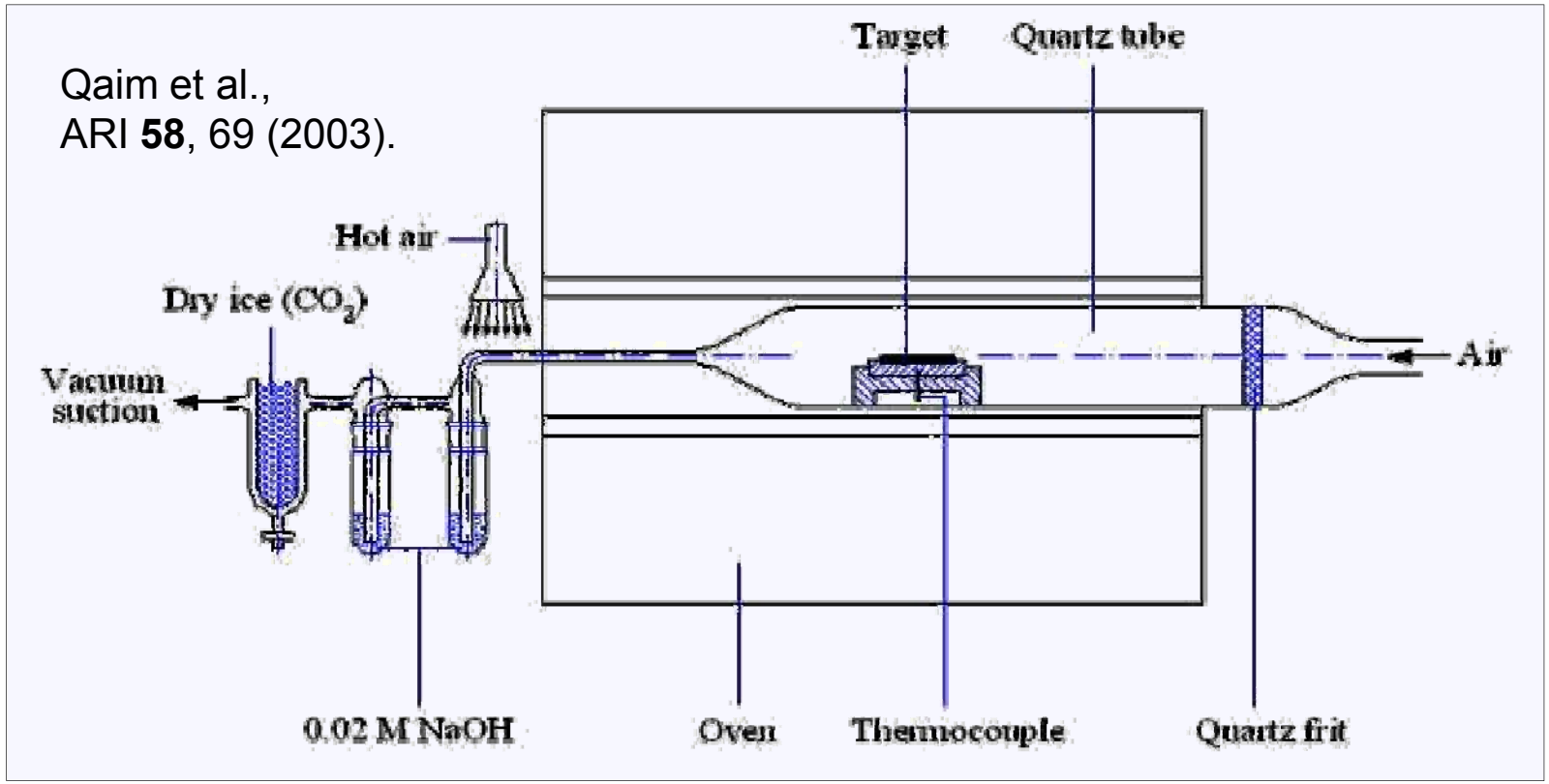
Routes for Production of ^{124}I

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

- All values calculated from excitation functions measured at Jülich

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

Distillation of Radioiodine



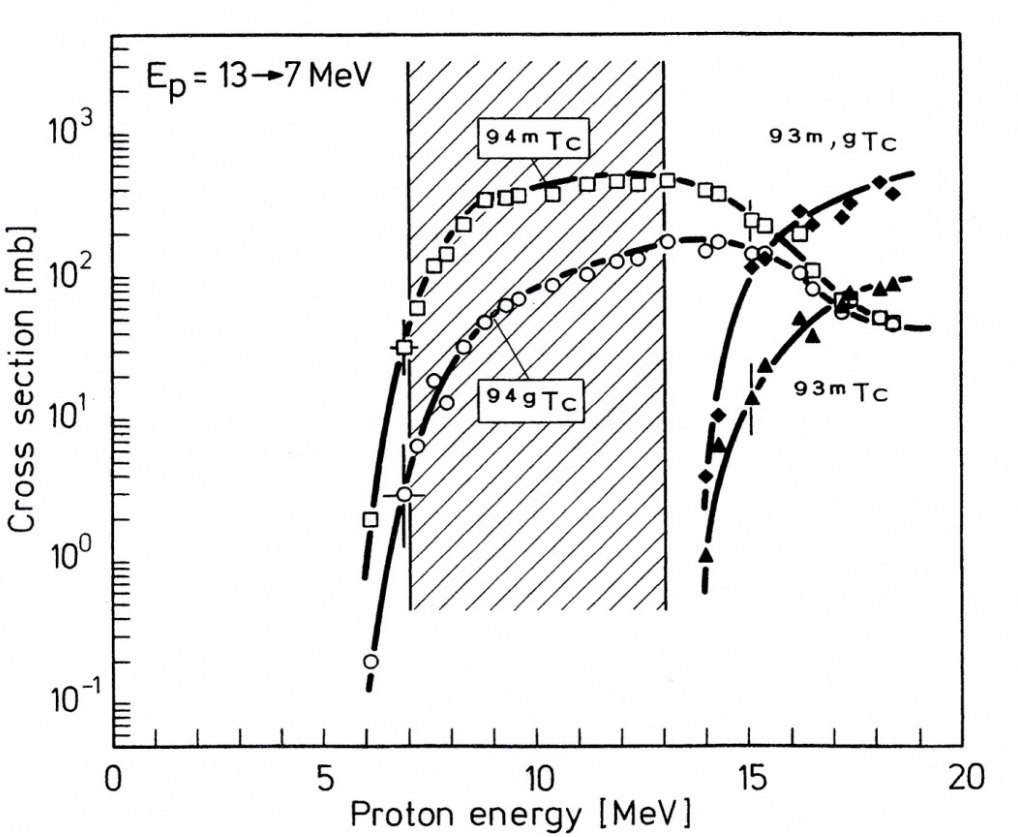
Distillation at 750 °C for 15 min

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

Formation of Isomeric States

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

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



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

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

Fundamental investigations mandatory

Qaim et al.,
NMB **27**, 323 (2000).

