Medical Radionuclides and Related Nuclear Data

Part III. Therapeutic Radionuclides

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Topics

- General considerations
- Decay data of therapeutic radionuclides
- Commonly used production methods of important therapeutic radionuclides
- Development of new production routes
- Conclusions and perspectives

Radioisotopes for Therapy

- Differentation between radiation therapy and internal radionuclide therapy is essential
  - Radiation therapy consists of treatment with external radiation sources
  - Internal radionuclide therapy involves the use of a radioisotope within the body either as a sealed source (brachytherapy) or via a biological pathway (endoradiotherapy).

- Of great significance in internal therapy are
  - Linear energy transfer (LET), similar to that in external radiation therapy
  - Range of ionising radiation in tissue

Internal Radionuclide Therapy

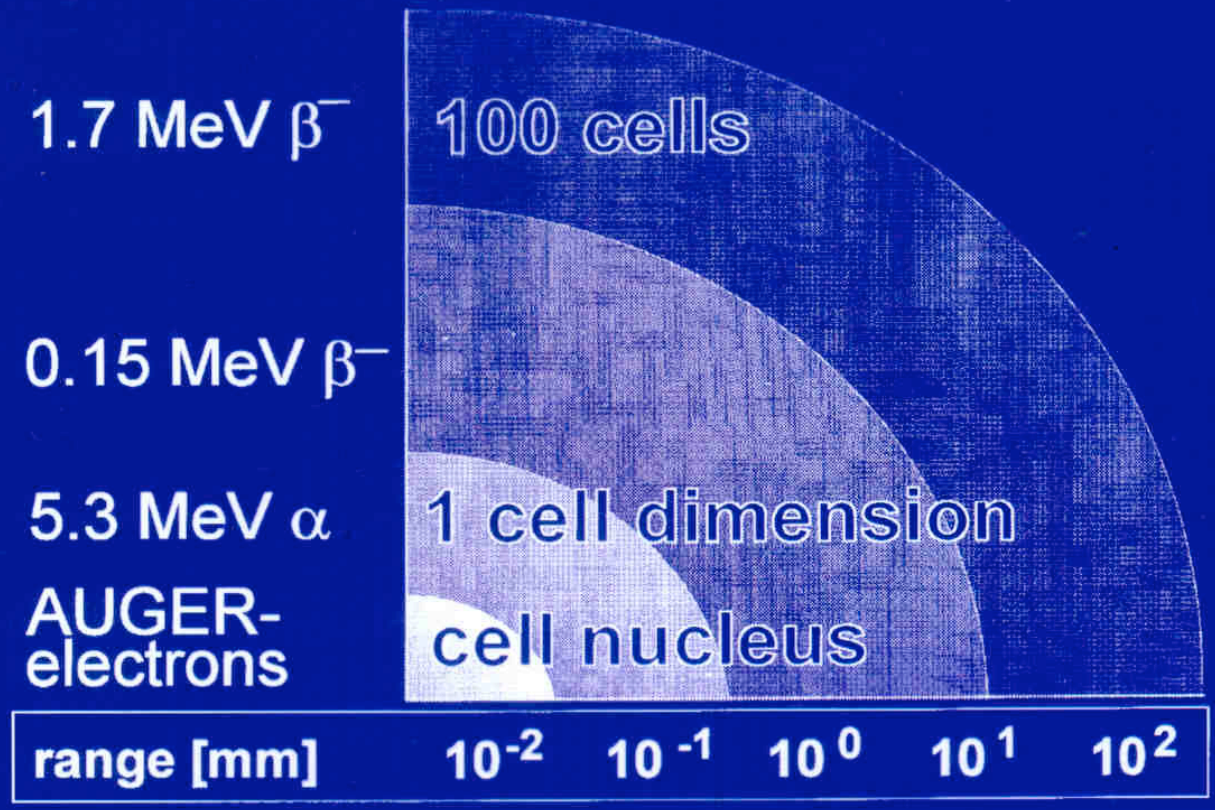
- **Brachytherapy**
  (insertion of sealed sources near the tumour)
  Examples: ^{192}Ir as wire
  ^{103}Pd and ^{125}I as seeds
- **Administration in cavities**
  (for pain palliation)
  Examples: ^{32}P colloid for arthritis
  ^{90}Y, ^{186}Re and ^{188}Re complexes for joint inflammation
- **Metabolic therapy**
  (incorporation of radionuclide via a biochemical path)
  Examples: ^{131}I for thyroid cancer
  ^{89}Sr, ^{186}Re and ^{153}Sm are bone seekers
- **Radioimmunotherapy**
  (administration of a radionuclide chemically conjugated to antibodies)
  Examples: low-energy high-LET value radionuclides

Internal radionuclide therapy is a fast developing field.

