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Development of Novel Radionuclides for Medical Applications

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Lecture given at the IAEA-Technical Meeting on Nuclear Data for Medical Applications, Vienna, Austria, 10 – 13 December 2018

Outline

- Introduction
- Commonly used radionuclides
- Novel radionuclides
  - non-standard positron emitters
  - novel therapeutic radionuclides
- Novel approaches to production of radionuclides (charged particle, neutron and photon induced reactions)
- New directions in radionuclide applications
- New developments at FZJ regarding radionuclides
- Conclusions and perspectives

Introduction: Radioactivity in Medicine

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Diagnostic investigations

- Perfusion rates
- Organ localisation
- Dynamic functional studies, e.g. turnover rates of
  - oxygen - glucose - fatty acids - amino acids
- Receptor occupancy

Studies performed at a molecular level

Radiation dose should be minimum

Radiotherapy

- External radiation therapy (with γ, n, p or heavy ion)
- Internal radionuclide therapy
  - brachytherapy - metabolic therapy - radioimmunotherapy

Selective specific dose needs to be applied.

Recent Talks and Reviews
by S.M. Qaim et al. (FZJ)

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Talks

- Int. Workshop on Targetry and Target Chemistry, Prague, August 2014
- 8th Int. Conf. on Isotopes, Chicago, August 2014
- National Workshop on Nuclear Data, Berkeley, May 2015
- European Workshop on Nuclear Data, PSI, November 2015
- Int. Conf. on Nuclear Data, Brugge, September 2016
- 9th Int. Conf. on Isotopes, Doha, November 2017
- Int. Conf. on Reaction Mechanisms, Varenna, June 2018

Reviews

- Uses of alpha particles, RCA **104**, 601 (2016)
- Nuclear data for radionuclide production, NMB **44**, 31 (2017)
- Development of theranostic approach, Pharmaceuticals **10**, 56 (2017)
- Development of novel radionuclides, JLCR **61**, 126 (2018)
- Production of theranostic pairs of radionuclides, JRNC **318**, 1493 (2018)

Radionuclides Commonly used in Nuclear Medicine

Diagnostic Radionuclides

- **For SPECT**

  γ-emitters (100 – 250 keV)

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

  (used worldwide)

- **For PET**

  β^+ emitters

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

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

  (fast developing technology)

Therapeutic Radionuclides (in-vivo)

- β^--emitters (^{32}P, ^{90}Y, ^{131}I, ^{153}Sm, ^{177}Lu)
- α-emitter (^{211}At, ^{223}Ra)
- Auger electron emitters (^{111}In, ^{125}I)
- X-ray emitter (^{103}Pd)

(increasing significance)

Production methods are generally well developed.

Novel Radionuclides in Medicine

- Non-standard positron emitters
  - to study slow metabolic processes
  - to quantify targeted therapy
- Novel low-range highly ionising radiation emitters for internal radiotherapy
  - for targeted therapy

Continuous development work is underway.

Emphasis is on accelerator-produced metal radionuclides.

Four Pillars of Radionuclide Development Work

- Nuclear data
  - decay properties
  - production cross sections
- High current targetry
- Chemical processing
  - isolation of radionuclide and recovery of enriched target material
- Quality control
  - radionuclidic, radiochemical, chemical, specific activity

Major Considerations in Use of Non-Standard Positron Emitters in PET

A.Decay data

- Positron energy generally high; e.g. **^{124}I**: 2.14 MeV; **^{76}Br**: 3.94 MeV
- Positron emission intensity low; e.g. **^{64}Cu**: 17.8 %; **^{124}I**: 22.0 %
- Energies and intensities of emitted photons; e.g. **^{86}Y**: 11 γ-rays

Higher accuracies in decay data are needed

Interference in imaging
(image distortion; low resolution, faulty quantification)

New analytical algorithms need to be developed

B. Reaction data

- Databases need to be strengthened in many cases
- Formation of isomeric states demands detailed studies

Non-Standard Positron Emitters

Example: Copper-64

($T_{½}$ = 12.7 h; $E_{β+}$ = 0.66 MeV; $I_{β+}$ = 17.8 %)

Production Routes

Nuclear process	Optimum energy range [MeV]	Thick target yield [MBq/μA·h]
$^{64}Ni(p,n)^{64}Cu$ a)	12 → 8	304 (Most suitable)
$^{64}Ni(d,2n)^{64}Cu$ a)	17 → 11	430
$^{68}Zn(p,\alpha n)^{64}Cu$ a)	30 → 21	116
$^{66}Zn(p,2pn)^{64}Cu$ a)	52 → 37	316
$^{64}Zn(d,2p)^{64}Cu$ a)	20 → 10	27
$^{66}Zn(d,\alpha)^{64}Cu$ a)	13 → 5	14
$^{nat}Zn(d,x)^{64}Cu$	25 → 10	57

