

INDC(NDS)-432 Distr.: MR

# INDC INTERNATIONAL NUCLEAR DATA COMMITTEE

# Summary Report of the Consultants' Meeting on Nuclear Data for Production of Therapeutic Radioisotopes

IAEA Headquarters Vienna, Austria 27 February to 1 March 2002

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April 2002

IAEA NUCLEAR DATA SECTION, WAGRAMER STRASSE 5, A-1400 VIENNA

Produced by the IAEA in Austria April 2002

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#### Abstract

This report summarizes the presentations, recommendations and conclusions of the Consultants' Meeting on Nuclear Data for Production of Therapeutic Radioisotopes. The purpose of this meeting was to discuss scientific and technical matters related to the subject and to advise the IAEA Nuclear Data Section (NDS) on the need and possible formation of a Coordinated Research Programme (CRP). Accurate and complete knowledge of nuclear data are essential for the production of radionuclides for therapy to achieve the specific activity and purity required for efficient and safe clinical application. The Consultants recommended updating and completing the data for production of radionuclides that are recognized to be important in therapy. In addition, the consultants recommend investigating other radionuclides that have a potential interest and for which there exists a medical rationale for the reactor and accelerator production of therapeutic radionuclides. The IAEA is in the unique and privileged position to address this important public health related problem. Therefore, the consultants highly recommend the formation of a CRP with the title: "Nuclear Data for Production of Therapeutic Radionuclides."

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# **1. OBJECTIVE AND AGENDA**

A Consultant's Meeting on Nuclear Data for Production of Therapeutic Radioisotopes was held at the IAEA Headquarters in Vienna, Austria, from 27 February to 1 March 2002. The purpose of the meeting was to discuss scientific and technical matters related to the subject and to focus on a description of specific research objectives that will serve as the basis for the preparation of the proposal.

Dr. F.F. Knapp of Oak Ridge National Laboratory, USA was elected as the chairman of the meeting. Dr. R.C. Haight of Los Alamos National Laboratory, USA was selected as rapporteur of the meeting. The detailed approved Agenda is attached (see Appendix 1). Other participating experts were Dr. A. Wambersie (Belgium), Dr. F. Tarkanyi (Debrecen, Hungary), and Dr. S.M. Qaim (Jülich, Germany). For the complete list of participants including affiliations and addresses see Appendix 2.

Dr. Alan Nichols, Head of the Nuclear Data Section, welcomed the participants and Dr. R. Paviotti-Corcuera, Scientific Secretary of the Consultants' Meeting, summarized the mechanisms and objectives of CRPs and the purpose of the meeting (see Appendix 3).

# 2. BIBLIOGRAPHICAL BACKGROUND

The IAEA has devoted considerable effort to improve the knowledge related to nuclear data for applications in medicine. Some of these activities are documented in the following reports:

Consultants' Meeting on Nuclear Data for Medical Radioisotope Production (IAEA, April 1981) Report INDC(NDS)-123.

Scope of the IAEA Nuclear Data Section Programme for Medical Applications. Advisory Group meeting on nuclear and atomic data for radiotherapy and related radiobiology. Okamoto, K. Proceedings of an advisory group meeting held in Rijswijk, Netherlands, 16-20 September 1985. Vienna (Austria). IAEA. 1987. 454 p. p. 5-25. Panel proceedings series.

IAEA Consultants' Meeting on Data Requirements for Medical Radioisotope Production. Tokyo (Japan). 20-24 Apr 1987, Okamoto, K. (ed.). Report INDC(NDS)-195/GZ.

Status Report on Cross-Sections of Monitor Reactions for Radioisotope Production, (IAEA, Vienna, 1989), Schwerer, O., Okamoto, K.(ed.). Report INDC(NDS)-218.

Advisory Group Meeting on Intermediate Energy Data for Applications, Working Group on Nuclear Data for Medical Applications (IAEA, Vienna, October 1990). Kocherov, N.P. (ed.) Report INDC(NDS)-245.

Status of Nuclear Data Needed for Radiation Therapy and Existing Data Development Activities in Member States. (IAEA, Vienna 9-11 December 1996). Kocherov, N.P. (ed.) Report INDC(NDS)-365.

Nuclear Data for Neutron Therapy: Status and Future Needs. IAEA-TECDOC-992. December 1997.

Handbook on Photonuclear Data for Applications: Cross-sections and Spectra. IAEA-TECDOC-1178, October 2000.

Charged Particle Cross-Section Database for Medical Radioisotope Production: Diagnostic Radioisotopes and Monitor Reactions. IAEA-TECDOC-1211. May 2001.

Other reports of note (not published by the IAEA or not specifically on nuclear) include:

Nuclear Data for Neutron and Proton Radiotherapy and for Radiation Protection. ICRU REPORT 63. March 2000.

Nuclear Data for Medical Applications. S.M. Qaim (Ed.), Radiochimica Acta. Vol-89 Special Issue. 4-5/2001.

Manual for Reactor Produced Radioisotopes IAEA- TECDOC (to be published).

Directory of Cyclotrons Used for Radionuclide Production in Member States, IAEA-TECDOC-1007 March 1998, update version to be published.

# 3. SUMMARY OF PRESENTATIONS

# **3.1.** Uses of Radionuclides in Therapy

A. Wambersie summarized the present situation in cancer therapy and other medical applications relevant to therapeutic applications of radionuclides. He discussed both the present place and expectations for the future for radionuclides.

Cancer management is a major medical and economical issue because of (1) the incidence of the disease and (2) selection and optimization of the treatment strategy. As an example in 1991, one million new cancer cases were detected in the United States (i.e., 400 per 100,000 of the population per year). The probability of death from cancer increases with the longevity of the population: the present estimates range between 25 and 30% for industrialized countries. This percentage is lower in developing countries, but it can be expected to increase as longevity is extended.

Experience shows that at the time of the first consultation, 30% of the patients already have disseminated disease and thus have a poor prognosis. Only 5% of these patients are cured, often after application of a complex combination of techniques that include chemotherapy, radiation therapy, immunotherapy and sometimes surgery. Among the 70% of the patients who still have localized disease at the time of the first consultation, 40% can be cured by surgery, radiation therapy or a combination of both techniques. However, 30% of these patients who have a localized form of the disease at the time of the first consultation die from their cancer. This group of patients with local failure constitutes the main challenge for new therapeutic approaches, in particular new developments in radiation therapy.

Wambersie continued with a short survey of the radiation therapy modalities.

External photon beam therapy: more than 80% of the cancer patients within industrialized countries are treated with radiation as part of their treatment. This percentage is lower in developing countries but there is evidence of an increase in some of them. External irradiation with photon beams delivered by linear accelerators, in energies from a few MV<sup>\*</sup> up to 20-25 MV, and is the present reference for radiation therapy modality. Fractionated irradiations over 4-6 weeks are applied. The benefit of any new technique should be evaluated by comparison with this reference therapy.

Brachytherapy ("Curietherapy"): sealed sources are used, including intracavitary and interstitial therapy. Intracavitary therapy takes advantage of natural cavities in the body to insert radioactive material, and deliver high doses to the "tumour" (target volume) while sparing the surrounding normal tissues. One of the best indications of intracavitary therapy is cervical carcinoma, for which, <sup>192</sup>Ir and <sup>137</sup>Cs sources are mainly used. The availability of high specific activity radioisotopes allows the design and production of sources of small size and is a major advantage in achieving high dose rates. Interstitial therapy implies the insertion of radioactive sources inside the target volume. <sup>192</sup>Ir wires are used, and <sup>103</sup>Pd and <sup>125</sup>I seeds have also been introduced for the treatment of cancer of the prostate (as permanent implants). This technique has experienced dramatic developments over recent years.

The recent use of sealed sources has shown great promise using catheter-based methods to prevent restenosis after transluminal angioplasty in coronary and peripheral arteries. Sources used for this application include <sup>192</sup>Ir and <sup>90</sup>Sr ( $^{90}$ Y).

Radionuclide therapy with unsealed sources: the use of unsealed sources is a promising field of development for radiation therapy. The main difference with the techniques summarized above (external beam therapy, brachytherapy) is that the use of unsealed sources achieves selectivity at the cellular level.

Metabolic therapy: administration of sodium iodide (<sup>131</sup>I) is a good example of the most efficient metabolic therapy due to the highly specific incorporation of iodine in the thyroid tissue. Bone seekers, such as <sup>89</sup>Sr, and, <sup>186</sup>Re and <sup>153</sup>Sm (attached to appropriate carrier) have been shown to be efficient for pain palliation in bone metastases.

Administration in cavities: <sup>32</sup>P colloids are useful for the treatment of some forms of arthritis, metastatic effusions, and so forth. In addition, complexes of <sup>90</sup>Y, <sup>186</sup>Re, <sup>188</sup>Re and <sup>169</sup>Er are routinely used in several countries for the treatment of painful synovial joint inflammation and can greatly improve the quality of life of the patient.

Radioimmunotherapy (RIT): RIT is the administration of radioisotopes chemically conjugated to antibodies or antibody-derived constructions such as small peptides. The antibodies can recognize and bind to antigen(s) of the tumour cells, serving as direct carriers for the radionuclide. RIT is a more challenging approach in therapy than in diagnosis because (1) higher activities are used (normal tissue toxicity), (2) non-uniform distribution of the radionuclide results in non-uniform dose distribution, (3) difficulty to deliver sufficient doses to the tumour cells, and (4) problems with the chemical stability of the radiolabeled compound.

RIT uses beta-, alpha-, and Auger-electron emitting radioisotopes. The most commonly used beta emitters are <sup>131</sup>I and <sup>90</sup>Y, and, there is no need to target every individual cell with these radioisotopes because the mean radiation range is 0.4-2.5 mm (i.e., "cross fire" can effectively

kill nearby cells). <sup>177</sup>Lu, <sup>153</sup>Sm and <sup>67</sup>Cu are promising alternatives, and are being evaluated in clinical trials.