Radioisotopes for Therapy

- Uptake of a radiopharmaceutical in tumour via physiological processes

Range of ionising radiation



Uptake of a Radiopharmaceutical in the Tissue

Concepts

- Radioimmuno reactions (monoclonal antibodies)
- DNA-precursors (attachment to cell nucleus)
- Receptor ligands (attachment to cell membrane)
- Tumour seeking agents (cell environment)

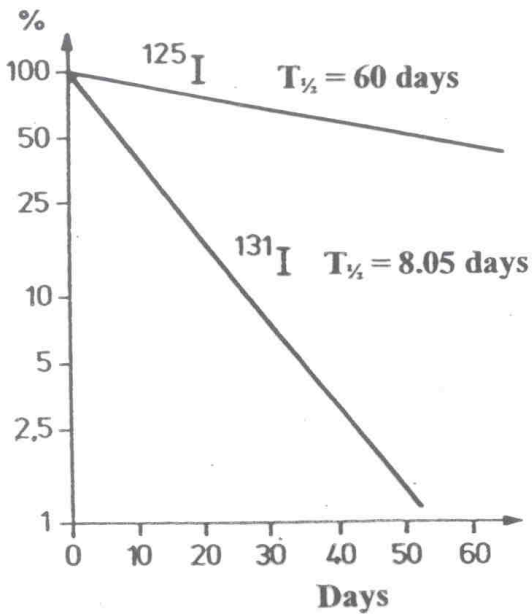
Problems

- Range of ionising radiation
- Tracer kinetics
- In-vivo stability of radiopharmaceutical
- Immuno chemical changes

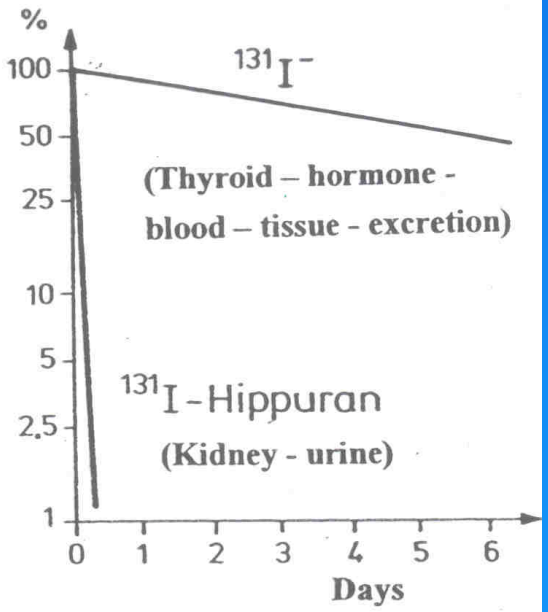
Endoradiotherapy is a developing field of study

Effective Half-life (T_{eff})

- Of considerable significance in the dosimetry of target organ
  - T_{phys} (physical half-life)
  - T_{bio} (biological half-life)



T_{phys}



T_{bio}

$$\lambda_{eff} = \lambda_{phys} + \lambda_{bio}$$

$$T_{eff} = \frac{\ln 2}{\lambda_{phys} + \lambda_{bio}} = \frac{T_{phys} \cdot T_{bio}}{T_{phys} + T_{bio}}$$

Decay Data of Therapeutic Radionuclides

Distinctive Features

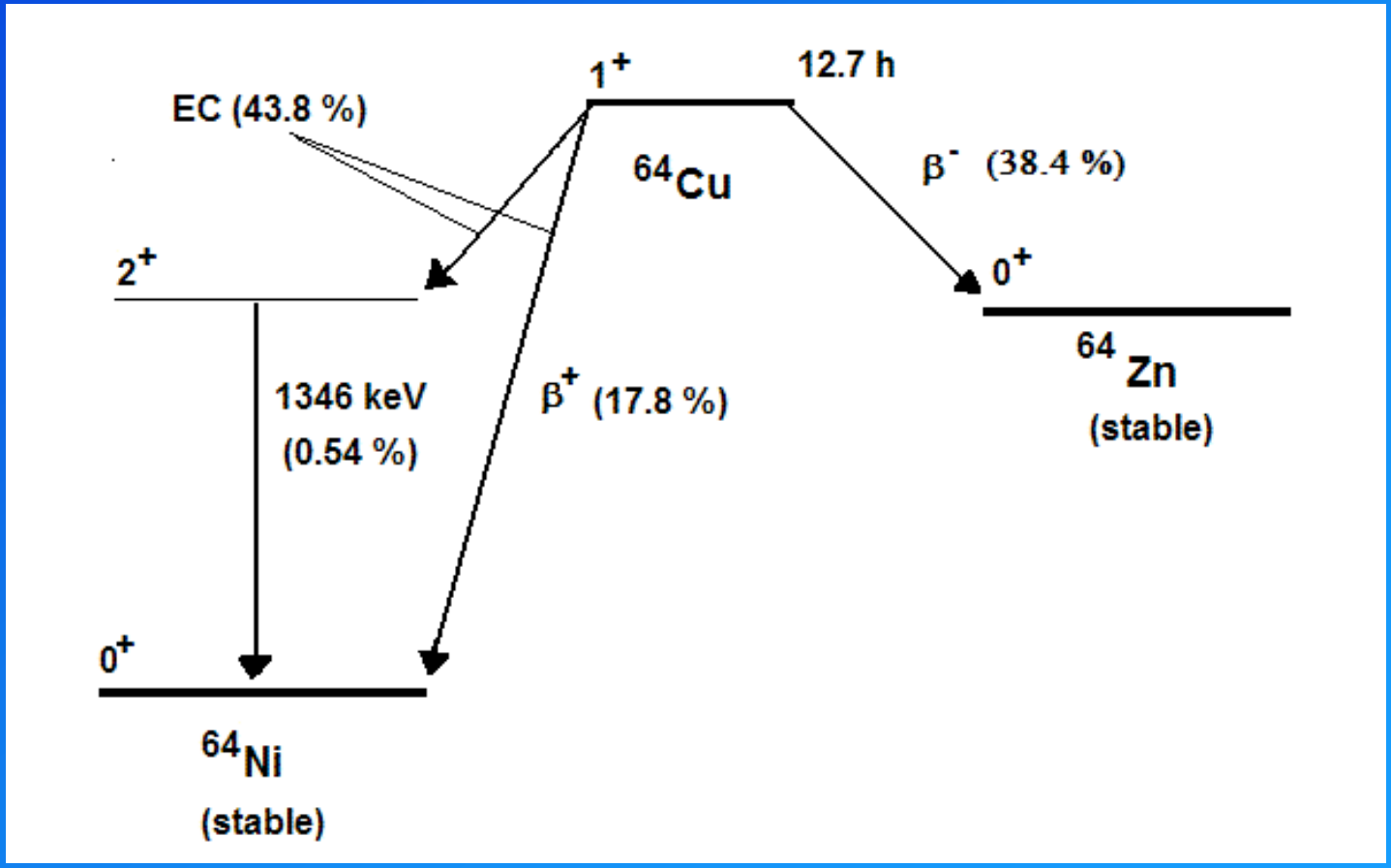
- $T_{1/2}$ relatively long
- I_{β^-} and I_{α} quite high
- I_{γ} rather low
- Energies of Auger and conversion electrons generally low

