PRODCTION OF MEDICAL RADIOISOTOPES AT THE FRM II RESEARCH REACTOR

H. GERSTENBERG*, A. KASTENMÜLLER,
A. DRRACK, C. MÜLLER
Technische Universität München, ZWE FRM II
85748 Garching – Germany

*Corresponding author: heiko.gerstenberg@frm2.tum.de

ABSTRACT

Due to its design as a heavy water moderated reactor with a very compact core FRM II, Germany's most modern and most powerful research reactor, offers excellent conditions for basic research using beam tubes. On the other hand it is equipped with various irradiation facilities to be used mainly for industrial purposes. From the very beginning of reactor operation a dedicated department had been implemented in order to provide a neutron irradiation service to interested parties on a commercial basis.

As of today the most widely used application is Si doping. The semiautomatic doping facility accepts ingots with diameters between 125 mm and 200 mm and a maximum height of 500 mm. The irradiation channel is located deep in the heavy water tank and exhibits a ratio of thermal/fast neutron flux density of > 1000. This value allows the doping of Si to a target resistivity as high as 1100 Ωcm within the tight limits regarding accuracy and homogeneity specified by the customer. Typically the throughput of Si doped in FRM II sums up to about 15 t/year.

Another topic of growing importance is the use of FRM II aiming the production of radioisotopes mainly for the radiopharmaceutical industry. The maybe most challenging example is the production of Lu-177 n.c.a. based on the irradiation of Yb_2O_3 to a high fluence of thermal neutrons of typically 1.5E20 cm^{-2}. The Lu-177 activity delivered to the customer is in the range of 750 GBq. With respect to further processing it turned out to be a highly advantageous to have the laboratories of ITG, the company extracting the Lu-177 from the freshly irradiated Yb_2O_3 on site FRM II.

Further irradiation facilities are available at FRM II in order to allow the activation of samples for analytical purposes or to irradiate samples for geochronological investigations using the fission track technique. Finally a project on the future installation of a facility dedicated to the irradiation of U-targets for the production of Mo-99 is in progress.

It is noteworthy that all of the irradiation facilities at FRM II have been certified according to the ISO 9001:2008 standard.

1. Introduction

The Technical University of Munich is operating the Forschungs-neutronenquelle Heinz Maier-Leibnitz (FRM II), Germany's youngest and most powerful research reactor on its campus in Garching. FRM II is a tank-in-pool type heavy water moderated reactor exhibiting a power of 20 MW. Its design has been optimized aiming excellent conditions for basic research using neutron beams. Consequently about 30 experimental instruments have been installed in an experimental hall within the reactor building and a second one in an adjacent neutron guide hall. A further neutron guide hall in a recently erected neighboring building is about to be taken into operation. Thanks to the openness of FRM II to external users scientists from all over the world are profiting from the excellent experimental conditions at FRM II.

Besides basic research, however, FRM II is also being used for industrial and commercial applications to the extent possible. In the first few years of reactor operation these activities were mainly focused on Si doping. More recently, in addition, a growing demand for the production of radioisotopes for medical and industrial applications has been observed and asked for. Consequently the irradiation facilities of FRM II are being used for those purposes to an increasing degree and a licensing procedure for the installation and operation of an additional irradiation device dedicated to the production of Mo-99/Tc-99m has been launched.

2. Characteristics of the research reactor FRM II

FRM II is a heavy water moderated, light water cooled research reactor exhibiting a thermal power of 20 MW. The moderator tank is filled with roundabout 11 m³ of heavy water. It is located within a 700 m³ light water pool. The reactor's main design feature is a single cylindrical fuel assembly, the so-called compact core, containing approximately 8.1 kg of highly enriched (92% U-235) uranium in form of U_3Si_2. Under standard conditions the reactor is operated in cycles of 60 days in a row. Typically the reactor is operated 4 cycles per year.