Alpha emitters deliver very high-LET radiation in a range of 50-90 micrometers. Specific attachment to or incorporation into cancer cells is essential for successful applications and is indicated mainly for microscopic/subclinical disease. <sup>213</sup>Bi and <sup>211</sup>As are examples of alpha emitters used in clinical trials.

Auger-electron emitters such as <sup>125</sup>I provide short-range (nanometer), densely ionizing radiation from the resulting electron "cascade" phenomenon. This decay process is specifically efficient when incorporated into DNA strands.

In conclusion, there is a wide range of radionuclides in use or being proposed for therapeutic applications. The issue to be addressed is whether the nuclear data for the production of these nuclides at the appropriate specific activity and purity, as well as the relevant decay data, are adequate for safe and efficient medical applications.

# **3.2. Other Presentations**

S.M. Qaim outlined nuclear data development activities being pursued at Forschungszentrum Jülich, Germany in support of production of therapeutic radioisotopes. Although previous work has focused on diagnostic radioisotopes, considerable effort is now being devoted to therapeutic radioisotopes produced by accelerators. Positron emitters, are produced with cyclotrons in the proton energy range up to 70 MeV, both therapeutic radioisotopes such as <sup>124</sup>I as well as analogue tracers, such as <sup>86</sup>Y for biodistribution studies of beta-minus-emitting therapeutic radioisotopes like <sup>90</sup>Y,. The production of beta-minus-emitting radionuclides (e.g. <sup>67</sup>Cu and <sup>89</sup>Sr) by neutrons is shown to be favourable from neutrons of d+Be reaction at a deuteron energy of 14 MeV. Low energy beta-minus, Auger electron and X-ray emitters include <sup>67</sup>Cu via the <sup>68</sup>Zn(p,2p) and <sup>70</sup>Zn(p,alpha) reactions and <sup>103</sup>Pd via the <sup>103</sup>Rh(p,n) reaction. Reactions induced by <sup>3</sup>He and <sup>4</sup>He beams are also being studied.

R.C. Haight reported on reactions with higher energy accelerators. The Isotope Production Facility (IPF) at Los Alamos, USA will begin operation in about a year with an intense 100 MeV proton beam after modifications from the former 800 MeV proton beam facility. Radioisotopes will be made with greater purity and specificity and data are required for the completely new targetry. Fast neutrons from spallation neutron sources are being investigated for possible radioisotope production. The cross sections as a function of incident neutron energy can be measured by prompt gamma-ray production cross sections at the WNR/LANSCE facilities. Finally, radioisotope production as discussed at the 2000 Workshop on Applications of the proposed Rare Isotope Accelerator (RIA) was reported. This high energy (400 MeV/A), high-current heavy-ion accelerator will be able to make large quantities of almost any radioisotope. Because of the very wide range of possible reactions and radioisotopes, it was recommended that this type of radioisotope production facility not be included in a Coordinated Research Programme by the IAEA, as its scope would exceed IAEA resources.

F.F. Knapp discussed radioisotopes produced by reactors. He emphasized that of the approximately 250 reactors world-wide, 30% are in developing countries. Thus the possibility of producing radioisotopes for therapy is wide-spread. He also stated that because the incidence of specific diseases differs in different parts of the world, implying that the demand for various radioisotopes could vary significantly. Mr. Knapp referred to a report by Frost and

Sullivan, J. Nucl. Medicine **39**, 13N-27N (1998), where a very large increase (100-fold) in the use of therapeutic radioisotopes was projected from the 2000 to 2020. Applications of reactor-produced radioisotopes include cancer therapy, synovectomy (arthritis), coronary restenosis therapy (following angioplasty to prevent closure of the artery), bone-pain palliation, and bone-marrow ablation. Examples of radioisotopes include <sup>166</sup>Ho (from <sup>166</sup>Dy parent), <sup>177</sup>Lu, <sup>188</sup>Re (from <sup>188</sup>W generator), <sup>229</sup>Th and <sup>225</sup>Ac.

F. Tarkanyi outlined work by the Charged Particle Nuclear Data Group in ATOMKI. Using cyclotrons at several laboratories, production cross sections for 13 therapeutic radioisotopes and 13 analog (tracer) radioisotopes have been measured with proton, deuteron, and <sup>3</sup>He beams up to 70 MeV. This work includes extensive investigations of diagnostic radioisotopes that was the subject of the previous CRP on Charged-Particle Cross-Section Database for Medical Radioisotope Production: Production: Diagnostic Radioisotopes and Monitor Reactions.

More complete summaries of these presentations are given in Appendix 4.

# 4. SUMMARY OF DISCUSSIONS

# 4.1. Selection of Therapeutic Radionuclides

S.M. Qaim presented a list of therapeutic radioisotopes and their production routes based on a recent publication, S.M. Qaim, Radiochimica Acta **89**, 297 (2001). Other consultants added to this list, which was divided into two categories:

Therapeutic radioisotopes, which have established clinical use - *"Established Radioisotopes"*. Less commonly used but potentially interesting radioisotopes where medical application has been demonstrated - *"Emerging Radioisotopes"*.

The selected radioisotopes are listed in Tables 1 and 2, respectively.

Production routes include the use of both nuclear reactors and charged particle accelerators. When thermal neutron capture reactions are involved reactor facilities are required. Fast neutron reactions, can be produced in reactors as well as in accelerator facilities, with spallation sources (especially for those reactions with thresholds well above the peak in the fission neutron spectrum). Many radioisotopes can only be produced using charged particles.

The consultants felt that data for most of the neutron-induced reactions are presumed to be available in the literature. Therefore, emphasis will be focused on compilation, evaluation and recommended data presentation in a user-friendly form. The same applies to many of the charged-particle reactions; only a few will require new measurements.

Radionuclide	T 1/2	E <sub>max</sub> in MeV	Production route	R/A *
<sup>32</sup> P	14.3 d	1.7 β <sup>-</sup>	<sup>31</sup> Ρ(n,γ)	R
			<sup>32</sup> S(n,p)	R,A
<sup>89</sup> Sr	50.5 d	<b>1.5</b> β <sup>-</sup>	<sup>89</sup> Y(n,p)	R,A
			<sup>88</sup> Sr(n,γ)	R
<sup>90</sup> Y	2.7 d	<b>2.3</b> β <sup>-</sup>	<sup>90</sup> Zr(n,p)	R,A
			<sup>89</sup> Υ(n,γ)	R
			<sup>235</sup> U(n,f) <sup>90</sup> Sr-> <sup>90</sup> Y generator	R
<sup>103</sup> Pd	17.0 d	Auger electrons, x-rays	<sup>102</sup> Pd(n,γ)	R
			<sup>103</sup> Rh(p,n)	А
			<sup>103</sup> Rh(d,2n)	А
<sup>125</sup> I	60.0 d	Auger electrons	<sup>124</sup> Xe(n,γ) <sup>125</sup> Xe -> <sup>125</sup> Ι	R
<sup>131</sup>	8.0 d	<b>0.6</b> β <sup>-</sup>	<sup>130</sup> Te(n,γ) -> <sup>131</sup> Te -> <sup>131</sup> Ι	R
			<sup>235</sup> U(n,f)	R
<sup>137</sup> Cs	30.97 y	<b>0.5</b> β <sup>-</sup>	<sup>235</sup> U(n,f)	R
<sup>153</sup> Sm	1.9 d	<b>0.8</b> β <sup>-</sup>	<sup>152</sup> Sm(n,γ)	R
<sup>186</sup> Re	17.0 h	1.1 β <sup>-</sup>	<sup>185</sup> Re(n,γ)	R
			<sup>186</sup> W(p,n)	А
			<sup>186</sup> W(d,2n)	А
<sup>188</sup> Re	17.0 h	<b>2.0</b> β <sup>-</sup>	<sup>186</sup> W(n,γ)-> <sup>187</sup> w(n,γ) <sup>188</sup> W	R
			->-> <sup>188</sup> Re generator	
			<sup>187</sup> Re(n,γ)	R
<sup>192</sup> lr	73.8 d	0.7 β <sup>-</sup>	<sup>191</sup> lr(n,γ)	R
			<sup>192</sup> Os(p,n) <sup>192</sup> Ir **	А

TABLE 1. ESTABLISHED THERAPEUTIC RADIOISOTOPES

\*(R = Reactor, A= Accelerator). Reactors are usually used for (n,p) reactions, but accelerator production would also be possible if the neutron production is sufficiently intense.
 \*\* New measurement required.