Status of Data

- Decay data generally well known
- Occasionally some uncertainty in I_{β^-} due to
  - use of impure samples
  - lack of high-precision β-ray spectroscopy
- Occasional uncertainty in low-energy electron spectra

Decay Scheme of Copper-64

- Preparation of thin, high-purity sample via the nuclear reaction $^{66}Zn(d,\alpha)^{64}Cu$
- Use of several counting methods (γ-and X-ray spectrometry; β-counting; γγ-coincidence, etc.)



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}Ni(p,n)	**^{169}Yb**	32.0 d	^{168}Yb(n,γ)
^{67}Cu	2.6 d	^{68}Zn(p,2p)	**^{177}Lu**	6.7 d	^{176}Lu(n,γ)
^{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 $\xrightarrow{\beta^-}$ ^{235}U(n,f)	**^{192}Ir**	73.8 d	^{191}Ir(n,γ)

Production is done using both nuclear reactors and cyclotrons

Production Methods of Important Therapeutic Radionuclides (Cont´d)

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

Examples of Endoradiotherapy

Thyroid therapy

^{131}I-iodide; 0.6 – 1.5 GBq; in case of benign tumour

- Biochemical concept (I-metabolism)
- Enrichment factor and uptake kinetics determined via γ-scintigraphy
- Radiation dose calculated using pharmacokinetics

Palliative therapy

(bones, joints, etc.)

[^{32}P]-Phosphate; [^{90}Y]-Citrate, etc.

- Tumour seeking agents
- Enrichment factors and uptake kinetics generally unknown (purely β^- emitters)
- Dosimetry is empirical

Other forms of therapy are in development.

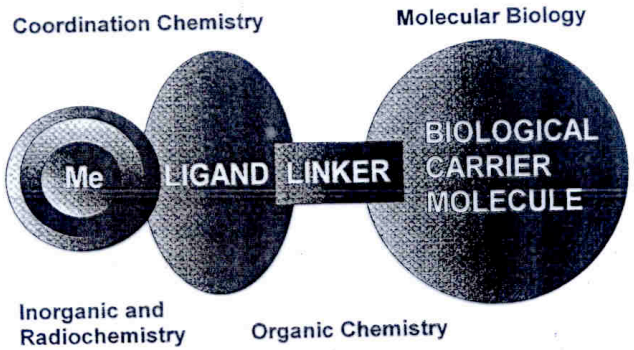
Preparation of Radiotherapeutical

- **Limited use of therapeutic radionuclides in simple ionic forms**

  Examples: $[^{131}I]I^-$ for thyroid cancer

  $[^{89}Sr]Sr^{2+}$ for bone metastases

- **Most applications demand one of the following forms**
  - **metal-ligand complex**
  - **particles or colloids**
  - **labelled biomolecules**
    - *radiohalogenation (in case of ^{80m}Br, ^{125}I, ^{131}I or ^{211}At)*
    - *coordinate bonding of metal cations via bifunctional chelators*



Multidisciplinary approach to the development of co-ordinately labeled radiopharmaceuticals.