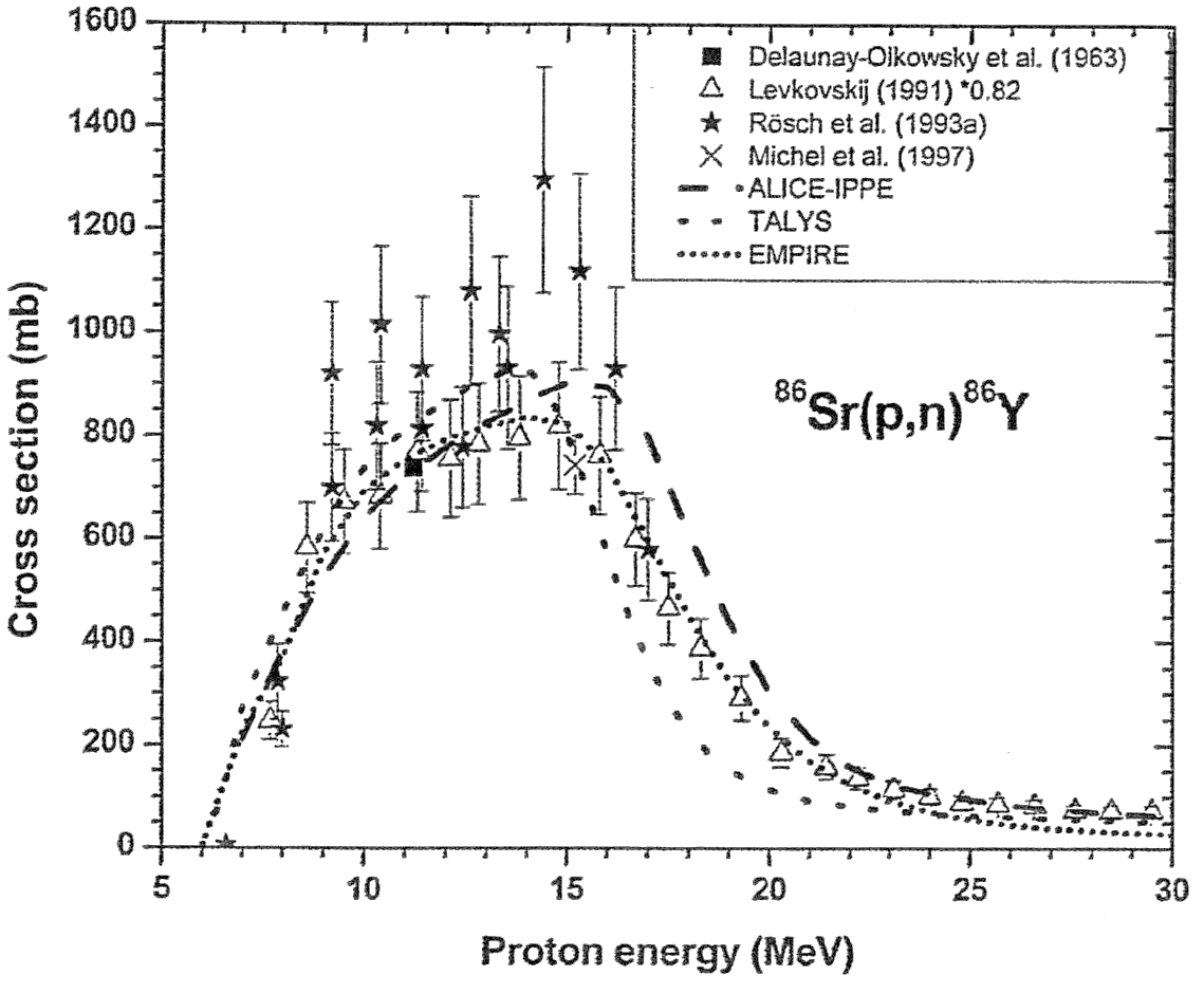
a) Using highly enriched target material; low enrichment leads to impurities.

Studies performed at Brussels, Cape Town, Debrecen, Jülich and Segrate

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

Example: Yttrium-86
($T_{½}$ = 14.7 h; $E_{β+}$ = 1.6 MeV; $I_{β+}$ = 34 %)

Excitation Function



Production method developed at Jülich (1993)

Data evaluated by Zaneb et al, ARI **104**, 232 (2015)