Radionuclide	T <sub>1/2</sub>	E <sub>max</sub> in MeV	Production route	R/A/Decay *
<sup>64</sup> Cu	12.7 h	<b>0.6</b> β⁻	<sup>63</sup> Cu(n,γ)	R
		<b>0.7</b> β <sup>+</sup>	<sup>64</sup> Ni(p,n)	A
			<sup>64</sup> Ni(d,2n)	А
			<sup>64</sup> Zn(n,p)	R
<sup>67</sup> Cu	2.6 d	<b>0.6</b> β <sup>-</sup>	<sup>67</sup> Zn(n,p)	R
			<sup>68</sup> Zn(p,2p)	A
			<sup>70</sup> Zn(p,alpha)	A
<sup>114m</sup> ln	49.5 d	Auger electrons	<sup>113</sup> In(n,γ)	R
			<sup>114</sup> Cd(p,n) **	A
			<sup>114</sup> Cd(d,2n) **	A
<sup>124</sup>	4.2 d	<b>2.1</b> β <sup>+</sup>	<sup>124</sup> Te(p,n)	A
			<sup>124</sup> Te(d,2n)	A
			<sup>125</sup> Te(p,2n)	А
<sup>166</sup> Ho	26.8 h	<b>1.9</b> β <sup>-</sup>	<sup>165</sup> Ho(n,γ)	R
			<sup>164</sup> Dy(n,γ)-> <sup>165</sup> Dy(n,γ)->	R
			-> <sup>166</sup> Dy -> <sup>166</sup> Ho	
<sup>169</sup> Yb	32.0 d	Auger electrons	<sup>168</sup> Υb(n,γ)	R
			<sup>169</sup> Tm(p,n) **	А
<sup>177</sup> Lu	6.7 d	<b>0.5</b> β <sup>-</sup>	<sup>176</sup> Lu(n,γ)	R
			<sup>176</sup> Yb(n,γ) <sup>177</sup> Yb-> <sup>177</sup> Lu	R
<sup>211</sup> At	7.2 h	5.9 α	<sup>209</sup> Bi(α,2n)	A
<sup>213</sup> Bi	45.6 m	8.4 α	decay of <sup>225</sup> Ac	D
<sup>225</sup> Ac	10.0 d	5.8 α	<sup>226</sup> Ra(p,2n) **	А
			decay of <sup>233</sup> U -> <sup>229</sup> Th	D

TABLE 2: EMERGING THERAPEUTIC RADIOISOTOPES

\*(R = Reactor, A= Accelerator). Reactors are usually used for (n,p) reactions, but accelerator production would also be possible if the neutron production is sufficiently intense. \*\* New measurement required

# 4.2. Specific Research Objectives and Tasks

A basic need will be the microscopic data, i.e. isotopic cross sections. Usually energy and spectrum-integrated data are used, and therefore the integrated data needs to be deduced from the microscopic cross sections and compared with the experimentally available integral data.

Reactor-produced radioisotopes:

- compile and evaluate the cross section as a function of the energy in the energy range 0-20 MeV to generate pointwise numerical data and graphical data with recommended evaluated cross sections.
- deduce spectrum-averaged data in the conventional way for thermal neutrons and validate the data by comparison with experimentally measured data from the literature (see Note).
- carry out new measurements when required.

Accelerator-produced radioisotopes:

- present cross sections as a function of energy in the energy range up to 40 MeV (except for a few cases where the energy range needs to go to 100 MeV) by generating pointwise numerical and graphical data with recommended evaluated cross sections.
- deduce from the microscopic cross sections the integral yield data as a function of incident energy, and generate pointwise numerical and graphical data with recommended evaluated cross sections.
- compare the deduced integral yields with the experimental thick target yields available in the literature.
- carry out new measurements when required.

All cases:

- experimental data and references collected in the compilation that are not already in the EXFOR library must be conveyed by the compiler to the IAEA Nuclear Data Section for inclusion in the EXFOR library.
- final form of the database has to be in the standard form (ENDF/B-6) to permit retrieval, graphical and checking capabilities of the data centers.
- there could be problems related to the specific activity and the presence of impurities, this issue should be addressed when considered important for the therapeutic application.
- decay data (half-lives, beta-decay energy spectrum, gamma-ray emission probabilities, Auger electron spectra, etc.) of the therapeutic radioisotopes must be checked and the data from the most recently published evaluation included. (e.g., MIRD, ICRU report on "Absorbed-Dose Specification in Nuclear Medicine" in press).

# 4.3. Possible Participants and Proposed Principles of Support

The programme requires participants in two distinct fields: evaluation of charged-particle induced reactions and evaluation of neutron-induced reactions. The production method, irradiation technology and evaluation process differ from the two kinds of particles. Hence, we propose specific participants for both fields. Attention should also be given to the decay properties of the radioisotopes.

The final product (i.e., the preparation of evaluated data files) requires special expertise, which is available in nuclear data centers and nuclear data groups.

This large volume of work can only be successful if completed with the participation of groups with well-proven experience in fields relevant to the aims of the proposed research programme and with the active assistance and coordination of the IAEA.

# 4.4. Expected Research Outputs

- Electronic database for use in Production of Therapeutic Radionuclides. (Radionuclide, production route, validated evaluated cross sections as a function of energy, decay data (half-lives, beta-decay energy spectrum, gamma-ray emission probabilities, Auger electron spectra, etc).Dataa in ENDF-6 format).
- Printed version of the database.
- TECDOC report.
- IAEA-NDS Worldwide Web online access to database.

# 4.5. Possible Participating Laboratories:

- Australian Nuclear Science and Technology Organization, ANSTO, Sydney, Australia
- Brookhaven National Laboratory, Upton, NY, USA
- China Institute of Atomic Energy, Beijing, China
- Comision Nacional de Energia Atomica (CNEA), Buenos Aires, Argentina
- Forschungszentrum Jülich GmbH, Jülich, Germany
- Institute of Nuclear Research (ATOMKI), Debrecen, Hungary
- Institute of Physics and Power Engineering, Obninsk, Russia
- Instituto Pesquisas Energeticas e Nucleares (IPEN), São Paulo, Brazil
- Japan Atomic Energy Research Institute, Tokai Mura, Japan
- Korea Atomic Research Institute, KAERI, Seoul, Korea
- Los Alamos National Laboratory, Los Alamos, USA
- Milano and ISPRA, Italy
- NAC, Faure, South Africa
- Oak Ridge National Laboratory, Oak Ridge, USA
- Research Institute of Atomic Reactors, Dimitrovgrad, Russia
- TRIUMF, Vancouver, Canada
- Vrije Universiteit Brussel, Brussels, Belgium

#### 5. CONCLUSIONS

The consultants appreciated the need for interdisciplinary collaboration involving radioisotope production, chemical processing, and specialists in nuclear medicine to assess the issues involved in recommending a Coordinated Research Programme that addresses the production of therapeutic radioisotopes. Accurate and complete knowledge of nuclear data are essential for the production of therapeutic radioisotopes with the specific activity and purity required for efficient and safe clinical application. No serious effort has ever been devoted to the evaluation of nuclear data for the reactor and accelerator production of therapeutic radioisotopes, and no other organization (e.g., NEA, International Radiological Society, Society of Nuclear Medicine, etc.) have addressed this topic thus, the IAEA is in the unique and privileged position to attend to this important public health related problem. The Consultants strongly recommend the implementation of a Coordinated Research Programme with the title: "Nuclear Data for Production of Therapeutic Radionuclides."

# 6. APPENDICES

#### **Appendix 1: Agenda**

# International Atomic Energy Agency Consultant's Meeting on

#### "Nuclear Data for Production of Therapeutic Radioisotopes"

# IAEA Headquarters, Vienna, Austria 27 February to 1 March 2002 Meeting Room F01-23

## AGENDA

#### Wednesday, 27 February

**09:00 - 09:20** Registration (IAEA Registration at the Entrance in Check Point 1)

## 09:30 - 10:30 Opening Session:

- Welcome address by Alan Nichols, Head, Nuclear Data Section (NDS)
- Round table self-introduction by the participants
- Election of Chairman and Rapporteur
- Discussion and adoption of Agenda (Chairman)
- General remarks about IAEA CRPs and objective of the CM (Scientific Secretary: R. Paviotti Corcuera)

## 10:30 - 10:45 Coffee break

#### 10:45 - 12:15 Session 1:

Presentations by Participants (15 minutes for each presentation and 5 minutes for discussion)

- 1. *Radionuclides for Therapeutic Applications: Biological and Medical Aspects Andre Wambersie*, Service de Radiotherapie Universite Catholique de Louvain Belgium
- 2. Recent Nuclear Data Development Work at Forschungszentrum, Jülich in Support of Production of Therapeutic Radionuclides. Syed M. Qaim, Forschungszentrum Jülich GmbH, Germany
- 3. Nuclear Data Needs for the Production of Radiotherapeutic Isotopes with Higher Energy Accelerators. **Robert C. Haight**, Los Alamos National Laboratory, USA
- 4. *Reactor-Produced Therapeutic Radioisotopes.* F. F. (Russ) Knapp, Jr. Oak Ridge National Laboratory, USA
- 5. Production and Application of Therapeutic Radioisotopes: Activity on the Related Nuclear Reaction Data. Ferenc Tarkanyi, Hungarian Academy of Sciences, Debrecen, Hungary



International Atomic Energy Agency

Consultants Meeting on

## "Nuclear Data For Production of Therapeutic Radioisotopes"

27 February - 01 March 2002, IAEA Headquarters, Vienna, Austria

#### BELGIUM

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## Appendix 3: Framework of a CRP and Objective of the Meeting Handouts









#### Task 1... Task 2... Task 3...

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Expected research outputs (results)

# Description of the products expected to emerge from the CRP

e.g. Electronic database Printed version TECDOC IAEA Web access

Country and Laboratory if possible, e.g.: USA, Lawrence Berkley National Laboratory Chile, Comision Nacional de Energia Atomica Hungary, Chemical Research Center France, Commissariat à l'Energie Atomique



## **Appendix 4: Extended Abstracts of Presented Papers**

Radionuclides for Therapeutic Applications: Biological and Medical Aspects. *Andre Wambersie* 

Recent Nuclear Data Development Work at Forschungszentrum Jülich in Support of Production of Therapeutic Radionuclides. *Syed M. Qaim*,

Nuclear Data Needs for the Production of Radiotherapeutic Isotopes with Higher Energy accelerators. *Robert C. Haight*,

Reactor-Produced Therapeutic Radioisotopes. F. F. (Russ) Knapp, Jr.,

Production and Application of Therapeutic Radioisotopes: Activity On The Related Nuclear Reaction Data. *Ferenc Tarkanyi* 



IAEA Consultant's Meeting on "Nuclear Data for Production of Therapeutic Radioisotopes", Vienna, 27 Feb.-1 March 2002

Radionuclides for therapeutic applications : biological and medical aspects (present status, development and expectations)

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## 1. Introduction

Different multidisciplinary therapeutic strategies and technical approaches are used today in cancer therapy. Among the techniques involving ionizing radiation, therapeutic applications of radioactive nuclides deserve a particular interest : some clinical indications are well established, while several others are now being investigated, and some of them are promising.