Novel Positron Emitters for Medical Applications Produced via Low-Energy Reactions (E ≤ 20 MeV)

Nuclide	Major production route	Energy range [MeV]	Application
^{55}Co (17.6 h)	^{58}Ni(p,α) ^{54}Fe(d,n)	15 → 7 10 → 5	Tumour imaging; neuronal Ca marker
^{64}Cu (12.7 h)	^{64}Ni(p,n)	14 → 9	Radioimmunotherapy
^{66}Ga (9.4 h)	^{66}Zn(p,n)	13 → 8	Quantification of SPECT
^{72}As (26.0 h)	^{nat}Ge(p,xn)	18 → 8	Tumour localisation; immuno-PET
^{76}Br (16.0 h)	^{76}Se(p,n)	15 → 8	Radioimmunotherapy
^{82m}Rb (6.2 h)	^{82}Kr(p,n)	14 → 10	Cardiology
^{86}Y (14.7 h)	^{86}Sr(p,n)	14 → 10	Therapy planning
^{89}Zr (78.4 h)	^{89}Y(p,n)	14 → 10	Immuno-PET
^{94m}Tc (52 min)	^{94}Mo(p,n)	13 → 8	Quantification of SPECT
^{120}I (1.3 h)	^{120}Te(p,n)	13.5 → 12	Iodopharmaceuticals
^{124}I (4.2 d)	^{124}Te(p,n)	12 → 8	Tumour targeting; dosimetry