Available Radiopharmaceuticals for Targeted Therapy

RADIOPHARMACEUTICAL	INDICATION	AVAILABILITY
[^{131}I] iodide	thyrotoxicosis, goiter thyroid carcinoma	+
Sodium [^{32}P] phosphate	polycythemia vera essential thrombocythemia	+
[^{131}I] MIBG	pheochromocytoma neuroblastoma paraganglioma, carcinoid medullary thyroid carcinoma	+
[^{89}Sr] chloride	bone metastases (palliation)	+
[^{90}Y] citrate	bone metastases (palliation)	+
[^{90}Y] colloid	synoviorthesis (knee) malignant pleural/peritoneal effusions	+
[^{186}Re] sulphide	synoviorthesis (medium size joints)	+
[^{169}Er] citrate	synoviorthesis (small joints)	+
[^{32}P] phosphate colloid	malignant effusion	+
[^{186}Re] HEDP	bone metastases (palliation)	clin.trial
[^{153}Sm] EDTMP	bone metastases (palliation)	clin.trial
[^{131}I]-,[^{90}Y]-,[^{67}Cu]- labelled antibodies	variety of tumours	clin.trial
[^{90}Y] particles	hepatoma	clin.trial
[^{131}I] lipiodol	liver malignancy	clin.trial

(+ = available for routine use, clin. trial = under investigation)

Development of New Routes for Production of Novel Therapeutic Radionuclides

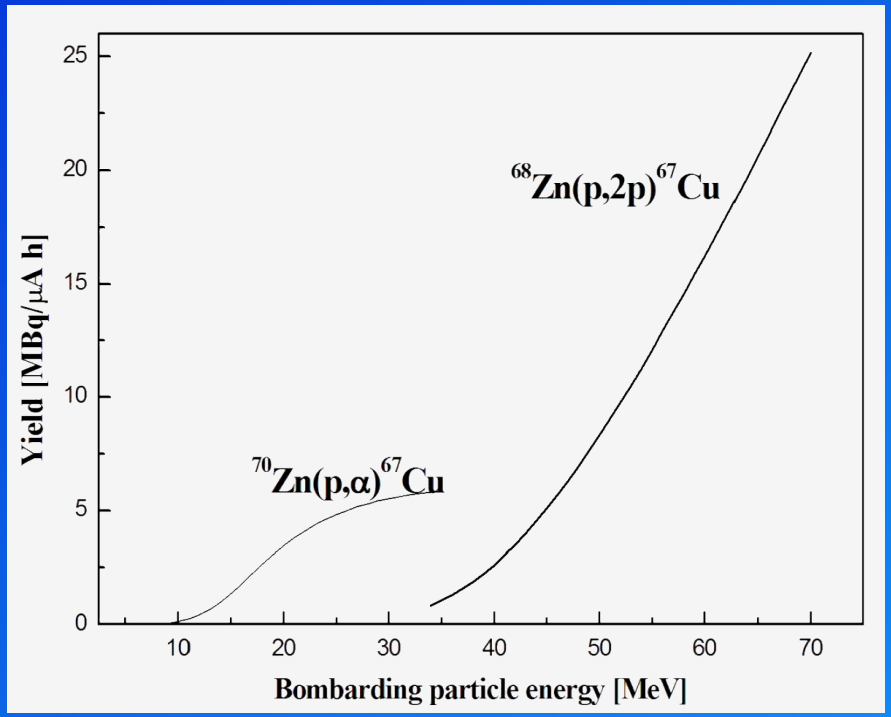
Aims

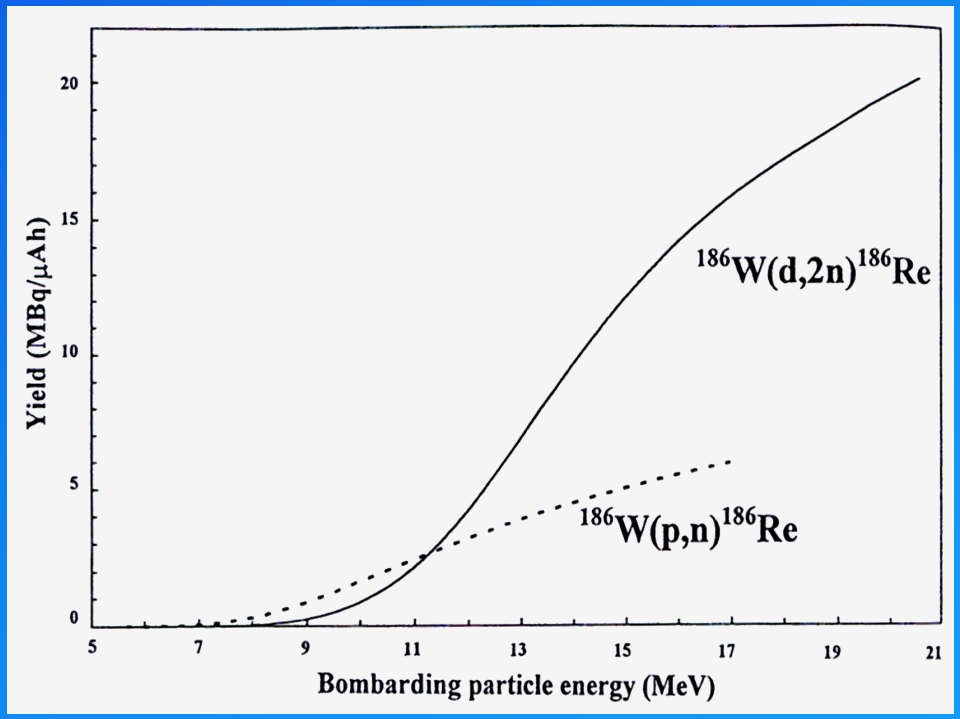
- Enhance the yield, purity and specific activity of presently used radionuclides
- Establish novel or future-oriented technology
- Development of novel therapeutic radionuclides
- Improve internal radiation dose dosimetry