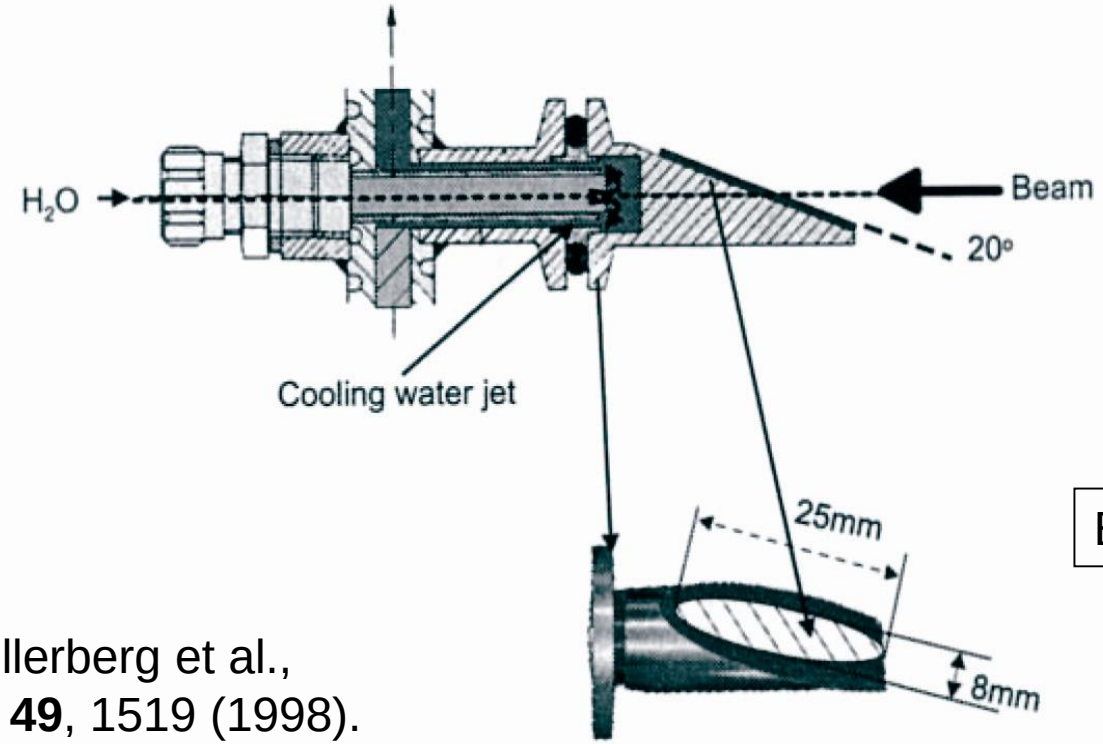
Considerable discrepancy suggests need of more precise measurement.

Solid Targetry

Sample preparation: Electrolysis, alloy formation, pellet

Heat dissipation: Efficient cooling, slanting beam

Example: Use of slanting beam



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

- Standard technology used in large scale production of several radionuclides (^{55}Co, ^{64}Cu, ^{124}I, etc.)

Beam current: 30 – 300 µA

Ion-Chromatographic Separation of Copper-64

Szelecsényi 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: > 99%

Separation Methods of ^{86}Y from $^{86}SrCO_3$ Target and Quality of Product*

Method	Energy range [MeV]	Separation yield [%]	Typical product batch yield [GBq]	Sr impurity [ng/mL]	Laboratory
Coprecipitation and ion-exchange	16 → 10	90	3.5	2.6	Jülich; 1993, 2002
Electrolysis	15 → 6	90	1.2	< 100	Tübingen; 2002 St. Louis; 2005
Single column cation-exchange	16 → 12	90	0.5	500	Jülich; 2009
Multiple column chromatography	14 → 6	80	0.7		Bethesda; 2004
Solvent extraction	16 → 10	89	0.5	1×10^3	Jülich; 2009
Precipitation	11 → 6	88	0.9	1.5×10^4	Wisconsin; 2008

*Radionuclidic purity: 97 %; Radiochemical purity: > 99 %

Coprecipitation followed by ion-exchange leads to purest form of ^{86}Y.

Non-Standard Positron Emitters for Medical Applications Produced via Low Energy Reactions

Qaim, JRNC **305**, 233 (2015)

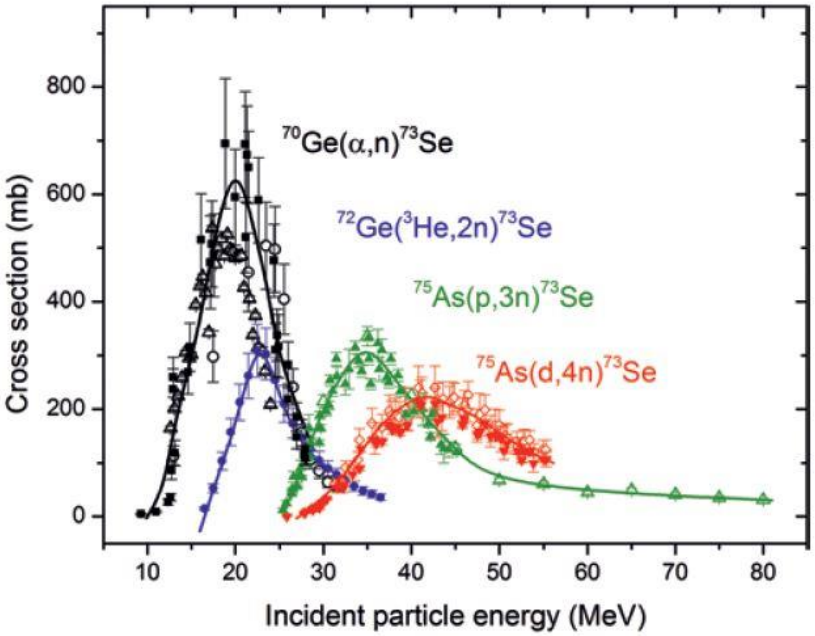
Nuclide	Major production route	Energy range [MeV]	Application
^{52}Mn (5.6 d)	^{52}Cr(p,n)	16 → 8	Multimode imaging (PET + MRI)
^{55}Co (17.6 h)	^{58}Ni(p,α) ^{54}Fe(d,n)	15 → 7 10 → 5	Tumour imaging; neuronal Ca marker
^{64}Cu (12.7 h)	^{64}Ni(p,n)	14 → 9	Radioimmunotherapy
^{66}Ga (9.4 h)	^{66}Zn(p,n)	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