Intermediate Energy Nuclear Reactions in Production of Novel Positron Emitters

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Problems

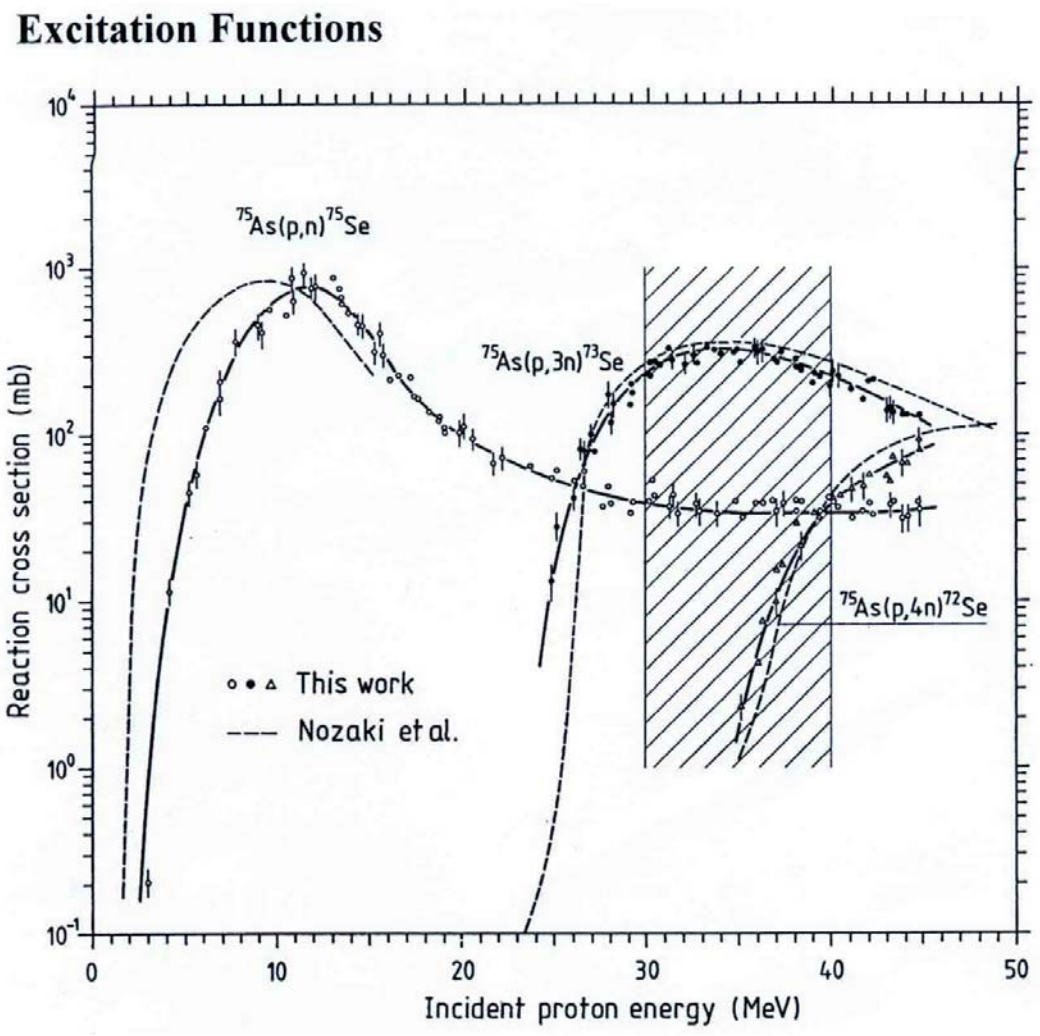
- Availability of high intensity cyclotrons
- Large number of competing nuclear reactions (higher significance of nuclear data)
- Targetry more challenging
- Radiochemical separations more demanding (impurity level may be higher)

Advantages

- Generally higher yield
- Occasionally high isotopic enrichment of target not very crucial

Considerable research and development work is called for.

Nuclear Data for Production of ^{73}Se via ^{75}As(p,3n)-Process



- Optimum energy range: E_p = 40 → 30 MeV
- Yield : 1.4 GBq/µA·h
- ^{72,75}Se impurity: < 0.2 %

The higher the projectile energy, the more are competing reactions.

Mushtaq et al.,
ARI **39**, 1085 (1988).

Production of some Novel Positron Emitters via Intermediate Energy Reactions (E > 20 MeV)

Nuclide	Production route	Energy range [MeV]	Theor. yield [MBq/μAh]	Radionuclidic impurity (%)
^{52}Fe (8.3 h)	^{55}Mn(p,4n)	100 → 60	22	^{55}Fe (< 2)
^{55}Co (17.6 h)	^{56}Fe(p,2n)	38 → 14	163	^{56}Co (1.6)
^{64}Cu (12.7 h)	^{68}Zn(p,αn)	30 → 21	116	^{67}Cu (< 0.5)
^{73}Se (7.1 h)	^{75}As(p,3n)	40 → 30	1400	^{72,75}Se (<0.2)
^{75}Br (1.6 h)	^{76}Se(p,2n)	24 → 20	1200	^{76}Br (2)
	^{75}As(^{3}He,3n)	36 → 25	278	^{76}Br (1.7)
^{83}Sr (32.4 h)	^{85}Rb(p,3n)	37 → 30	160	^{85}Sr (0.2)
^{124}I (4.2 d)	^{125}Te(p,2n)	22 → 15	93	^{125}I (0.7)
	^{126}Te(p,3n)	36 → 26	190	^{125,126}I (~1.5)