The efficacy of radionuclides in therapy often depends on technical factors such as specific activity, purity, chemical presentation, availability, etc. These factors are closely related, at least partly, to the production methods. This justifies the organization of the present Consultant's meeting by the IAEA.

Brief information on cancer, its socio-economic aspects, and some data concerning cure rate are presented first. 2. Incidence and socio-economical relevance of cancer

Cancer was known to exist in antiquity. A bone tumour has been observed in a 14-year-old pharaoh who succumbed and was mummified, only to be accurately diagnosed three millennia later. Chinese and Arabic medical writings also document clinical cases so well that some can clearly be identified today as cancer from the description [9]. The appearance of infiltration, like legs of a crab, gave rise to the name "cancer" in the times of Galen (130-200 A.D.).

However, with increasing longevity of the population resulting from improved control of epidemic and infectious diseases, the frequency of cancer and the often associated suffering has raised the cancer awareness in the  $20^{th}$  century.

In developing countries, cancer cases have risen from 2 million in 1985 to 5 million in 2000, and are projected to number 10 million in 2015. By contrast, in developed countries, where there were 5 million cases in 1985 as well as in 2000, no increase is projected to 2015.

For example, in the USA, in 1991, more than one million invasive cancers occurred, i.e. an incidence of about 400 per 100,000 per year. In addition, more than 600,000 non-melanomatous skin cancers occurred; most of them can now be cured. In developed countries, the probability of dying from cancer is 20-25 % and is expected to further increase. 3. Cancer cure rate and role of radiation therapy (short review)

At the time of the first consultation, 70 % of the patients still have a localized disease. Among them, 40 % (i.e. about ~2/3) are cured mainly by surgery, radiation therapy of a combination of both techniques. As a multidisciplinary approach is more and more frequently adopted in modern cancer therapy strategies, it becomes less relevant to try to identify the relative merits of the different techniques.

At the time of the first consultation, 30 % of the patients have already disseminated disease (distant metastases). However, among them, 5 % can be cured, often after application of complex techniques combining chemotherapy, radiation therapy, immunotherapy and sometimes surgery.

In total, today 55 % of the patients die from their cancer (Table 1). One has to stress that, in this group 30 % had only localized disease at the time of the first consultation. They thus die from their cancer because of the failure of the first (local) treatment (surgery or radiation therapy). Improving these results is an important challenge/target for new radiation therapy modalities, for the coming years, including application of radionuclides under different forms.

In the industrialized countries, about 70 % of the cancer patients are referred today to radiation therapy, sometimes as the sole treatment or often as part of a combined treatment involving surgery and/or chemotherapy. This percentage is lower in developing countries but it improves in some of them.

Table 1

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Cancer cure rate : today situation (schematic) Among 100 cancer patients •70 % have still a localized disease at the time of the first consultation ••40 % (~2/3) are cured by surgery and/or radiation therapy ••30 % (~1/3) die due to local failure •30 % have already a disseminated disease at the time of the first consultation ••5 % can be cured by complex, multidisciplinary treatment Total cure rate : 45 % Total failure rate : 55 %

#### 4. The radiation therapy techniques

The role and the potential benefit of any new radiation therapy modality has to be evaluated relative to the other recognized techniques.

4.1 External beam therapy

More than 80 % of the patients referred today to radiation therapy departments are treated with external <u>photon</u> beam therapy, at least for part of their treatment.

Treatment is delivered with photon beams produced by linear accelerators with energies ranging from a few MV up to 20-25 MV. Fractionated irradiation, over 4-6 weeks, is currently applied. The benefit of any new proposed technique needs to be evaluated by comparison with this reference therapy modality [4].

Recently complex photon beam therapy techniques have been introduced, such ad IMRT (Intensity Modulated Radiation Therapy), tomotherapy, "gamma knife, etc. These new techniques intend to match, as closely as possible, the "Treated Volume" to the Planning Target Volume [6][8].

Other beam qualities have been introduced in external beam therapy to improve :

(1) the physical selectivity of the irradiation : electron beam, proton beams, etc;

(2) the radiobiological selectivity of the irradiation (at least for some tumour types) : fast neutron beams, heavy-ion beams (carbon, neon, etc).

4.2 Brachytherapy with sealed sources

Brachytherapy techniques, with sealed sources, include intracavitary therapy and interstitial therapy.

Intracavitary therapy takes advantages of natural cavities to insert radioactive material close to the invaded organs. It allows to deliver high doses to the Planning Target Volume, while sparing the surrounding normal tissues (see definitions in Appendix).

One of the best indications of intracavitary brachytherapy is treatment of cervical carcinoma [3]. Applications were initially using radium, they are today performed with <sup>137</sup>Cs and <sup>192</sup>Ir (Fig.1) Purity requirements are important for <sup>137</sup>Cs sources. High specific activity of <sup>192</sup>Ir allows preparation of small size sources, which is a definitive advantage specifically for afterloading, high-dose-rate(HDR) applications.

Intracavitary applications are also performed for oesophagus and bronchus cancer, mainly for palliative purposes. A new technique, which became rapidly popular in cardiology, consists of inserting radioactive material into arteries to prevent restenosis after angioplasty. "Endovascular brachytherapy" is performed for coronary and peripheral (femoral) arteries. Beta-and gamma emitters are used for that purpose [11][12].

Interstitial brachytherapy, using sealed sources, implies insertion of a number of radioactive needles, wires or seeds into the Planning Target Volume. High doses can be delivered to this volume, avoiding irradiation of the surrounding normal tissues. Needles and wires are removed after the appropriate computed time (*temporary implants*); seeds can be left in situ (*permanent implants*)(Fig 2)[5].



#### Fig 1.

Typical dose distributions for an intracavitary application used for the treatment of cervix carcinoma. The dose distributions obtained for radium and <sup>192</sup>Ir are very similar. Doses are very high in the immediate vicinity of the sources; they decrease rapidly with the distance, following the "inverse square law". As a consequence, irradiation of "organs at risk" such as bladder and rectum is reduced. (ICRU, Report 38, 1985)[3]



#### Fig.2

Seed implant with 68 <sup>125</sup>I seeds of 19.2 MBq each; total activity 1310 MBq. Dose distribution computed in the central plane of the application perpendicular to the cranio-caudal axis. Only the isodoses encompassing the seeds are shown.

The technique of permanent seed implant for the treatment of prostatic cancer has become very popular. <sup>125</sup>I were used initially, <sup>103</sup>Pd seeds have been introduced more recently. These two radionuclides emit very low energy x rays, 28 and 21 keV (average energy) respectively. These low-energy x rays are rapidly absorbed by the patient tissues and do not constitute a radioprotection hazard for the staff and family. The two radionuclide have different half-lives, 60 days and 17 days for <sup>125</sup>I and <sup>103</sup>Pd, respectively. The therapeutic consequences of this difference in half-lives (thus dose-rates) still needs to be evaluated.

(from Wambersie and Battermann, 2001)[13]

4.3 Unsealed sources of radionuclides for therapy applications

In contrast with external beam therapy and brachytherapy with sealed sources (where both cancer cells and normal tissues are included in the PTV), administration of radionuclides, as unsealed sources, aims at a <u>selectivity at a cellular level</u>.

Among the numerous unsealed radionuclides in use, or in development for therapy, only some of the most frequently applied and some other ones used in radioimmunotherapy could be reviewed.

#### Iodine-131

The current recognized indications for <sup>131</sup>I therapy are for both benign and malignant disease. They are based on a <u>most selective affinity</u> of the thyroid tissue for iodine. <sup>131</sup>I for hyperthyroidism is used to treat diffuse toxic goiter (Graves' disease), toxic nodular goiter, and solitary toxic nodule.

For malignant thyroid conditions, the indications for <sup>131</sup>I are postoperative ablation of residual normal thyroid remnants, treatment of microscopic residual disease postoperatively, treatment of recurrent disease and treatment of metastatic disease.

Meta-iodobenzylguanidine (<sup>131</sup>I-MIBG) has been investigated for treatment of pheochromocytomas and other neuroendocrine lesions such as neuroblastoma, carcinoid, medullary thyroid carcinoma and paraganglioma.

# Phosporus-32

As a well established indication, <sup>32</sup>P (sodium phosphate) is used for intravenous administration for polycythemia vera and thrombocytosis.

Colloidal chromic <sup>32</sup>P has multiple indications based on intracavitary administration and its lack of systemic absorption. The most common use is as adjuvant therapy of intraperitoneal metastasis from ovarian or endometrial carcinoma. Chromic <sup>32</sup>P is also used to treat malignant pleural effusions, pleural mesotheliomas and malignant pericardial effusions. Cystic craniopharyngiomas are another indication for colloidal <sup>32</sup>P.

#### Strontium-89

"Sr is used for palliation of pain in bone metastases. "Sr is an analog of calcium and concentrates in osteoblastic bone cancer lesions. After intravenous injection of ionic "Sr, it is rapidly cleared from the blood and about 50 % of the injected activity is deposited in bone. Normal bone appears to take up only a small fraction of the administered activity and retains it for much shorter period of time compared to the osteoblastic bone lesions.

Hormonal treatment may be combined with <sup>89</sup>Sr. External beam therapy may also be combined for local management of severely painful sites.

# Rhenium-186

<sup>186</sup>Re has been complexed with a bone-seeking phosphorate to form <sup>186</sup>Re-HEDP (hydroxy- ethylene- diphosphorate). It has been used in patients with bone metastases from breast and prostate cancer.

<sup>186</sup>Re-labeled monoclonal antibodies have been used for intraperitoneal administration in metastatic ovarian carcinoma.