New Trends

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

Comparative Studies on Production of Copper-67 and Rhenium-186





- *Different production yields using different reactions*
- *Choice of production method depends on the available projectile and its energy*

Routes for Production of ^{64}Cu

Production route	Suitable energy range [MeV]	Integral yield [MBq/μA·h]
$^{64}Zn(n,p)^{64}Cu$	Fission spectrum	14.5*
$^{64}Ni(d,2n)^{64}Cu$	19 → 15	389
$^{64}Ni(p,n)^{64}Cu$	12 → 9	241
$^{nat}Zn(d,x)^{64}Cu$	25 → 10	50
$^{66}Zn(d,\alpha)^{64}Cu$	13 → 7	6.6
$^{68}Zn(p,\alpha n)^{64}Cu$	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 method of choice

Specific Activity of Reactor Produced Radionuclides

often depends on

- **isotopic abundance of target isotope**
- **(n,γ) cross section**
- **neutron flux density**

- **Demand on specific activity depends upon the mode of accumulation of the labelled therapeutical at the tumour surface**
- **If receptor-based interactions are involved, a high dilution with the stable isotope cannot be tolerated**

Rare earth isotopes (lanthanoids) can be advantageously produced since the (n,γ) cross section is high.

- **Trivalent lanthanoids show affinity for tumours**

Improving the Specific Activity

Example: Samarium-153

($T_{½}$ = 46.3 h, E_{β^-} = 0.8 MeV, I_{β^-} = 100 %)

- *An important therapeutic radionuclide of increasing significance*

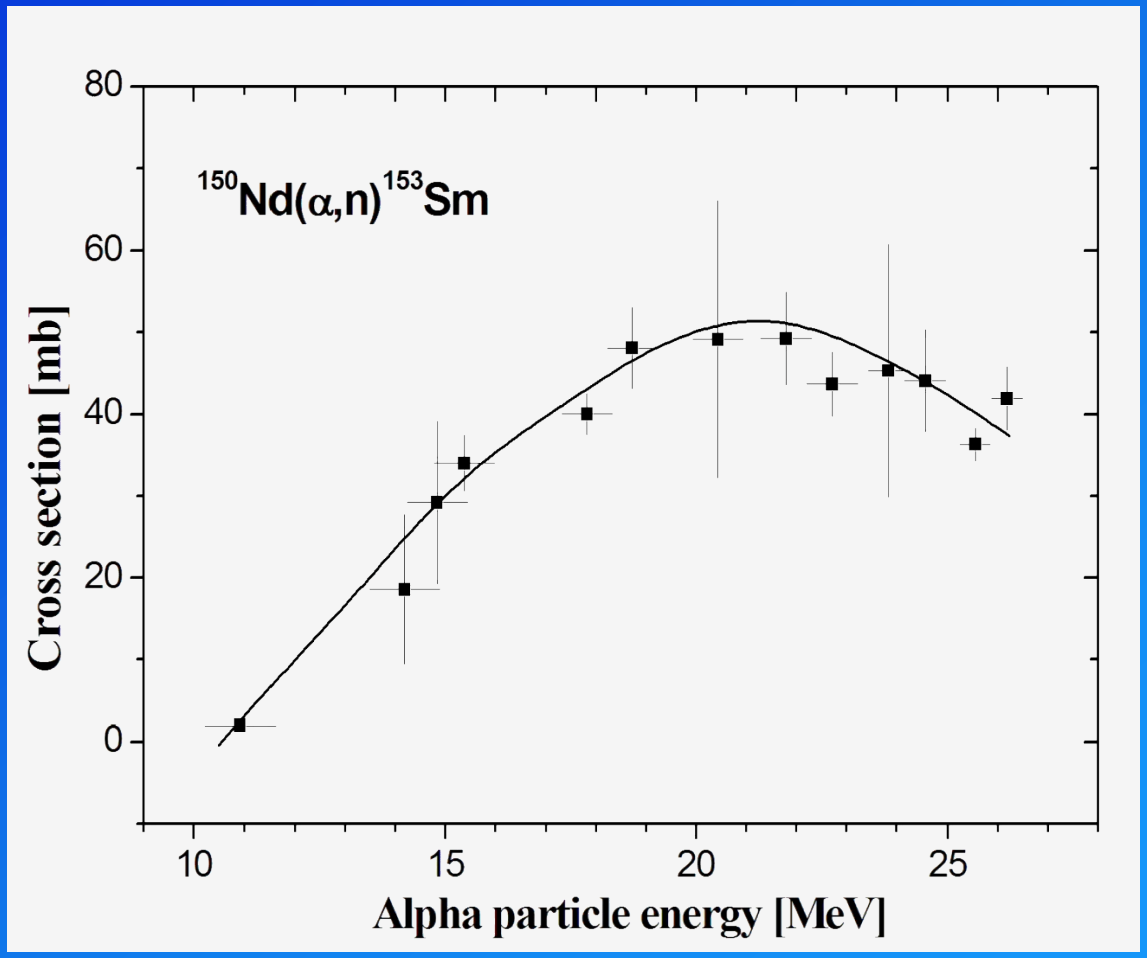
Commonly used production method:

$^{152}Sm(n,\gamma)^{153}Sm$

- high yield
- low specific activity

Sm-153

New Route: $^{150}Nd(\alpha,n)^{153}Sm$



^{153}Sm-yield:

(E_α = 25 → 15 MeV)
2.2 MBq/μA·h

- Production in GBq amounts possible
- Product: „no-carrier-added“

Palladium-103

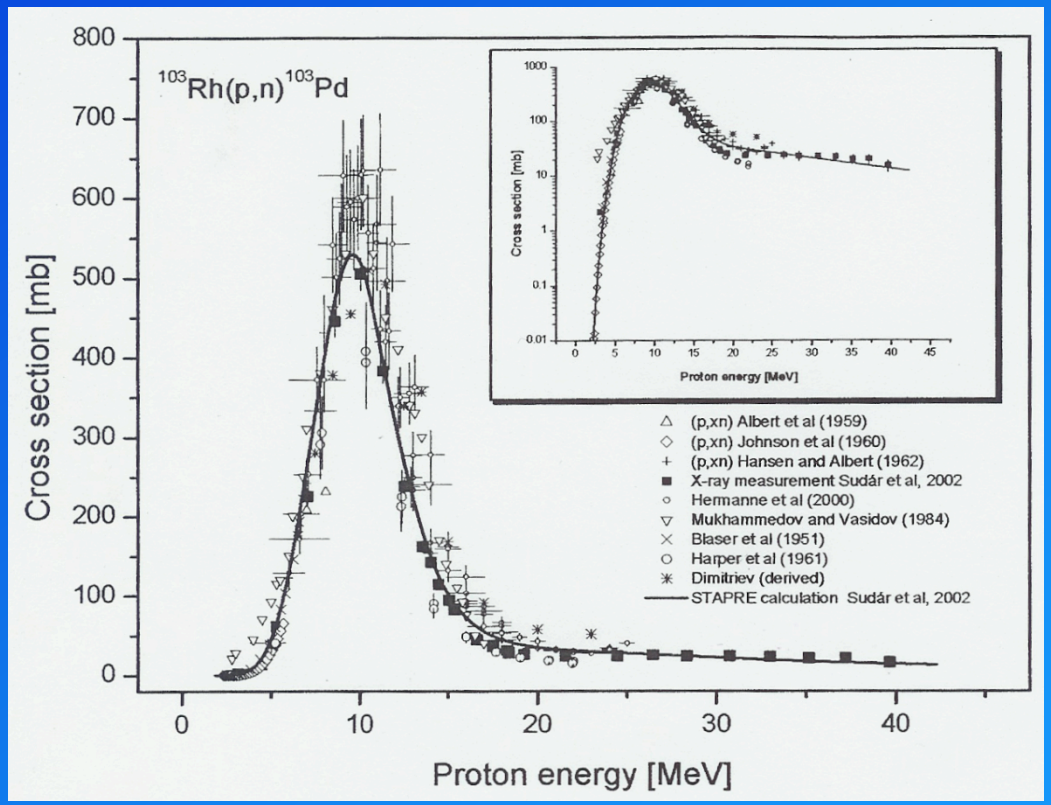
($T_{½}$ = 17.0 d; EC = 100 %; X-rays)

- *Extremely important radionuclide for prostate cancer treatment*

Measurement: Stacked-foil technique; X-ray-spectrometry

Theory: Hauser-Feshbach calculation (code: STAPRE)

Excitation Function



^{103}Pd-yield:

(E_p = 14 → 7 MeV)