Non-Standard Positron Emitters Produced via Multiple Particle Reactions

Example: ^{73}Se ($T_{½}$ = 7.1 h; $E_{\beta+}$ = 1.3 MeV; $I_{\beta+}$ = 65 %)

Qaim et al, RCA **104**, 601 (2016)

Excitation Functions



Yield and Impurity

Nuclear reaction	Energy range [MeV]	Yield of ^{73}Se [MBq/μAh]	^{72,75}Se impurity [%]
^{75}As(p,3n)	40 → 30	1406	0.1
^{75}As(d,4n)	40 → 33	700	0.2
^{72}Ge(^{3}He,2n)	35 → 15	130	1.8
^{70}Ge(α,n)	26 → 13	300	0.5

^{75}As(p,3n)^{73}Se reaction is the method of choice.

Novel Therapeutic Radionuclides

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(Useful low-range highly-ionising radiation emitters)

^{47}Sc ($T_{½}$ = 3.4 d; E_{β}- = 610 keV)

^{67}Cu ($T_{½}$ = 2.6 d; E_{β}- = 577 keV)

^{186}Re ($T_{½}$ = 3.7 d; E_{β}- = 1070 keV)

^{149}Tb ($T_{½}$ = 4.1 h; E_{α} = 3970 keV)

^{225}Ac ($T_{½}$ = 10.0 d; E_{α} = 5830 keV)

^{117m}Sn ($T_{½}$= 13.6 d; Conversion electrons)

^{193m}Pt ($T_{½}$ = 4.3 d; Auger electrons)

^{195m}Pt ($T_{½}$ = 4.0 d; Auger electrons)

Scandium-47

($T_{½}$ = 3.4 d; E_{β^-} = 610 keV; I_{β^-} = 100 %; E_{γ} = 159.4 keV (68 %)

cf. Review
Qaim, Scholten, Neumaier, JRNC **318**, 1493 (2018)

Production route	Irradiation	Batch yield	Laboratoy
$^{47}Ti(n,p)^{47}Sc$	Fission spectrum	1.6 GBq	Brookhaven, 1998
$^{48}Ti(\gamma,p)^{47}Sc$	40 MeV	186 MBq (3 g TiO_2 target)	Argonne, 2018
$^{46}Ca(n,\gamma)^{47}Ca \xrightarrow{\beta^-} {}^{47}Sc$	High thermal neutron flux	600 MBq 1 mg target, ^{46}Ca (31.7 % enriched)	Grenoble/PSI, 2014
$^{48}Ti(p,2p)^{47}Sc$	48 < 150 MeV	900 MBq Purity not acceptable	Brookhaven, 1998
$^{48}Ca(p,2n)^{47}Sc$	24 → 17 MeV	~ 10 MBq	Warsaw, 2017

All methods of ^{47}Sc production need further development.

Actinium-225

($T_{½}$ = 10.0 d; E_{α} = 5830 keV; I_{α} = 100%)

Production Routes

Separation from nuclear waste	(max. 100 GBq) per year	Transuranium Laboratory, Karlsruhe, Apostolidis et al, 2001
$^{226}Ra(p,2n)^{225}Ac$	Radioactive target; technology established but further development is underway	Karlsruhe, München, other places
$^{232}Th(p,x)^{225}Ac$	Cross sections measured; chemical separations achieved; check of impurities continues; technology in development	Moscow, Los Alamos, Brookhaven, Nantes, other places