- High intensity intermediate energy cyclotrons are very beneficial.
- Several other potentially useful positron emitters could also be produced.

Production of Novel Positron Emitters via Generator Systems

Parent nuclide ($T_{1/2}$)	Daughter nuclide ($T_{1/2}$)	Production method of parent	Energy range [MeV]	Theor. yield of parent [MBq/μAh]
^{44}Ti (60.4 a)[a]	^{44}Sc (3.9 h)	^{45}Sc(p,2n)	32 → 18	~ $3 \cdot 10^{-3}$
^{52}Fe (8.3 h)[b]	^{52m}Mn (21 min)	^{55}Mn(p,4n)	100 → 60	22
^{62}Zn (9.1 h)[b]	^{62}Cu (9.7 min)	^{nat}Cu(p,xn)	30 → 18	230
^{72}Se (8.5 d)	^{72}As (26.0 h)	^{75}As(p,4n)	45 → 35	8
^{122}Xe (20.1 h)[b]	^{122}I (3.6 min)	^{127}I(p,6n)	65 → 43	230
		^{124}Xe(p,3n)	43 → 35	500
^{140}Nd (3.4 d)[c]	^{140}Pr (3.4 min)	^{141}Pr(p,2n)	30 → 15	210
		^{nat}Ce(^{3}He,xn)	35 → 20	12

a) $T_{1/2}$ of parent too long
b) $T_{1/2}$ of parent rather short
c) In-vivo generator system

Production of Novel Positron Emitters via α-Particle Induced Reactions

Nuclide ($T_{1/2}$)	Production route	Energy range [MeV]	Theor. yield [MBq/μAh]	Radionuclidic impurity (%)
^{30}P (2.5 min)[a]	^{27}Al(α,n)	28 → 10	740	-
^{38}K (7.6 min)[a]	^{35}Cl(α,n)	22 → 7	270	-
^{73}Se (7.1 h)[b]	^{70}Ge(α,n)	28 → 13	126	^{72,73}Se (0.5)
^{82}Sr (25.3 d)[b]	^{82}Kr(α,4n)	60 → 20	~ 3	^{85}Sr (120)

a) Produced exclusively via the α-particle induced reaction.

b) Applicable if intermediate energy proton beam not available; yield is, however, considerably smaller than via the (p,xn)-process.