#### Radioimmunotherapy (RIT)

Radioimmunotherapy refers to the therapeutic administration of radionuclides chemically conjugated to antibodies or antibody-derived constructions. The antibodies can recognize and bind to antigen(s) on tumour cells and usually serve as direct carriers for the radionuclide [10].

In principle, all tumour sites throughout the body are irradiated, with relative sparing of normal tissues.

The use of radiolabeled antibodies for therapy has been more challenging than for diagnostic purposes for a variety of reasons including : -normal tissue toxicity due to the larger radionuclide activities that are administered in therapy; -the heterogeneity of the radionuclide distribution that results in a non-uniform dose distribution (this is generally not an issue for diagnosis provided that the tumour/background ratio is sufficient for tumour detection); -the difficulty to deliver tumoricidal doses, especially to solid tumours, with acceptable toxicity.

In principle, different types of radionuclides are suitable for radioimmunotherapy.

# <u>Beta emitters</u>

(such as <sup>131</sup>I and <sup>90</sup>Y) have been the most popular radionuclides for clinical RIT trials. There is no need to target every individual cancer cell since the mean radiation range is about 0,4 to 2,5 mm (possibility of "cross fire" irradiation). Alternatives that are being tested include : <sup>177</sup>Lu, <sup>153</sup>Sm and <sup>67</sup>Cu.

#### <u>Alpha emitters</u>

produce high-LET radiations with a limited range of 50-90 •m. They are promising particularly to treat microscopic disease; for large GTVs the radionuclide distribution may not be uniform (in contrast with the beta emitters, a uniform distribution of the alpha emitting radionuclides is necessary because of the lack of "cross fire").

The available alpha emitters have a relatively short half-life :  $t_{1/2} = 45.6$  minutes for <sup>213</sup>Bi, 61 minutes for <sup>212</sup>Bi and 7.2 hours for <sup>211</sup>At. Because of their short half-life, a significant proportion of the atoms may decay before reaching their target (this is an argument in favor of BNCT) [2]. As an alternative approach, alpha emitters can be injected in the tumor itself.

#### <u>Auger-electron-emitters</u>

are released as a consequence of the cascade of inner shell vacancy transitions initiated by the creation of an inner atomic shell vacancy by either electron capture or internal conversion processes. Very lowenergy electrons (< 5 keV), generated by ultrasoft xray interactions, have a high RBE because of the local clustering of ionization events.

Auger emitters are especially toxic if the targeting molecule localizes in the nucleus of the target cell and preferably comes to direct contact with the DNA. Nucleosides or nucleoside analogs, labeled with Auger emitters, may be incorporated into DNA during Sphase.

Compared to alpha emitters, Auger emitters produce a different geometric distribution of the ionizations. The tracks of the alpha particles are linear and have ranges expressed in tens of micrometers. The distribution of ionizations following the decay of an Auger-electron emitter is anisotropic with effective ranges expressed in nanometers.

A number of radionuclides have been considered and investigated for therapeutic applications in the for of unsealed sources. Only part of them could have been cited in this short review (see in particular : [1][7][10]).

# <u>Appendix : ICRU recommendations on concepts in</u> <u>radiation therapy : definition of relevant volumes</u>

A malignant tumour cannot be considered as a volume (sphere, "ball") which would contain ALL cancer cells and ONLY cancer cells, the normal cells/tissues/ structures being located outside the shell of that sphere/ball. In order to avoid frequent confusion between the "clinically detectable" tumour and the volume with "subclinical invasion", as well as to take into account all uncertainties in radiation therapy delivery, the ICRU has recommended the following definitions that are now accepted worldwide by the radiation therapy community.

#### Gross Tumour Volume

The Gross Tumour Volume (GTV) is the gross palpable, visible or clinically demonstrable location and extent of the malignant growth. Its shape, size and location may be determined by clinical examination, CT, MRI or other imaging techniques.

# Clinical Target Volume

The Clinical Target Volume (CTV) includes the GTV and a "safety margin" to take into account subclinical (microscopic) invasion of cancer cells (Fig.3).

#### <u>Planning Target Volume (PTV)</u>

Around the CTV, an additional "safety margin" has to be added in order to take into account all uncertainties during the successive steps of the therapy procedures (e.g., physiological organ movements, inaccuracy in patient beam positioning, etc).

(Ref : ICRU Reports [4][6][8])



#### Fig 3

Schematic illustration of the relation between GTV(s) and CTV(s) in different clinical situations.

a)Simple case with one GTV and the corresponding CTV (for example skin tumour). At the level of the GTV (black), the cellular density is the highest (as an average, about 10° cells per mm<sup>3</sup>), but may be heterogeneous (e.g. due to necrosis). The width of the safety margin is selected so that, in principle, no cancer cell is present outside the limits of the CTV. The cancer cell density decreases between the border of the GTV and the outer limit of the CTV, but the variation of the cell density with distance is not known and depends on tumour type and location. In some situations, a natural anatomical border may limit subclinical extension, e.g., parietal pleura in mediastinal lymphoma.

b) Two GTVs are present : the primary tumour, GTV-T, and a metastatic fixed lymph node, GTV-N (for example, a tumour of the tonsil with a homolateral cervical lymph node). A safety margin for microscopic invasion has to be taken around each GTV which leads to the definition of two CTVs : CTV-T corresponding to the primary tumour and its safety margin, and CTV-N for the lymph node and its safety margin. Actually, since in this example the two CTVs are close to each other and because there are certainly malignant cells between the two GTVs, only a single CTV is selected (CTV-TN), which includes the two GTVs and a common safety margin. (ICRU, [8])

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# Recent Nuclear Data Development Work at Forschungszentrum Jülich in Support of Production of Therapeutic Radionuclides

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An extensive nuclear data development programme, with particular reference to medical applications, has been under way at Jülich for more than two decades. The emphasis has been previously on diagnostic radionuclides [cf. 1]. In recent years, however, considerable effort has been devoted to therapeutic radionuclides as well [cf. 2]. A brief outline of the activities in this direction is given below.

# A. $\beta^+$ - emitters as analogues of the rapeutic radionuclides.

In endotherapy with purely  $\beta^-$ -emitting particles, therapy planning and dosimetry could be done advantageously using a  $\beta^+$ -emitting analogue. Two radionuclides developed in this regard are <sup>83</sup>Sr (T<sub>1/2</sub> = 32.4 h; I<sub>β+</sub> = 24 %; E<sub>β+</sub> = 1.2 MeV) and <sup>86</sup>Y (T<sub>1/2</sub> = 14.7 h; I<sub>β+</sub> = 33 %; E<sub>β+</sub> = 1.2 MeV). The former is an analogue of the therapeutic radionuclide <sup>89</sup>Sr (T<sub>1/2</sub> = 50.5 d) and the latter of <sup>90</sup>Y (T<sub>1/2</sub> = 64.1 h). <sup>86</sup>Y is produced largely via the <sup>86</sup>Sr(p,n)-reaction at a smallsized cyclotron (E<sub>p</sub> = 14  $\rightarrow$  10 MeV) and the data have been measured [3]. For the production of <sup>83</sup>Sr, however, the reaction <sup>85</sup>Rb(p,3n) at a medium-sized cyclotron (E<sub>p</sub> = 37  $\rightarrow$  30 MeV) has been utilized. In this case the number of competing reaction channels is large. A careful detailed study on all the (p,xn) reactions on <sup>85</sup>Rb up to 100 MeV was therefore performed in collaboration with NAC, Faure, South Africa, to determine the optimum production conditions for <sup>83</sup>Sr [4].

# **B.** $\beta^+$ - emitters as the rapeutic radionuclides

A few  $\beta^+$ -emitters have found use as therapeutic radionuclides. Two major examples are <sup>64</sup>Cu (T<sub>1/2</sub> = 12.7 h; I<sub>β+</sub> = 18 %; E<sub>β+</sub> = 0.7 MeV) and <sup>124</sup>I (T<sub>1/2</sub> = 4.2 d; I<sub>β+</sub> = 23 %; E<sub>β+</sub> = 1.8 MeV). We measured the excitation function of the <sup>64</sup>Ni(p,n)<sup>64</sup>Cu reaction from threshold up to 20 MeV [5] and suggested this route over the energy range E<sub>p</sub> = 12  $\rightarrow$  9 MeV for the production of <sup>64</sup>Cu. The method is now in use in several laboratories. Regarding <sup>124</sup>I, we performed extensive and comparative studies on the reactions <sup>124</sup>Te(d,2n)<sup>124</sup>I [6], <sup>124</sup>Te(p,n)<sup>124</sup>I [7] and <sup>125</sup>Te(p,2n)<sup>124</sup>I [8]. The (p,n) reaction was investigated in collaboration with ATOMKI, Debrecen, Hungary, and the (p,2n) reaction with NAC, Faure, South Africa. The highest purity <sup>124</sup>I is obtained via the <sup>124</sup>Te(p,n)-reaction over the energy range  $E_p = 13 \rightarrow 9$  MeV.

## C. Use of fast neutrons

Several  $\beta$  -emitting therapeutic radionuclides are produced in a nuclear reactor using the (n,p) process. Two examples are:  ${}^{67}Zn(n,p){}^{67}Cu$  (T<sub>1/2</sub> = 2.6 d; I<sub>β</sub>- = 0.6 MeV) and  ${}^{89}Y(n,p){}^{89}Sr$  (T<sub>1/2</sub> = 50.5 d; I<sub>β</sub>- = 1.5 MeV). The cross sections of those reactions in a fission neutron spectrum are rather low and so the yields of the products are also low. We measured excitation functions of those two reactions using quasi-monoenergetic neutrons from a DD neutron source at the Jülich variable energy compact cyclotron CV28 [9, 10]. The data were then averaged for a 14 MeV d(Be) breakup neutron spectrum. The (n,p) cross section with breakup neutrons was found to be about 6 times higher than that for the fission neutron spectrum [2]. The use of breakup neutrons for production of some therapeutic radioisotopes thus deserves more attention.