6.6 MBq/μA·h

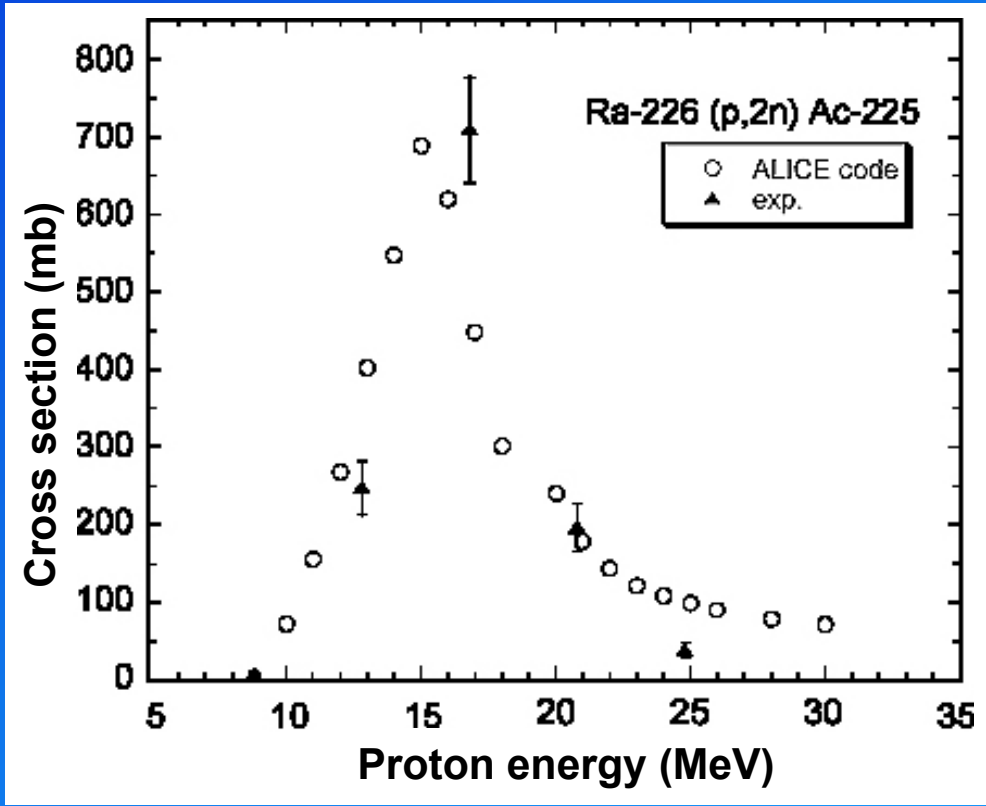
Establishing Novel Technology

Example: Actinium-225

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

Presently used Route: Separation from nuclear waste (Th-229)

New Route: $^{226}Ra(p,2n)^{225}Ac$



- Radioactive target
- Chemical processing very demanding
- **^{225}Ac-yield:**
  (E_p = 22 → 10 MeV)
  ca. 7 MBq/μA·h
- Production in GBq amount possible

Studies Related to Future Technologies

***Example*:** Measurement of σ(n,p) with 14 MeV „d(Be)-breakup“-neutrons

(Simulation study for production at a spallation neutron source)

Therapeutic radionuclide	Nuclear reaction	Reaction cross section (mb)	
		Fission neutrons	14 MeV d(Be) neutrons
^{32}P	^{32}S(n,p)^{32}P	69	152
^{67}Cu	^{67}Zn(n,p)^{67}Cu	1.07	5.13
^{89}Sr	^{89}Y(n,p)^{89}Sr	0.31	0.91
^{153}Sm	^{153}Eu(n,p)^{153}Sm	0.015	0.26

- ***Spallation neutron source would be more suitable than a fission reactor for production of therapeutic radionuclides via (n,p) process***

Development of Novel Therapeutic Radionuclides

***Example*: ^{149}Tb ($T_{½}$ = 4.1 h, E_α = 3.97 MeV, I_α = 16.7 %)**

- *Potentially interesting radionuclide due to low α-particle energy*

Production Methods

(a) ^{nat}Gd(p,xn)^{149}Tb (E_p > 100 MeV)

(b) ^{165}Ho(p,spall)^{149}Tb (E_p > 200 MeV)
Mass separation

(c) ^{141}Pr(^{12}C,4n)^{149}Tb (E > 120 MeV)

Production reactions are rather exotic; the yields are low; intensive chemical processing or mass separation is essential

Development of Novel Therapeutic Radionuclides

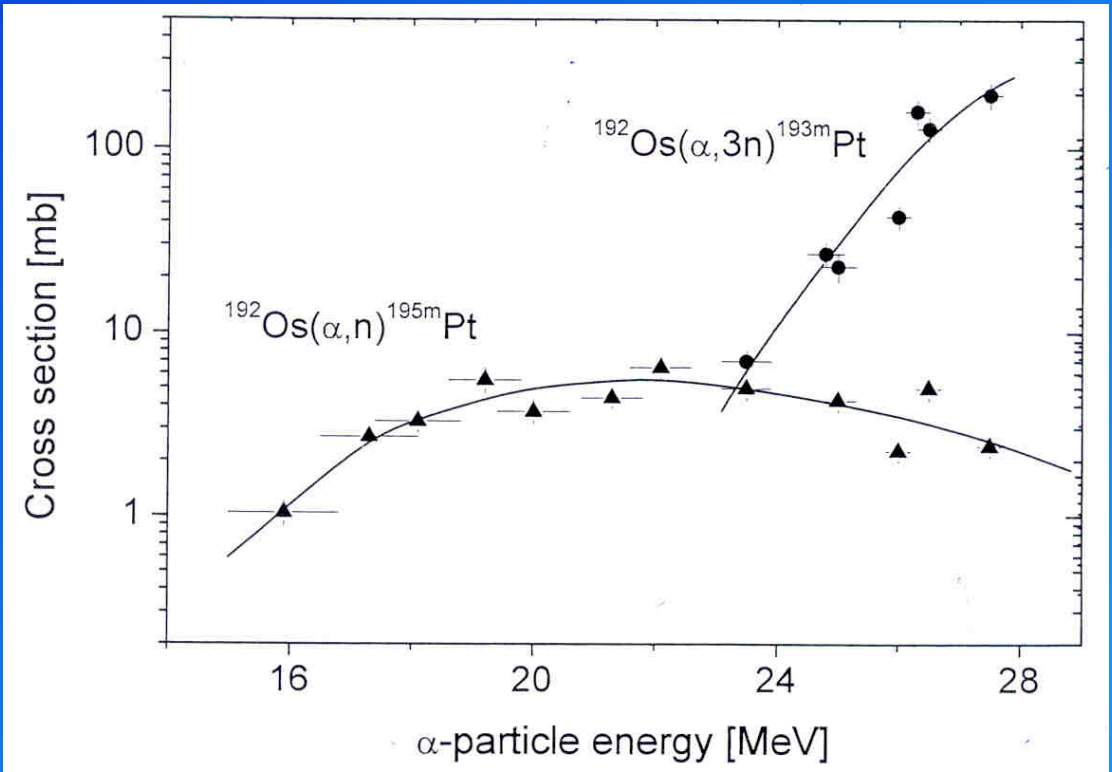
Examples: **^{193m}Pt** ($T_{½}$ = 4.33 d; Auger electrons ~ 33 per decay)