Development Work Related to Therapeutic Radionuclides

Aims

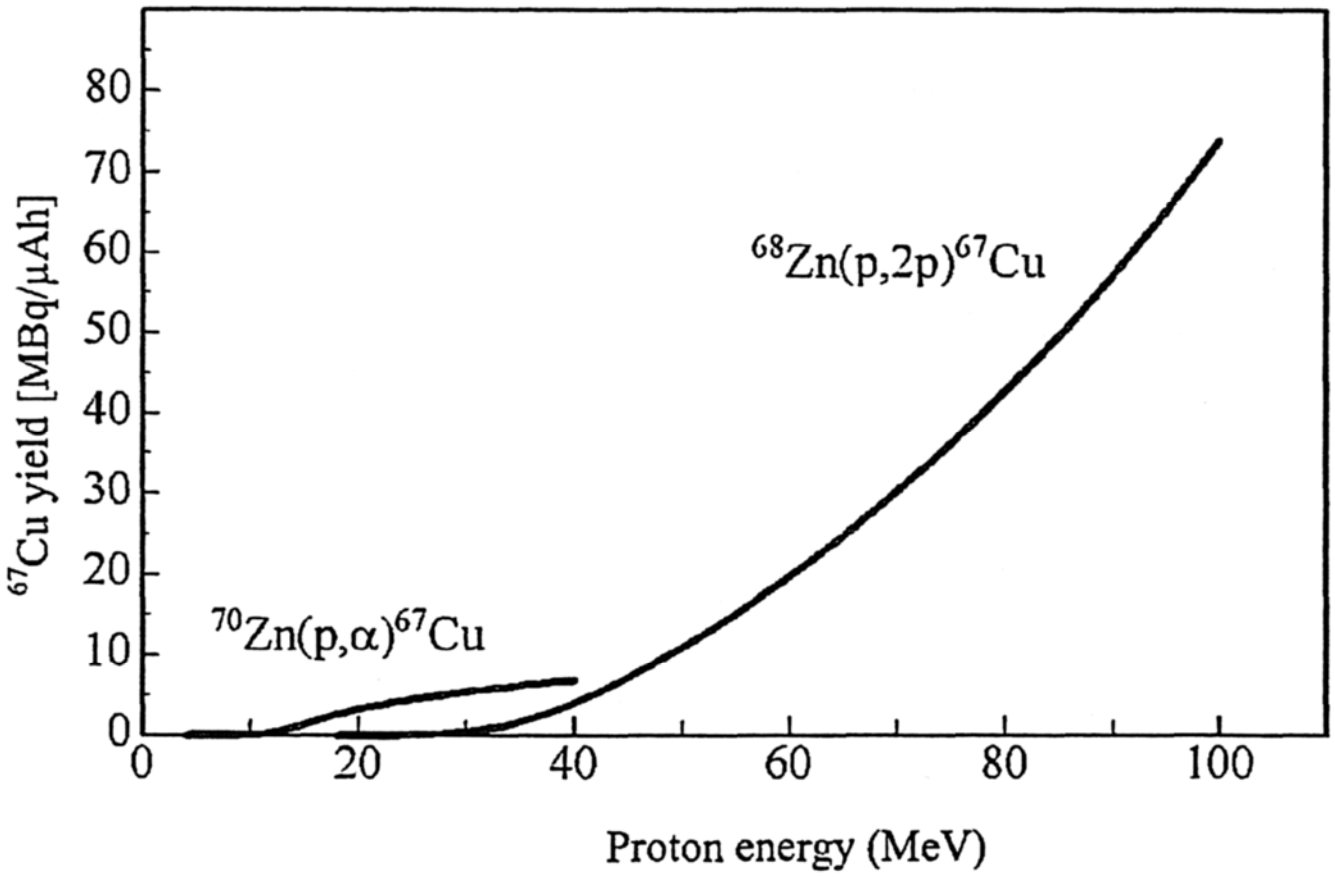
- Enhance the yield, purity and specific activity of presently used radionuclides
- Development of novel therapeutic radionuclides
- Improve internal radiation dosimetry

New Trends

- Low-range high-intensity radiation emitters (α-particles, low-energy electrons, X-rays)

Copper-67

($T_{½}$ = 2.58 d; E_{β^-} = 577 keV; I_{β^-} = 100 %)



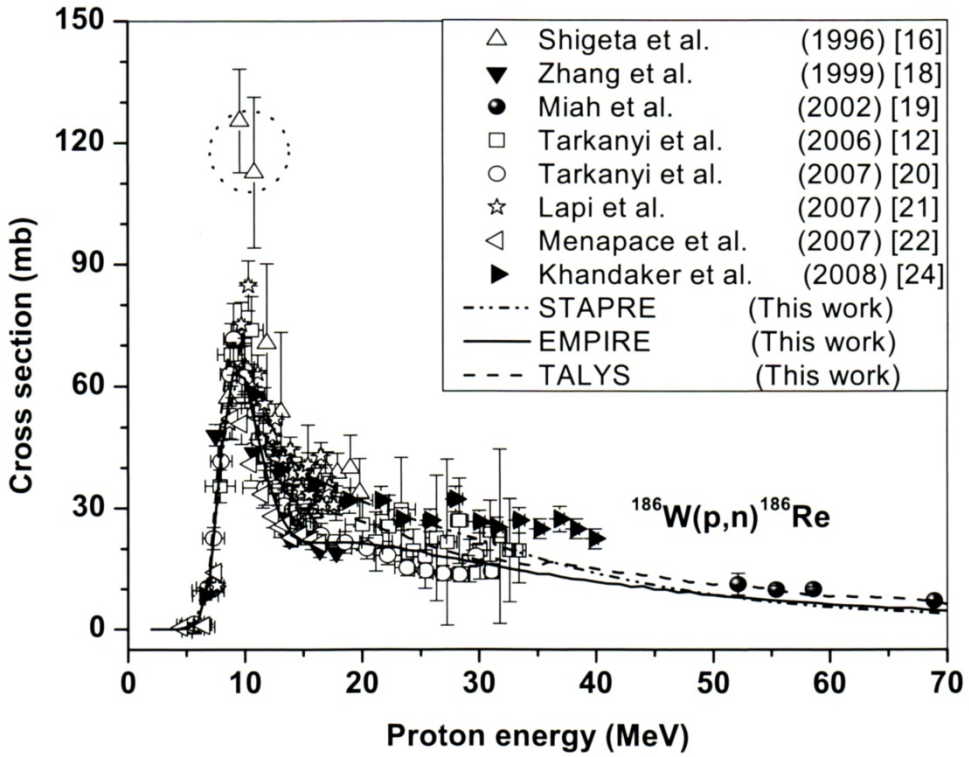
Qaim et al
IAEA-Technical Report
No. 473 (2011)