#### **D.** Low energy $\beta^-$ , Auger electron and X-ray emitters

For several well-established therapeutic radionuclides, there exist still some discrepancies in the production data. We recently completed comprehensive studies on the production of <sup>67</sup>Cu ( $T_{\frac{1}{2}} = 2.6 \text{ d}$ ) via the <sup>68</sup>Zn(p,2p)-reaction in the energy range from threshold up to 71 MeV [11] and of <sup>103</sup>Pd ( $T_{\frac{1}{2}} = 17.0 \text{ d}$ ; EC = 100 %) via the <sup>103</sup>Rh(p,n)-reaction up to 40 MeV [12].

Considerable effort is now devoted to the investigation of alternative routes of production of known therapeutic radionuclides as well as to develop new radionuclides. Among the first group of measurements include a recently completed study on the <sup>70</sup>Zn(p, $\alpha$ )<sup>67</sup>Cu reaction [13] and on-going studies on <sup>102</sup>Ru(<sup>3</sup>He,2n)<sup>103</sup>Pd and <sup>100</sup>Ru( $\alpha$ ,n)<sup>103</sup>Pd reactions. As far as development of new therapeutic radionuclides is concerned, in collaboration with Mainz University we recently suggested [14] the use of the pure Auger electron emitter <sup>140</sup>Nd (T<sub>1/2</sub> = 3.4 d). Cross section measurement on the production reaction <sup>140</sup>Ce(<sup>3</sup>He,3n)<sup>140</sup>Nd is now in progress. Similarly studies on <sup>3</sup>He- and  $\alpha$ - particle induced reactions on isotopes of osmium are under way to ascertain whether <sup>195m</sup>Pt (T<sub>1/2</sub> = 4.0 d) and <sup>193m</sup>Pt (T<sub>1/2</sub> = 4.3 d) can be

produced in sufficient quantities. These two low energy electron emitting radionuclides are of considerable potential therapeutic interest.

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#### LA-UR-02-1982

# Consultants' Meeting on the Production of Radiotherapuetic Isotopes IAEA, Vienna February 27-March 1, 2002

# Nuclear Data Needs for the Production of Radiotherapeutic Isotopes with Higher Energy Accelerators

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#### Abstract

Nuclear data needs for the production of radiotherapeutic isotopes with higher energy accelerators are outlined. The Isotope Production Facility at Los Alamos requires data for proton-induced reactions up to 100 MeV. The Rare Isotope Accelerator will require data for heavy ions. For both of these facilities and for other high-intensity accelerators, neutron-induced reactions can be important.

## I. Introduction

Interest in using radioactive isotopes for therapeutic application is increasing because of favorable clinical results. The specificity of these isotopes and their chemical and biochemical compounds gives hope that, for some diseases, these isotopes could be the "silver bullet" for effecting a cure or at least for improving the quality of life of the patient.

As others in this Consultants' Meeting will describe, the most attractive therapeutic isotopes maximize the dose to the target volume, minimize the dose outside the target volume, and have a half-life that is consistent with the planned therapy. The first two criteria generally imply radiations of short range: x-rays, low-energy gamma rays, Auger electrons, beta rays, or alpha particles.

We should also keep in mind also the isotopes that support biodistribution studies. For example, <sup>88</sup>Zr is a parent of <sup>88</sup>Y, which can be used to determine the location of the therapeutic <sup>90</sup>Y, which has only a very weak gamma-ray branch in addition to the beta-

ray. A high specific activity of <sup>88</sup>Y is required to trace the <sup>90</sup>Y, and the decay of <sup>88</sup>Zr offers this high specific activity. The requirement of high specific activities extends to other isotopes and should be a consideration for the production modalities.

The production of radioactive isotopes for therapeutic (as well as diagnostic) application requires a range of production facilities and techniques. For isotopes with short halflives where there is no longer-lived precursor, production facilities near the patient-treatment facility is required. For other isotopes, more centralized production facilities are appropriate if they can reduce the cost of production. A reliable supply of such isotopes is essential so that, even for those that can be produced by central facilities, more than one central facility is necessary to avoid disruptions in supply when technical, funding, or regulatory difficulties force a facility to suspend production. One large facility, which will come on line in a year or two, is the Isotope Production Facility at Los Alamos.

In this presentation, I will discuss three areas of radioisotope production probably not covered by the other participants: (1) the new Isotope Production Facility at Los Alamos, (2) the possibility of assessing isotope production rates in reactions induced by fast neutrons, and (3) the desirability of making radioisotopes with the future Rare Isotope Accelerator.

# **II. Isotope Production Facility at Los Alamos**

The Isotope Production Facility at the Los Alamos National Laboratory's Neutron Science Center (LANSCE) is a new facility for isotope production. It follows many years of successful isotope production with the 800 MeV intense proton beam. Because of the termination of medium-energy research at the Los Alamos Meson Physics Facility (LANSCE), the accelerator is being used now mostly as a driver for spallation neutron sources and "Area A" is no longer available for isotope production. Instead a beam line spur is being established to direct 100 MeV protons to isotope-production targets. This \$20M project is nearing completion now with anticipated radioisotope production projected to begin in 2003.

Because of the marked change in proton beam energy for this facility from 800 to 100 MeV, new targetry is being designed. Cross section data are being assessed and needs are being identified both for data to fill gaps in the literature data and also for resolution of data discrepancies. [1]

Neutron-induced reactions are also of interest at this facility. At this energy of 100 MeV, many neutrons are made especially at the entrance to the target assembly. These neutrons then can induce reactions to produce desired isotopes or contaminating isotopes. Often the neutron reaction cross sections are unknown over this large range of energies – up to about 100 MeV. Fortunately, these cross sections can be measured or at least estimated by the techniques described in Section III.

Nearly all isotopes for therapeutic or diagnostic application (the isotopes themselves or their precursors) are produced either by charged particle beams, by fission products from reactors, or from radioactive actinide sources. Production by fast neutrons might be thought to be difficult because sources of fast neutrons are usually much less intense than those for charged-particle beams. However, advances in accelerator technology, in target development, and in the possible use of accelerators for energy production offers the possibility that neutron source intensities might become much greater than those available now even in fission reactors. Thus we should keep in consideration isotopes that are not easily made with present techniques but that could be made with fast neutrons. To calculate the production rates, both the neutron flux spectrum and the activation cross section as a function of neutron energy must be known. The neutron flux spectrum is a subject of high interest in programs to assess the accelerator transmutation of radioactive waste, and much progress has been made in understanding and parameterizing the intensity and energy distribution of the neutrons in macroscopic target assemblies. The activation cross sections as a function of neutron energy are often not well known in this energy range, which can extend to several hundred MeV.

Examples of neutron-induced reactions include the (n,p) and (n,n'p) reactions, which can yield neutron-rich isotopes that are difficult to produce by other reactions. Calculations of the production cross sections are notoriously difficult because these reactions are a small part of the total reaction cross section and the nuclear reaction models are particularly sensitive to optical model parameters, level densities, and the contributions from pre-equilibrium reactions. Thus, experimental measurements of these cross sections are highly desirable. One therapeutic isotope that is difficult to make with charged particle beams is the neutron-rich isotope  ${}^{67}$ Cu, which is used in the treatment of non-Hodgkins lymphoma and other diseases. This isotope can be made by the (n,np) reaction on  ${}^{68}$ Zn (isotopic abundance = 18.8%) and the (n,p) reaction on  ${}^{67}$ Zn (4.1%), but the cross sections are not well known over a wide range of neutron energies.

Conventional activation techniques can often be used to measure the production cross section of isotopes that are created by fast neutrons if mono-energetic or quasimonoenergetic neutron sources are available in the energy range of interest. An alternate method, used at Los Alamos, covers a wide range of neutron energies all at once. This method is the detection of prompt gamma rays in a time-of-flight experiment with a pulsed, spallation neutron source [2,3]. The gamma rays are measured with high-resolution germanium detectors and individual lines are compared with calculations to relate the partial cross sections to the activation cross section. This approach requires good knowledge of the spectroscopy of excited states of the activation product. If the spectroscopy is simple of if several gamma-ray transitions are observed, then the deduced activation cross sections can have high credibility.

# IV. Rare Isotope Accelerator

The Rare Isotope Accelerator (RIA) in the US is a major project intended to produce large amounts of radioisotopes for physics and nuclear chemistry research and also for applications. This project is in the beginning stages and is expected to produce its first beams within the next 10 years. A Rare Isotope Applications Workshop was held in Los Alamos on October 30-31, 2000 [4]. Among the applications considered was the production of medical isotopes both for diagnostic application as well as for therapy.

The conclusions of one presenter [5] (and I believe they were agreed to by others) included the following:

RIA would excel as a research tool for new production techniques, isotope yields, targeting techniques. It would provide a vastly expanded array of isotopes. It would offer new and novel ways of producing existing commercial isotopes with possible cost reductions. And it might make economical the production of new isotopes, which were previously too expensive or inaccessible.

On the other hand, RIA was not viewed as a commercial supplier of isotopes because it would be a unique supplier of certain isotopes, it could not guarantee the availability of these isotopes, and it probably would not be competitive in production costs for isotopes that could be made elsewhere.

The number of possible reactions for producing a given isotope with RIA is huge, and therefore one might ask if progress could be made in this field through a Coordinated Research Project when many other production sources (reactors, cyclotrons, linacs neutron sources, etc.) need to be considered. I believe that this issue should be discussed at this Consultants' Meeting.

# V. Summary

Some considerations are given for nuclear data needs in the production of radiotherapeutic isotopes with higher energy accelerators. For the Isotope Production Facility, data are needed for protons up to 100 MeV and for neutron-induced reactions. Neutron-induced reactions could play an important role for isotopes that are difficult to produce in other ways. The Rare Isotope Accelerator will offer a wide range of isotopes, mostly for research purposes.