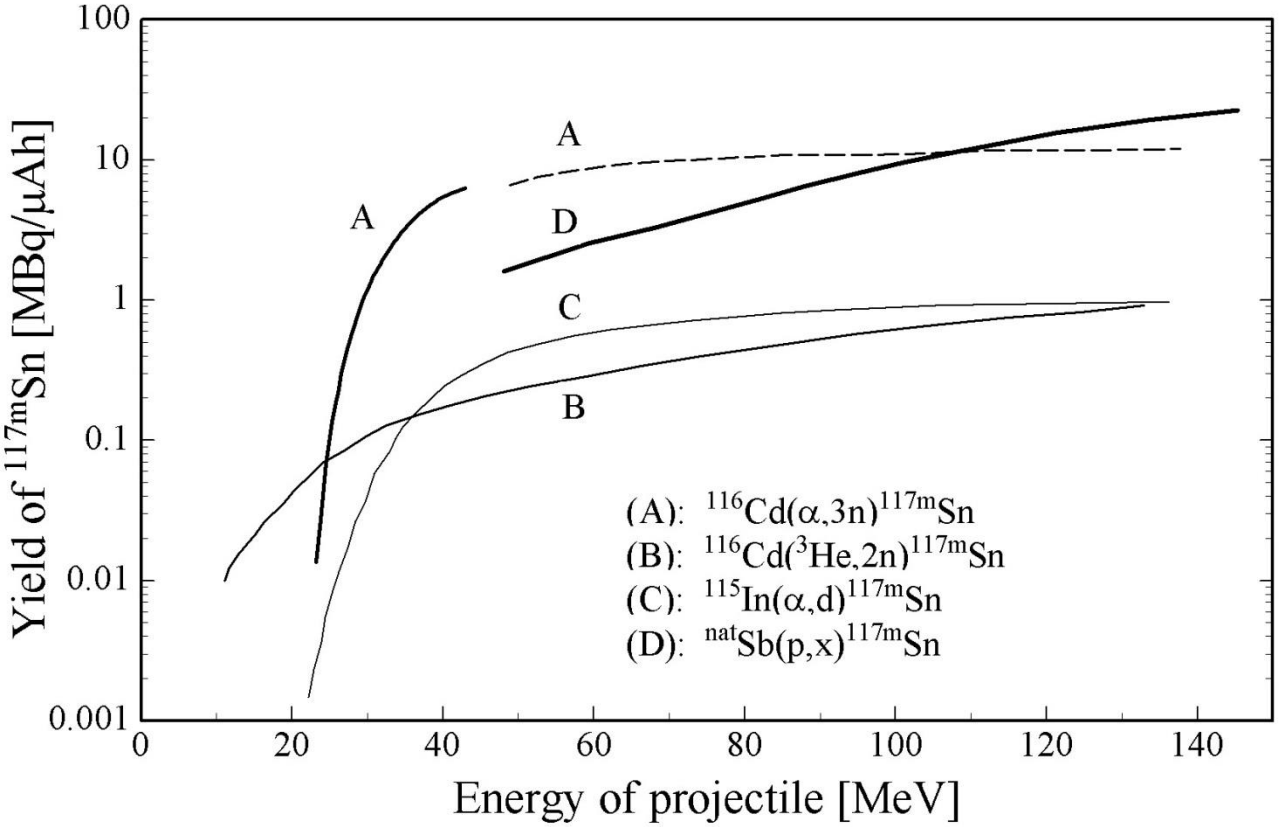
All methods of ^{225}Ac production need further development.

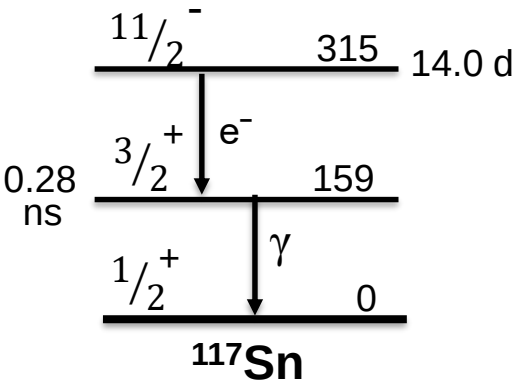
Production of Tin-117m

High spin isomer (I = 11/2⁻)
Source of conversion electrons

Routes: ^{117}Sn(n,n´γ); ^{116}Cd(α,3n); ^{116}Cd(^{3}He,2n); ^{115}In(α,d); ^{nat}Sb(p,x)

Qaim, Nucl. Med. Biol. **44**, 31 (2017).





Qaim, Döhler,
IJARI **25**, 645 (1984)

Adam Rebeles et al.,
NIM **B266**, 4731 (2008)

Ermolaev et al.,
JRNC **280**, 319 (2009)

^{116}Cd(α,3n)-reaction is most promising.

Targeted α-Radiation Therapy

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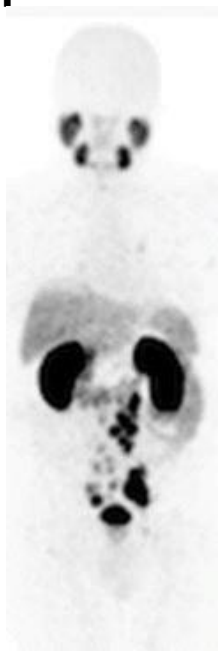
Example: ^{213}Bi ($T_{½}$ = 46 min; E_{α} = 5900 keV) from ^{225}Ac generator

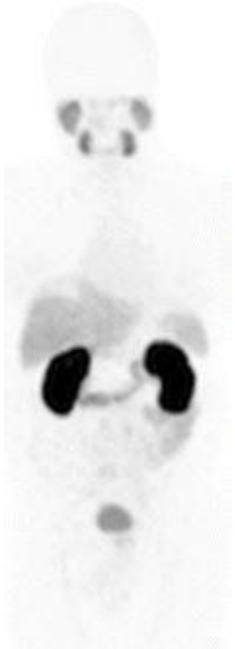
Prostate-specific membrane antigen radioligand therapy (PSMA-RLT)

- ^{177}Lu-PSMA successfully applied, but some patients show radioresistance to β^- radiation
- **New approach**: ^{213}Bi-PSMA

M. Sathekge et al., EJNMMI **44**, 1099 (2017)



^{68}Ga-PSMA (PET-CT scan)
Pre-therapy



^{68}Ga-PSMA (PET-CT scan)
Post-therapy
(11 months after ^{213}Bi-PSMA)

Targeted α-radiation therapy appears promising.