Reaction ^{68}Zn(p,2p)^{67}Cu at E_p = 70 → 30 MeV most promising, but needs an intermediate energy accelerator.

Rhenium-186

($T_{½}$ = 3.7 d; E_{β^-} = 1070 keV; I_{β^-} = 92.5 %)

Evaluated Data



Hussain et al., RCA **98**, 385 (2010)

Production route: $^{186}W(p,n)^{186}Re$

E_p = 18 → 8 MeV
Yield = 5 MBq/μA·h

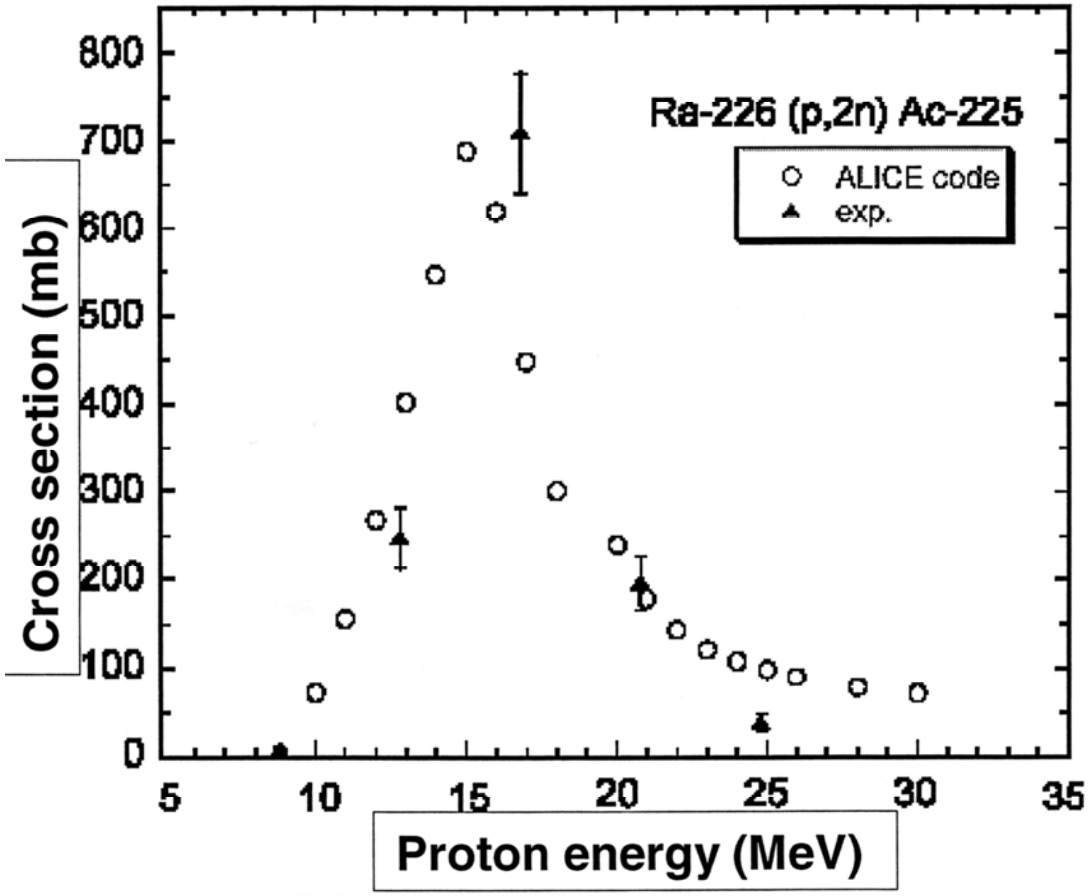
Target: Natural W and enriched ^{186}W

Product: High specific activity; yield and purity are under investigation

Results from three nuclear model calculational codes (EMPIRE, STAPRE, TALYS) are consistent.