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

High-spin isomers

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

Excitation Functions



^{195m}Pt-yield:

$E_α$ = 24 → 18 MeV

0.013 MBq/μA·h

^{193m}Pt-yield:

$E_β$ = 28 → 24 MeV

0.25 MBq/μA·h

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

Combination of PET and Endoradiotherapy

- Internal radiotherapy using a pure β^- emitter (^{89}Sr, ^{90}Y, etc.) entails rather uncertain radiation dosimetry
- Mixing an isotopic β^+ emitter with the therapeutic radionuclide allows a better therapy planning through PET measurement of the β^+ emitter.

Examples : ^{86}**Y**(^{90}Y) ^{83}**Sr**(^{89}Sr)

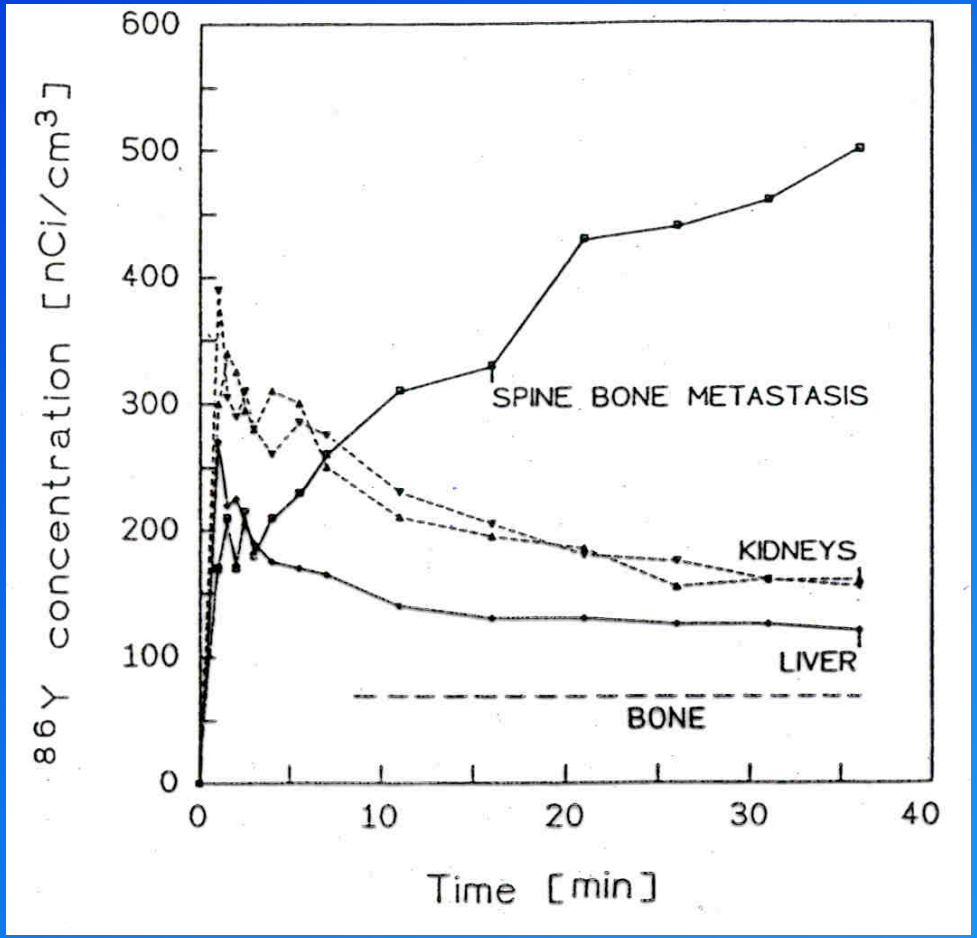
Production : ^{86}Sr(p,n)^{86}Y ^{85}Rb(p,3n)^{83}Sr

Production of the positron emitter is done using a cyclotron

Combination of PET and Endoradiotherapy

(Determination of Uptake Kinetics and Enrichment Factor)

- Addition of β^+ emitting ^{86}Y analogue to the therapy nuclide ^{90}Y
- Pharmacokinetic data obtained using PET



- Exponential uptake of [^{86}Y]-citrate in bone metastasis
- Enrichment factor (bone metastasis/normal bone): 8 (at 5h)

Accurate dosimetry and therapy planning possible

Conclusions and Perspectives

- Decay data of prime importance in choosing a therapeutic radionuclide; status of data generally good; more precise information on low-energy electrons may be needed.
- Production of commonly used therapeutic radionuclides mainly done using a nuclear reactor; strong need to enhance the specific activity. Some therapeutic radionuclides produced at accelerators.
- New demands related to low-energy high intensity radiation emitters. Considerable research and development work needed to produce them in required quality and quantity.
- Endoradiotherapy (ERT) is a fast developing field and has great potential. New chemical and biochemical concepts and ideas on tumour targeting are needed. A combination of PET and ERT leads to better therapy planning.