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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 yet 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,γ), the inelastic (n,n',γ) and the (n,p) reactions. The (n,γ) 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,γ) platinum-199 (β- 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,γ)ytterbium-177(β-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 currrently 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 (Iyer 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 implenmtation of therapeutic radiopharmaceuticals.

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

Radioisotope	Therapeutic Agents	Applications
High Energy Beta-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,γ)radium-229(β^-decay)actinium-229(β-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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