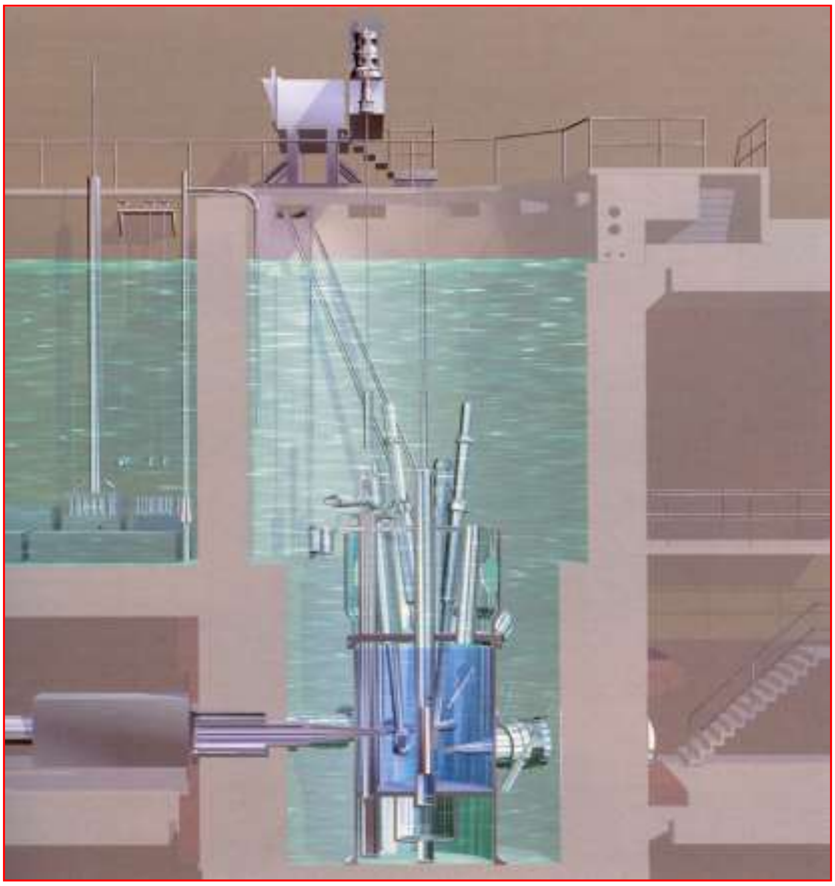


Fig 1: FRM II reactor pool and moderator tank (dark blue) with some key components

For scientific and commercial applications FRM II is equipped with 11 beam tubes allowing the operation of approximately 30 neutron scattering instruments, a cold neutron source (liquid D_2 at 24 K), a hot neutron source (irradiation heated carbon block at approximately 1900 °C), a high intensity positron source, a facility for cancer treatment by means of direct irradiation with fast neutrons and 5 irradiation facilities - one of them for gamma irradiations in spent fuel assemblies. Except for the gamma irradiation device all of the irradiation channels are located within the heavy water moderator tank and consequently provide high values of the thermal/fast neutron flux density ratio Φ_{th}/Φ_f between 300 and more than 10000.

3. Isotope production

3.1 Lu-177

Lu-177 is a β-emitting radioisotope with a half-life of 6.71 d and a maximum β-energy of 490 keV. The ß-radiation is associated with the emission of 2 low energy (113 keV and 208 keV) γ-quanta that in addition have only an emission probability of 6.5% and 11%, respectively. These nuclear properties make Lu-177 one of the most promising isotopes for targeted radionuclide therapy. Consequently the demand for the production of this isotope is increasing rapidly since a few years.

The targeted radionuclide therapy is based on a molecule that is similar to a key-lock system suitable to be connected to a tumor specific receptor on the one hand and that carries the radionuclide to be used for either diagnostics or therapy on the other hand. One of the major advantages of Lu-177 is that due to the relatively low energy of the β-radiation the energy deposition in human tissue is restricted to a range of only few mm. Consequently the radiation damage to the healthy tissue surrounding the tumor is minimized. At the same time the γ-component being emitted by means of the decomposition of Lu-177 allows the precise localization of the treated area in the human body. As of today Lu-177 is used for cancer treatment in a large variety of organs, e.g. for neuroendocrine tumors of the gastrointestinal tract or metastasizing prostate cancer.