Novel Approaches to Production of Medical Radionuclides

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Charged Particle Induced Reactions

- Development of **solid targetry** at PET cyclotrons (e.g. ^{52}Mn, ^{124}I)
- Irradiation of **solutions** at PET cyclotrons (e.g. ^{44}Sc, ^{68}Ga, ^{86}Y, ^{89}Zr, ^{94m}Tc)
- Proton induced reactions up to 120 MeV (e.g. ^{52}Fe, ^{73}Se, ^{83}Sr, ^{152}Tb, etc.)
- α-particle induced reactions up to 70 MeV (e.g. ^{43}Sc, ^{117m}Sn, etc.)
- ***Exotic routes***

  - heavy-ion induced reactions (e.g. ^{152}Tb) NSW
  - spallation and on-line mass separation (e.g. ^{149}Tb, ^{152}Tb) CERN

Fast Neutron and High Energy Photon Induced Reactions

- Use of (n,p) or (γ,p) reaction (e.g. ^{47}Sc, ^{67}Cu, etc.)

Continuous development work is underway

New Directions in Radionuclide Applications

- **Theranostic approach**

  (combination of PET / Targeted therapy)

  $^{44}Sc/^{47}Sc$, $^{64}Cu/^{67}Cu$, $^{86}Y/^{90}Y$, etc.

- **Multimode imaging**

  (combination of PET/CT and PET/MRI)

- **Radioactive nanoparticles**

  Possible improvement in delivery of radionuclide to tumour

Continuous radionuclide research is underway.

Theranostic Approach in Medicine

- Combination of diagnosis and therapy using two suitable radionuclides of the same element **(personalized medicine)**.
  - quantitative diagnosis using a non-standard β^+ emitter and PET
  - targeted therapy using a β^-, α- particle or Auger electron emitter

- Examples of theranostic pairs of metallic radionuclides

  ^{44}Sc (3.9 h) / ^{47}Sc (3.4 d)

  ^{64}Cu (12.7 h) / ^{67}Cu (2.6 d)

  ^{83}Sr (32.4 h) / ^{89}Sr (50.5 d)

  ^{86}Y (14.7 h) / ^{90}Y (2.7 d)

  ^{124}I (4.2 d) / ^{131}I (8.0 d)

  ^{152}Tb (17.5 h) / ^{161}Tb (6.9 d)

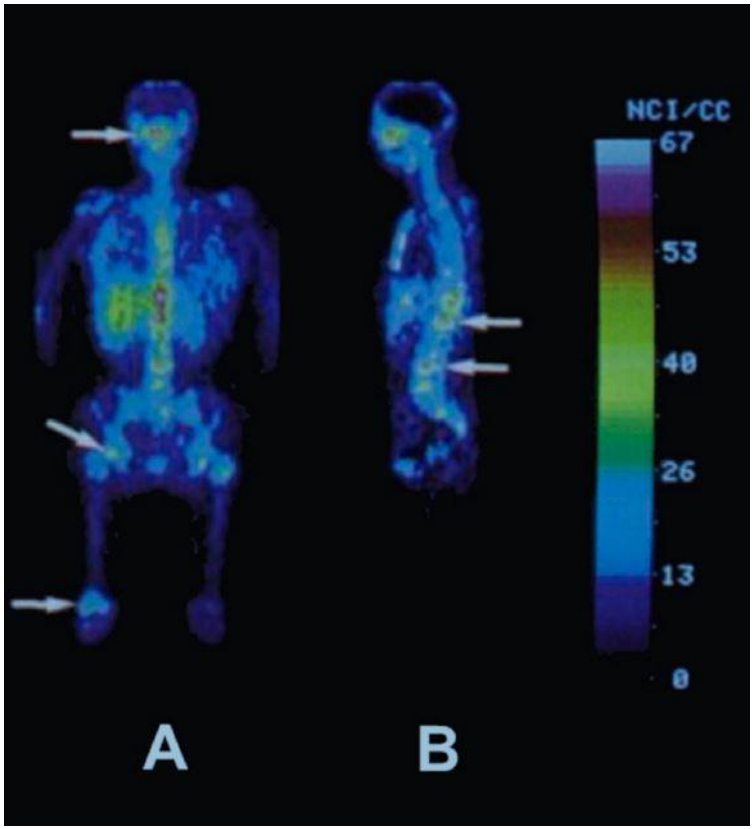
For recent review cf.
Qaim et al.,
JRNC **318**, 1493 (2018).

The pair ^{86}Y/^{90}Y has been most successfully applied.

Theranostic Approach

Example: $^{86}Y/^{90}Y$ pair

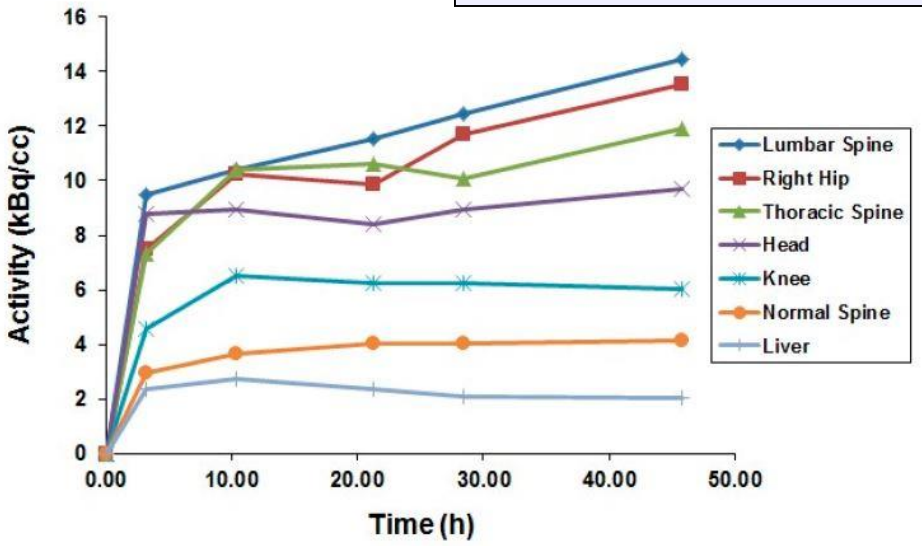
- Addition of β^+ emitting ^{86}Y analogue to the therapy nuclide ^{90}Y
- Uptake of [^{86}Y] citrate determined using PET