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IAEA-Consultants Meeting, "Nuclear Data for Production of Therapeutic Radioisotopes," Vienna, Austria, February 27-March 1, 2002.

#### **Reactor-Produced Therapeutic Radioisotopes**

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#### Introduction and Background -

The significant worldwide increase in therapeutic radioisotope applications in nuclear medicine, oncology and interventional cardiology requires the dependable production of sufficient levels of radioisotopes for these applications (Reba, 2000; J. Nucl. Med., 1998; Nuclear News, 1999; Adelstein and Manning, 1994). The issues associated with both accelerator- and reactor-production of therapeutic radioisotopes is important. Clinical applications of therapeutic radioisotopes include the use of both sealed sources and unsealed radiopharmaceutcial sources. Targeted radiopharmaceutical agents include those for cancer therapy and palliation of bone pain from metatstatic disease, ablation of bone marrow prior to stem cell transplantation, treatment modalities for mono and oligo- and polyarthritis, for cancer therapy (including brachytherapy) and for the inhibition of the hyperplastic response following coronary angioplasty and other interventional procedures (For example, see Volkert and Hoffman, 1999). Sealed sources involve the use of radiolabeled devices for cancer therapy (brachytherapy) and also for the inhibition of the hyperplasia which is often encountered after angioplasty, especially with the exponential increase in the use of coronary stents and stents for the peripheral vasculature and other anatomical applications. Since neutron-rich radioisotopes often decay by beta decay or decay to beta-emitting daughter radioisotopes which serve as the basis for radionuclide generator systems, reactors are expected to play an increasingly important role for the production of a large variety of therapeutic radioisotopes required for these and other developing therapeutic applications. Because of the importance of the availability of reactor-produced radioisotopes for these applications, an understanding of the contribution of neutron spectra for radioisotope production and determination of those cross sections which have not vet been established is important. This contribution will focus on the issues associated with the reactor-production of therapeutic radioisotopes of current and projected interest.

# Types of Nuclear Reactions Important for Reactor Production of Medical Radioisotopes -

Production of radioisotopes in a reactor requires encapsulation of high chemical purity and usually highly enriched target materials. The reactor production yields are dependent upon the neutron flux and neutron spectrum of the reactor and these factors as well as a good understanding of the neutron cross section values is required to predict production yields. Not only are accurate values of the neutron cross sections important, but the occurrence of neutron resonances and possible burn-

up (i.e. neutron capture) by the product of interest are important. The nuclear reactions of primary interest for reactor production of beta-emitting therapeutic radioisotopes by "direct" production include the radiative  $(n,\gamma)$ , the inelastic  $(n,n',\gamma)$  and the (n,p) reactions. The  $(n,\gamma)$  is the most common production pathway, which can also include multi neutron captures of both neutron capture products, such as the production of tungsten-188 from tungsten-186 and the production of dysprosium-166 from dysprosium-164 (Table 1).

Although the potential list of reactor-produced radioisotopes for therapeutic applications is not limitless, there are a large number of candidates which are of current or expected interest. The intermediary role or use of product radioisotopes which then decay by beta-decay is also useful for reactor production of various therapeutic radioisotopes, and examples in this category include the platinum-198( $n,\gamma$ ) platinum-199 ( $\beta$ - decay)gold-199 process. Another example is subsequent neutron capture of intermediate isotopes formed by beta-decay when the resulting nuclide has a high cross section to capture a neutron to form the product of interest.

In other cases, the reactor-produced radionuclide has a short half-life and decays to a carrier-free product which has a low cross section for neutron capture, which can be obtained by batch separation processes. There are a variety of reactor-produced rtherapeutic radioisotopes in this category, which includes the production of lutetium-177 by the ytterbium-176(n, $\gamma$ )ytterbium-177( $\beta$ -decay)lutetium-177 process, which is potential interest for production of very high specific activity lutetium-177 in nuclear reactors of moderate and perhaps low neutron flux which are available in the Member States. In addition, the (n,p) reaction can have some importance for providing no-carrier-added products, although reaction yields are usually low, such as production of copper-67 by the zinc-67(n,p)copper-67, and scandium-47 by the titanium-47(n,p)scandium-47 pathways.

There is also rapidly growing interest in the use of alpha-emitting radioisotopes for therapy, particularly for cancer treatment. In some cases, radioactive parents from "extinct" radioactive decay processes, such as thorium-229, can be recovered from uranium-233 decay products. The thorium-229 represents a convenient source from which actinium-225 is recovered, which is the parent for the actinium-225/bismuth-213 generator system. There is wide interest in the use of bismuth-213 (10 hour half-life, 8 MeV alpha) for cancer therapy because of the very high LET. Although the lower Z alpha-emitting radioisotopes of interest for therapeutic applications are usually not reactor produced, it should be noted, that thorium-229 could also be reactor-produced *via* the three successive neutron captures of radium-226, discussed later.

# Examples of Important Clinical Applications of Reactor-Produced Therapeutic Isotopes -

Although the production of therapeutic medical radioisotopes in reactors has always been of interest, recent advances in complementary technologies over the last decade have dramatically increased the importance of these radioisotopes. Example include the advances in the biological preparation of monoclonal antibodies and the solid-state synthesis of peptides targeted to specific receptors expressed on tumor cells. Chemical attachment of radioisotopes to these targeted carriers represents an important and effective method for localization of these therapeutic radioisotopes for tumor killing, and many such agents are currently in clinical trials.

In cases where specific carrier molecules such as peptides are bound to the extracellular receptors and then internalized into the target cells - and especially if nuclear targeting is possible - the use of

low energy Auger emitting radioisotopes if of great interest for lethal delivery of radiation to the target cells (Mariani, et al., 2000).. Reactor-produced radioisotopes of interest in this category include iodine-125, ruthenium-103 and platinum-195*m*, which has the highest Auger yield (Mariani, *et al.*, 2000).

# Examples of Reactor-Produced Medical Radioisotopes of Current Interest -

The increased impetus for the use of unsealed radioactively-labeled agents for various therapeutic applications is illustrated by new developments in the synthesis and evaluation of new ligands as carriers for tumor-targeted therapy. There is broad interest in applications of beta-, Auger- and alpha-emitting reactor-produced radioisotopes for therapy. To date, most routine clinical applications have focused on beta-emitting radioisotopes and several examples are provided in **Tables 1**. The Agency is in the process of publishing the *Radioisotope Production in Nuclear Reactors*, which describes the production pathways and processing methods for many beta-emitting radioisotopes of current interest (lyer and Knapp, 2002). Although tabulation of cross section data for many of the required neutron capture reactions are available in compilations in the literature, in some cases, accurate production cross section values are not available, which are required by researchers and institutions to evaluate and predict production of several therapeutic radioisotopes of current interest. In addition, burn-up cross section data are important.

# Important Clinical Applications of Reactor-Produced Therapeutic Radioisotopes -

In addition to the use of high and low energy beta-emitting radioisotopes for treatment of solid tumors, these various radioisotopes are also widely used for the clinical palliative treatment of pain associated multiple skeletal metastases. The energy of the beta emission can also be tailored for treatment of rheumatoid arthritis, dependent upon the size of the synovial joint. (i.e. yttrium-90 *vs.* rhenium-186 *vs.* erbium-169 for large, medium and small joints, respectively). One of the more recent applications which is expected to have broad application is the use of therapeutic radioisotopes - including high energy beta- and gamma emitting - for the inhibition of restenosis after coronary angioplasty - use both catheter-based approaches where the radioactive source is inserted through a catheter to the post-angioplastic site and the use of radiolabeled stents. In the last few years tremendous interest has grown for the use of alpha-emitting radioisotopes for the therapy where rapid and specific targeting is possible, such as the use of bismuth-213-labeled antibodies for the treatment of blood borne acute myeloid leukemia, and radium-224 is now routinely available in Germany for the treatment of ankylosing spondylitis.

# Technical Analysis of Present Status -

The study by Frost and Sullivan published in the *Journal of Nuclear Medicine* (Vol. 39, pp 13N-27N) estimated that the revenues for the therapeutic radioisotope market in the U.S. will increase over 100 fold from 2000 to 2020 (1996, \$45 million; 2000 estimated as \$62 million; estimated as > 6 billion in 2020). Presumably such estimated required 100-fold increases in the therapeutic radioisotope market must also reflect the international trend, and clearly result from recent and expected advances in the development and clinical implenentation of therapeutic radiopharmaceuticals.

Table 1.Examples of Reactor-Produced Therapeutic Radioisotopes of Current Interest<br/>for Cancer Therapy, Bone Pain Palliation, Marrow Ablation and Coronary<br/>Restenosis Therapy

Radioisotope	Therapeutic Agents	Applications	
High Energy Beta	a-Emitters		
Dysprosium-166	Parent for Dy-166/Ho-166 Generator		
Holmium-166	Ho-EDTMP	Bone pain palliation, marrow ablation	
Rhenium-188	Peptides, Antibodies	Tumor therapy, marrow ablation, bone pain palliation, restenosis therapy	
Medium and Low Energy Beta-Emitters			
Lutetium-177	Peptides	Therapy of somatostatin receptor expressing tumors	
Rhenium-186 Peptides, Antibodies		Bone pain palliation, tumor therapy, restenosis therapy	
Low Energy Gamma and X-Ray Emitters			
Palladium-103         Radiolabeling of coronary stents and other devices		Restenosis and tumor therapy	
Ytterbium-169 Radiolabeling of coronary stents and other devices		Restenosis therapy	

As has been discussed earlier, beta emitting, alpha-emitting and also Auger-electron emitting radioisotopes are of interest for various therapeutic applications. Since many therapeutic radioisotopes are characterized by beta decay, they are often directly produced in a nuclear reactor, since neutron capture by the target nuclide forms an radioactive or unstable product which decays by beta emission. Key examples include holmium-166, lutetium-177 and rhenium-188. In the same context, parent radioisotopes for generator systems which form a beta-emitting daughter radioisotope which are directly reactor-produced. Important examples tungsten-188 - parent of the tungsten-188/rhenium-188 generator - and dysprosium-166 - parent of the dysprosium-166/holmium-166 generator system. A third important production system is recovery of generator parent radioisotopes which are produced during nuclear fission. An important example is strontium-90, isolated from fission products, which is the parent for the strontium-90/yttrium-90 generator system. Another example is the recovery of radioactive parents from "extinct" radioactive decay processes, such as thorium-229, which is recovered from uranium-233 decay products. The thorium-229 represents a convenient source from which actinium-225 is recovered, which is the parent for the actinium-225/bismuth-213 generator system. As an example where accurate neutron cross section values are required, since the reactor-production of thorium-229 is also possible via the radium-226  $(3n,\gamma)$  radium-229( $\beta$  decay) actinium-229( $\beta$ -decay) thorium-229 pathway.