Actinium-225

($T_{½}$ = 10.0 d; E_{α} = 5.8 MeV; I_{α} = 100 %)



Apostolidis et al,

ARI **62**, 383 (2005).

- Radioactive target
- Chemical separation tedious
- ^{225}Ac yield:

  E_p =22 → 10 MeV

  7 MBq/µAh

- **Production of ^{225}Ac in GBq quantities is possible and technology is being developed.**

Pt-193m

($T_{½}$ = 4.33 d; Auger electrons ~ 33 per decay)

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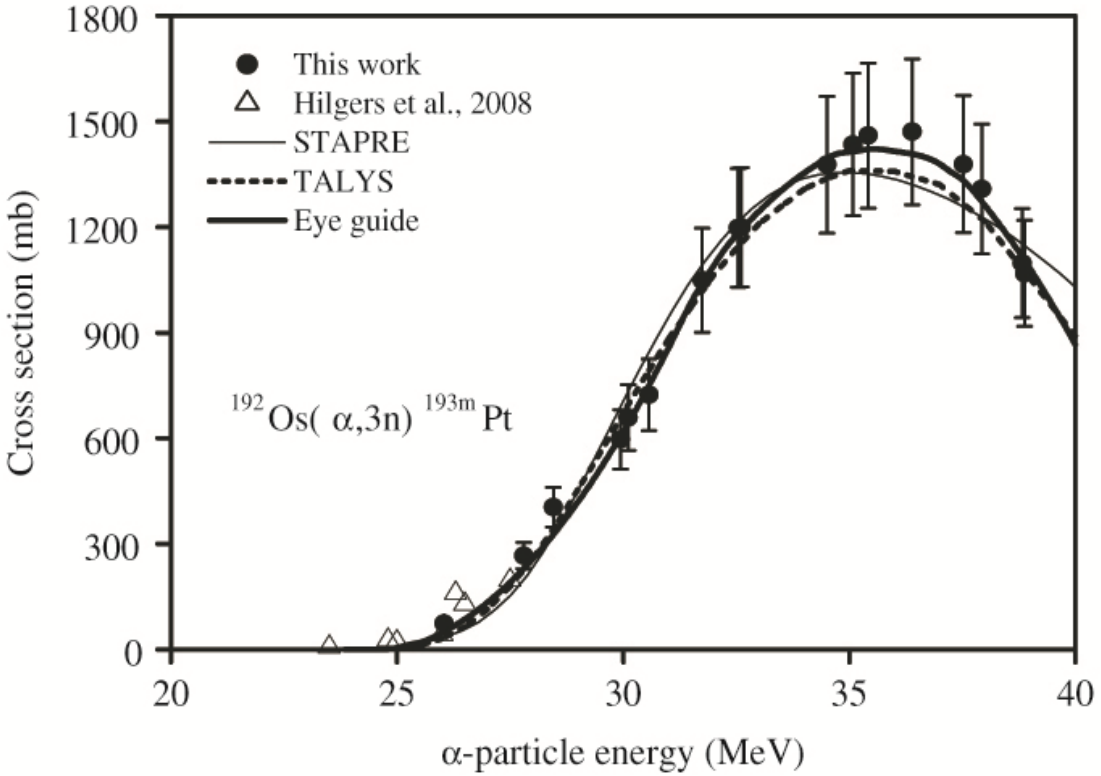
High-spin isomer

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

Excitation Function



^{193m}Pt-yield:

E_α = 40 → 30 MeV

10 MBq/μA·h

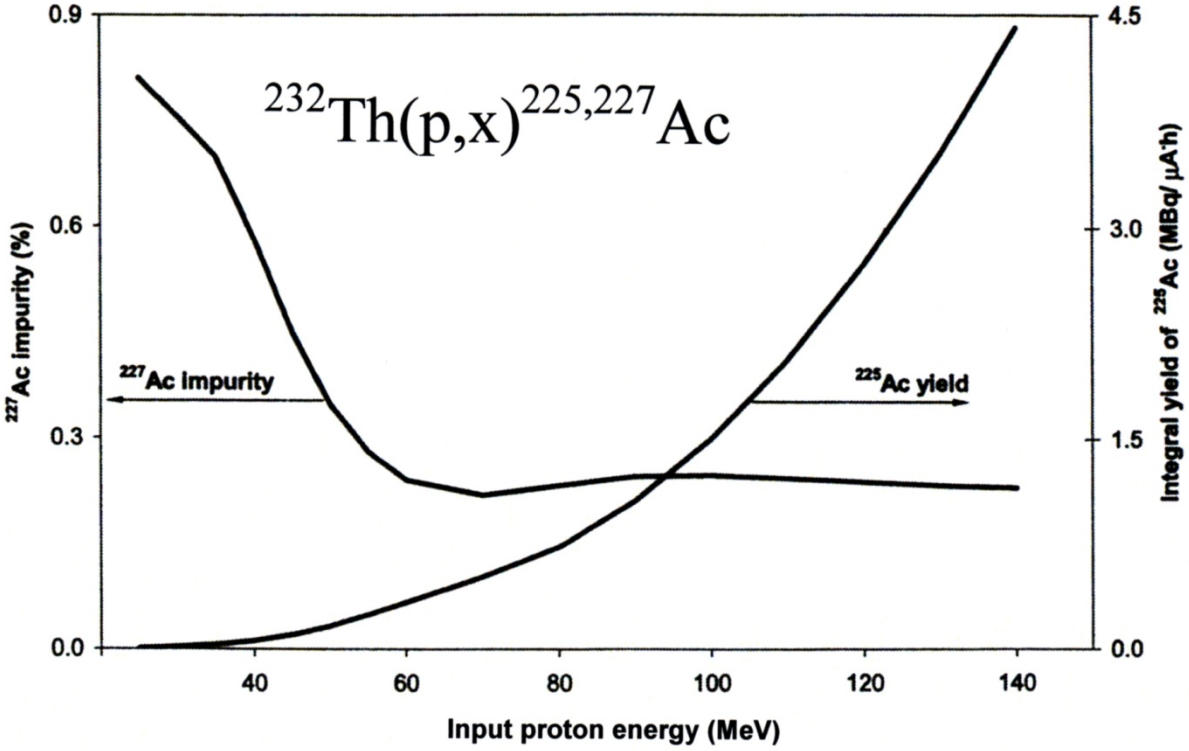
Production of high-specific activity ^{193m}Pt in sufficient Quantity is feasible

Uddin et al.,
ARI **68**, 2001 (2010).

Actinium-225 Production via $^{232}Th(p,x)$-Process

Data measurements: Ermolaev et al., RCA **100**, 223 (2012)
Weidner et al., ARI **70**, 2602 (2012)

Yield and Purity



Ermolaev et al., RCA 2012

E_p = 140 → 20 MeV

^{225}Ac yield

4.2 MBq/μAh

The yield is lower than in the $^{226}Ra(p,2n)^{225}Ac$ process, but this method avoids the handling of a radioactive target.

All methods of ^{225}Ac production need further development.

Production of some Potentially Useful Therapeutic Radionuclides using Intermediate Energy Multiple Particle Cyclotrons

Radionuclide ($T_{1/2}$)	Radiation emitted	Production route	Energy range (MeV)
^{67}Cu (2.6 d)	β^-	^{68}Zn(p,2p)	80 → 50
^{77}Br (2.4 d)	Auger electrons	^{75}As(α,2n)	35 → 15
^{117m}Sn (13.6 d)	Conversion electrons Auger electrons	^{116}Cd(α,3n)	40 → 25
^{131}Cs (9.7 d)	Auger electrons	^{133}Cs(p,3n)^{131}Ba➞ ^{131}Cs	40 → 25
^{153}Sm (1.9 d)	β^-	^{150}Nd(α,n)	30 → 15
^{193m}Pt (4.3 d)	Conversion electrons Auger electrons	^{192}Os(α,3n)	38 → 25
^{211}At (7.2 h)	α	^{209}Bi(α,2n)	30 → 20
^{225}Ac (10.0 d)	α	^{226}Ra(p,2n)	30 → 18

Increasing use of cyclotrons in production of therapeutic radionuclides

Conclusions

- There is constant need of development of novel radionuclides. New demands are related to longer lived non-standard positron emitters and low-energy highly ionising radiation emitters for internal radiotherapy.
- Development work involves both nuclear data research and technological innovation; interdisciplinary approach is vital.

Conclusions (cont´d)

- Small-sized cyclotrons are conveniently used for production of several novel positron emitters, e.g. ^{64}Cu, ^{86}Y, ^{94m}Tc, ^{124}I, etc.

  Purity of product is high; yield is, however, rather low.

- High intensity intermediate energy cyclotrons have great potential for extending the list of novel positron emitters and therapeutic radionuclides.

- The α-particle beam possesses some advantages regarding production of therapeutic radionuclides.

Combination of interesting science and useful technology