(A) Anterior (B) Sagittal

Arrows show metastases

Herzog et al., JNM **34**, 2222 (1993).



Accurate dose calculation possible

Rösch, Herzog, Qaim, Pharmaceuticals **10**, 56 (2017)

Multimode Imaging: MRI/PET

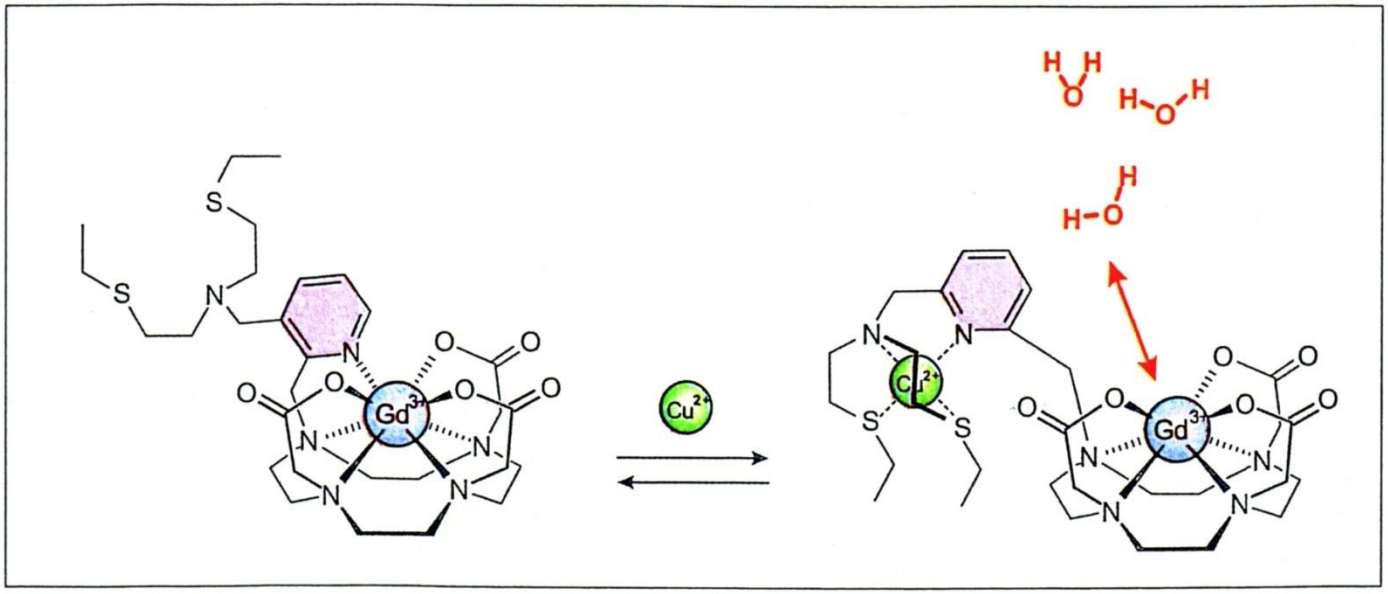
- Combining good resolution of MRI with dynamic and quantitative nature of PET

Possibilities

- use of radioactive contrast agents
  (Positron emitters needed: ^{52}Mn, ^{52}Fe, ^{57}Ni, etc.)
- development of ***intelligent contrast agent***, e.g. by chemically binding the MRI contrast agent Gd with another metal, for example Cu, through pyridine

Fast developing modality;
enhancing application in organ imaging.

Intelligent Contrast Agent



R. Herges, Nachr. Chemie **59**, 817 (2011).

- Gd^{3+} is an important contrast agent in MRI
- In presence of Cu^{2+} and pyridine, Gd^{3+} forms complex with a free co-ordination space where water is quickly bound.
- The complex increases the contrast appreciably (decreasing the toxicity of Gd)
- If Cu^{2+} is β^+ emitting ^{64}Cu, multimode imaging is possible.

Combination of Radioactivity and Nanotechnology

Concept

- Transport of the radionuclide via a “drug delivery system” to the malignant tissue, where the emitted radiation allows imaging or causes therapeutic effect.
  (Radionuclides would be the same as in normal use)

Current targeting strategies for metallic radionuclides

- monoclonal antibodies (mAb)
- peptides

Often insufficient delivery of radionuclide to tumour site

Drug delivery systems based on nanotechnology

• liposomes • iron oxide • polymers

Nanocarrier systems could provide platforms to improve delivery of radionuclides to tumour sites.