# **Description of Overall Objective -**

It is recommended that the overall project should initially involve distribution of a questionnaire requesting guidance and input from sites in *Member States* which have interest in the production

and/or availability of reactor-produced therapeutic radioisotopes on those therapeutic radioisotopes of interest, and on neutron cross section data which may be required to all sites in the *Member States*. The characteristics of the reactors available - including neutron, flux spectra and target handling facilities - in the Member States will also help identify those therapeutic radioisotopes of interest for production. The stage of the project focused on developing the required information should include identifying those sites which have the experimental and analytical/computational capabilities for performing the required irradiations and for calculating neutron cross section values which can be used to predict radioisotope production rates and institutions where research reactors and irradiation facilities are available to obtain the experimental data required for such calculations.

# Description of Specific Result Expected from CRP -

It would be expected that the CRP may result in the preparation of a *Report* or *Manual* providing a compilation of neutron spectral cross section values for the reactor production of those therapeutic radioisotopes of current and projected interest and for those reactions for which cross section values or accurate values are not available.

# Possible Participants from CRP -

The participants in this CRP should first of include institutions which have access to research reactors where the necessary irradiations and product analysis can be conducted. In addition, individuals who have the computational capability for data analysis. The Agency has regularly published a manual of *Directory of Nuclear Research Reactors* (Latest Edition, 1998), from which a list of potential participating reactor sites can be obtained.

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# Production and application of therapeutic radioisotopes Activity on the related nuclear reaction data

Consultants Meeting on "Nuclear data for production of therapeutic radioisotopes" 27 February - 1 March 2002, Vienna, Austria.

# Institute of Nuclear Research (ATOMKI), Debrecen, Hungary *F. Tárkányi*

The Charged Particle Nuclear Data (CPND) Group in the ATOMKI has been involved in measurement, compilation, evaluation and application of nuclear reaction data for more than 15 years. The main field of activity is charged particle induced reactions.

The research is mainly focused on non-energy related applications: medical radioisotope production, monitoring the parameters of charged particle beams, thin layer activation to control wear and corrosion. Last years we have started to extend our activities to measurements of fast neutron reaction data and charged particle reaction data related to waste transmutation.

The CPND Group itself has extended experimental experience at the Debrecen MGC 20E cyclotron and at other accelerators in collaboration with universities in Hungary or laboratories in Germany (INC, Forschungszentrum Jülich), Belgium (Cyclotron Laboratory, Vrije Universiteit of Brussel), Japan (CYRIC, Tohoku University, Sendai and National Institute of Radiological Sciences, Chiba), Finland (Cyclotron Lab., Abo Akademi, Turku), Czech Republic (Nuclear Research Institute, Rez) and South-Africa (National Accelerator Centre, Faure). Activities in the field of compilation and data evaluation are done in close collaboration with IAEA in the frame of independent projects and of the Nuclear Reaction Data Center Network. Eight scientists (six physicists and two chemists) are contributing to the nuclear data project (most of them only part-time).

An important field of the nuclear data activity actually lies in the medical radioisotope production. The members of ATOMKI CPND group are involved in every day radioisotope production of diagnostic radioisotopes for PET and SPECT. The team was also involved in the IAEA-CRP on development of a recommended database for production of diagnostic radioisotopes reactions for nuclear medicine by charged particle induced reactions and presently is engaged in the extension and upgrading of this database.

In the field of nuclear reaction data related to production and application of therapeutic radioisotopes the effort at ATOMKI is presently focused on the measurement of the production cross sections of the therapeutic radioisotopes and of the so called analog radioisotopes used for investigation of uptake and biodistribution processes. The aim of the studies is twofold: to complete the available database and clarify the discrepancies found during compilation and on the other side, to contribute to the research of the application of new therapeutic radioisotopes. Some attempts have already been made also in the field of compilation and critical evaluation of the relevant literature data. In the future we would like to continue both the experimental and the evaluation work in this field.

The investigated reactions are summarized in Table 1 and Table 2.

Radioisotope	Nuclear reaction	Energy range (MeV)	Partner institute	Compilation(c) Evaluation (e)
<sup>186</sup> Re	<sup>186</sup> W(p,n) <sup>186</sup> W(d,2n)	0-40 0-20	VUB, Brussel VUB, Brussel	C C
<sup>103</sup> Pd	<sup>103</sup> Rh(p,n) <sup>103</sup> Rh(d,2n)	0-40 0-20	VUB, Brussel VUB, Brussel	C C
<sup>111</sup> Ag	<sup>110</sup> Pd(d,n)	0-20	VUB, Brussel	
<sup>198</sup> Au	<sup>198</sup> Pt(p,n) <sup>198</sup> Pt(d,2n)	0-40 0-20	VUB, Brussel VUB, Brussel	
<sup>199</sup> Au	<sup>198</sup> Pt(d,n)	0-20	VUB, Brussel	
<sup>64</sup> Cu	<sup>64</sup> Ni(d,2n)	0-20	VUB, Brussel	
<sup>111</sup> In	<sup>111</sup> Cd(p,n) <sup>112</sup> Cd(p,2n)	0-35 0-35	NRI, Rez NRI, Rez	c,e c,e
<sup>131</sup>	<sup>131</sup> Te(p,n)	0-18		c,e
<sup>51</sup> Cr	<sup>48</sup> Ti(α,n)	0-40	NRI, Rez	
<sup>131</sup> Cs	<sup>129</sup> Xe(α,2n) <sup>131</sup> Ba	0-40	VUB Brussel	
<sup>101m</sup> Rh	<sup>102</sup> Pd(p,x) <sup>101</sup> Pd	0-36	VUB, Brussel	
<sup>46</sup> Sc	<sup>48</sup> Ti(d,α)	0-20	VUB Brussel	С
<sup>99m</sup> Tc	<sup>100</sup> Mo(p,pn) <sup>99</sup> Mo <sup>100</sup> Mo(p,2n) <sup>100</sup> Mo(d,p2n) <sup>99</sup> Mo <sup>100</sup> Mo(d,3n)	0-40 0-40 0-50 0-50	VUB, Brussel VUB, Brussel VUB, Brussel VUB, Brussel	с с с с

Table 1. Investigated reactions related to production of therapeutic radioisotopes

Table 2. Investigated reactions for production of analog radioisotopes

Radioisotope	Therapeutic Partner	Nuclear reaction	Energy range (MeV)	Partner institute
<sup>83</sup> Sr	<sup>89</sup> Sr	$^{nat}$ Kr( $\alpha$ ,x) $^{82}$ Kr( $^{3}$ He,2n) $^{83}$ Kr( $^{3}$ He,3n) $^{nat}$ Kr( $^{3}$ He,x) $^{nat}$ Rb(p,x)	0-120 0-36 0-36 0-90 30-70	INC FZ Julich INC, FZ Julich INC, FZ Julich INC, FZ Julich CYRIC, Tohoku Univ
<sup>124</sup> I <sup>103</sup> Ag	<sup>125</sup> I, <sup>131</sup> I <sup>111</sup> Ag	<sup>124</sup> Te(p,n) <sup>102</sup> Pd(d,n) <sup>104</sup> Pd(p,2n)	0-20 0-20 0-40	INC, FZ Julich VUB, Brussel VUB Brussel
<sup>192</sup> Au, <sup>194</sup> Au	<sup>199</sup> Au, <sup>198</sup> Au	<sup>192</sup> Pt(p,n) <sup>192</sup> Pt(d,2n) <sup>194</sup> Pt(p,n)	0-40 0-20 0-40	VUB, Brussel VUB, Brussel VUB, Brussel
<sup>60, 61, 62</sup> Cu	<sup>67</sup> Cu, <sup>64</sup> Cu	<sup>62</sup> Ni(d,n) <sup>60</sup> Ni(d,2n) <sup>60</sup> Ni(d,n) <sup>64</sup> Zn(p,x) <sup>62</sup> Zn <sup>60</sup> Ni( <sup>3</sup> He,3n) <sup>60,61</sup> Ni( <sup>3</sup> He,x)	0-20 0-20 0-2 0-70 0-36 0-36	VUB, Brussel VUB, Brussel VUB, Brussel NAC Faure INC, FZ Julich INC, FZ Julich
<sup>109</sup> In <sup>209,210</sup> At	<sup>111</sup> In, <sup>114m</sup> In <sup>211</sup> At	<sup>111</sup> Cd(p,3n) <sup>209</sup> Bi( <sup>3</sup> He,2n) <sup>209</sup> Bi( <sup>3</sup> He,3n)	0-35 0-26 0-26	NRI Rez
<sup>75</sup> Br, <sup>76</sup> Br	<sup>80m</sup> Br	<sup>78</sup> Kr(p,x) <sup>78</sup> Kr(d,x)	0-20 0-14	INC, FZ Julich INC, FZ Julich

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