New Developments at FZJ Regarding Medical Radionuclides

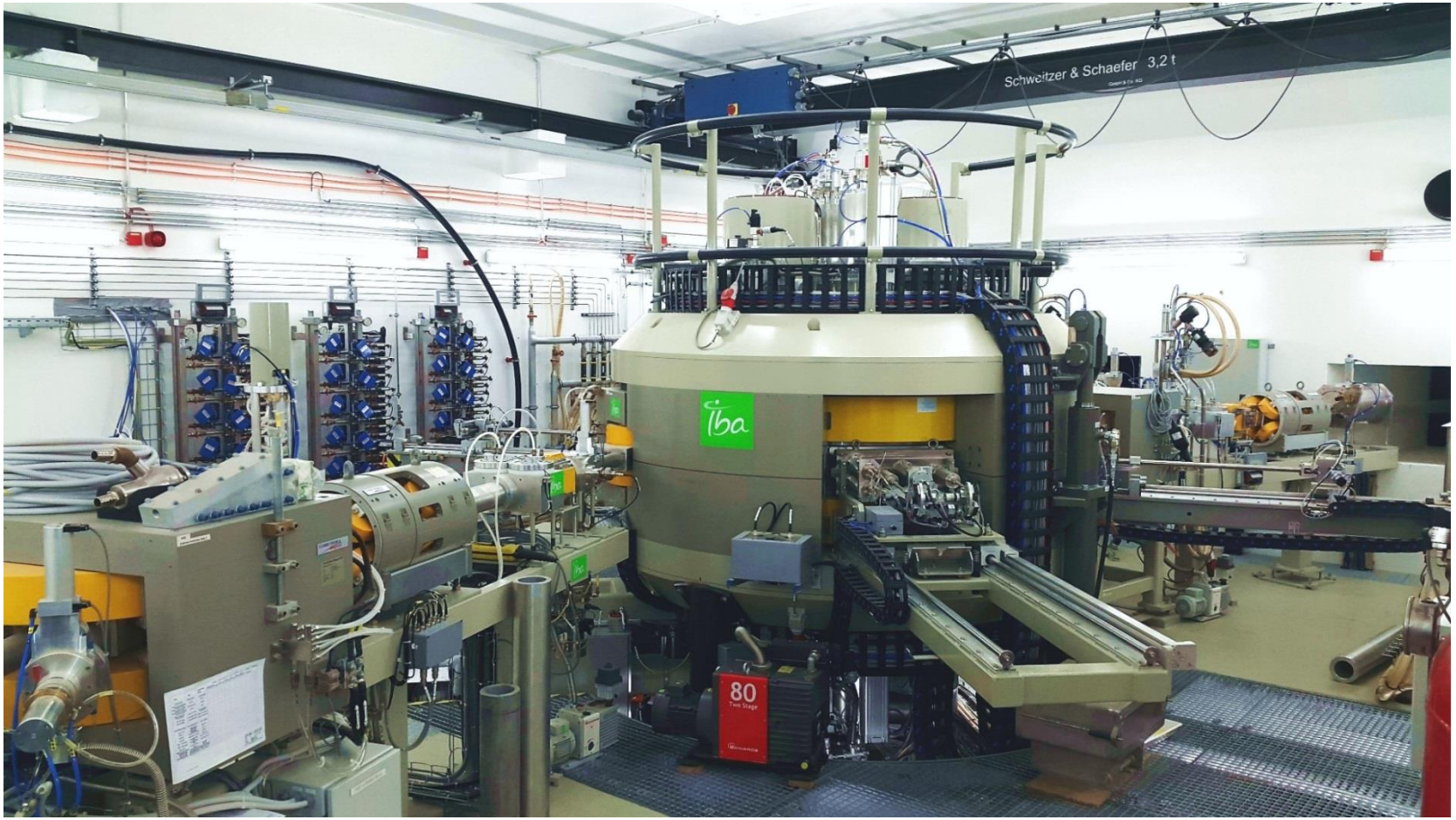
- New laboratories
  (cyclotron, radiochemistry, hot cells, radiopharmacy,
  SPECT, PET, MRI, all in one big institute)
- New cyclotron 30XP (IBA)
- Cross section measurements near reaction thresholds using BC 1710
- Partial use of 78 MeV d at JULIC
- New irradiation facility at COSY with $E_p \leq 150$ MeV
  (very low current)

All four pillars of development work are followed.

Pace of work very slow; overemphasis on safety aspects; but hope sustains life.

New Cyclotron: Cyclone 30XP (IBA)

at FZ Jülich



(Multiple particle machine)

Conclusions and Perspectives

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- Medical radionuclide production technology is well established; yet novel radionuclides are needed.
  - Novel positron emitters to study slow metabolic processes, multimode imaging and theranostic approach.
  - Novel β^- and α-emitters for targeted therapy.
- Significance of accelerators is increasing.
- Development work involves interdisciplinary research, with emphasis on nuclear data studies, combined with technological innovations.
- Radiotracer research is opening up new vistas in nuclear medicine.

Interesting science and human-health related technology; future perspectives are bright.