In general there are two routes for the production of Lu-177: The use of Lu-176 as starting material offers the advantage of a very high neutron absorption cross section of 2050 b and consequently the chance to produce a high activity of Lu-177 even in a moderate neutron flux density or in a short exposure or time. There are however two penalties to be paid in this method: the production of the long lived metastable Lu-177m (T1/2 = 161 d) possibly leading to waste disposal problems and the fact that the desired Lu-177 is contained in a matrix of inactive Lu -176. The competitive method, introduced by the Isotopes Technologies Garching GmbH(ITG) and mainly used at FRM II uses Yb_2O_3 enriched in almost 100% Yb-176 as starting material and takes advantage of the nuclear reaction

$$^{176}Yb(n,\gamma)^{177}Yb \xrightarrow{\beta^-} {}^{177}Lu$$

Typically about 1 g of Yb2O3 is irradiated in a sealed quartz ampoule that in addition is inserted in an Al capsule as a mechanical protection. In FRM II the irradiation is carried out in a water cooled channel exhibiting a thermal neutron flux density of 1.3E14 cm^{-2} s^{-1}. Due to the drastically lower neutron absorption cross section of Yb-176 (σ = 2.4 b) a long exposure time of typically 2 weeks is required to produce a specific activity of 800 GBq/g Yb-176. Due to the production path via the short lived isotope Yb-176 (T1/2 = 1.9 h) and the subsequent chemical isolation the product Lu-177 is produced non carrier added (n.c.a.). In addition the undesired metastable Lu-177m (T1/2 = 160 d) level is not populated using this production route.]

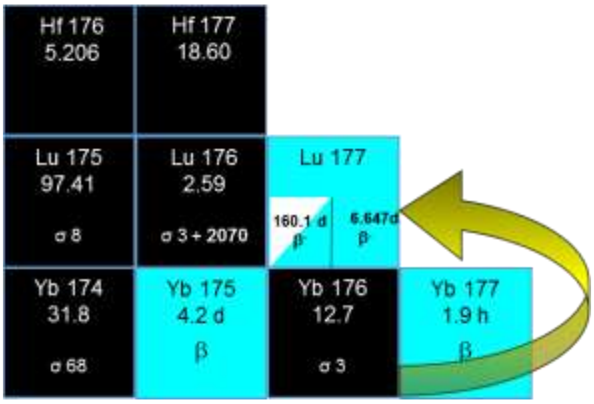


Fig.: 3: Excerpt from the chart of nuclides illustrating the production of Lu-177 n.c.a.

3.2 Ho-166 microspheres

A different approach of using radioisotopes for cancer treatment is the Holmium radioembolization of liver metastases. The method has been developed by the Dutch company Quirem Medical up to the status of clinical applications.

The idea of the method is to introduce a large number of organic microspheres carrying a core of radioactive Ho-166 into the hepatic artery. The microspheres have a mean diameter of 60 µm and are transported with the blood stream until they get stuck in one of the liver capillaries. Similar to Lu-177 Ho-166 decays under emission of β-particles with a high maximum energy of 1.85 MeV accompanied by low energy (< 100 keV) γ-radiation. Due to its half-life of 26.8 h almost the patient is exposed to almost the entire β-dose of the radioactive Ho-166 within few days. In addition the γ-component of the radiation allows the precise imaging of the treated organ.

The major challenge regarding the preparation of Ho-166 microspheres is first of all of course the activation up to the desired dose as it has to be implemented by calculating the appropriate irradiation time in a well-known irradiation position. In addition it is essential to reduce the mechanical damage to the microspheres to the extent possible. For this purpose the temperature increase within the sample during irradiation must be minimized to be < 60°C and to provide a well thermalized neutron spectrum with a high ration of thermal/fast neutron flux density.

At FRM II two irradiation channels of the pneumatic rabbit system have been identified to meet the above requirements and qualified by means of calibration experiments in cooperation with the customer. The corresponding neutron flux parameters are:

RPA1 : Φ_{th} = 3.3E13 $cm^{-2}s^{-1}$ Φ_f = 2.0E09 $cm^{-2}s^{-1}$;
RPA5 : Φ_{th} = 3.6E13 $cm^{-2}s^{-1}$ Φ_f = 5.9E09 $cm^{-2}s^{-1}$;

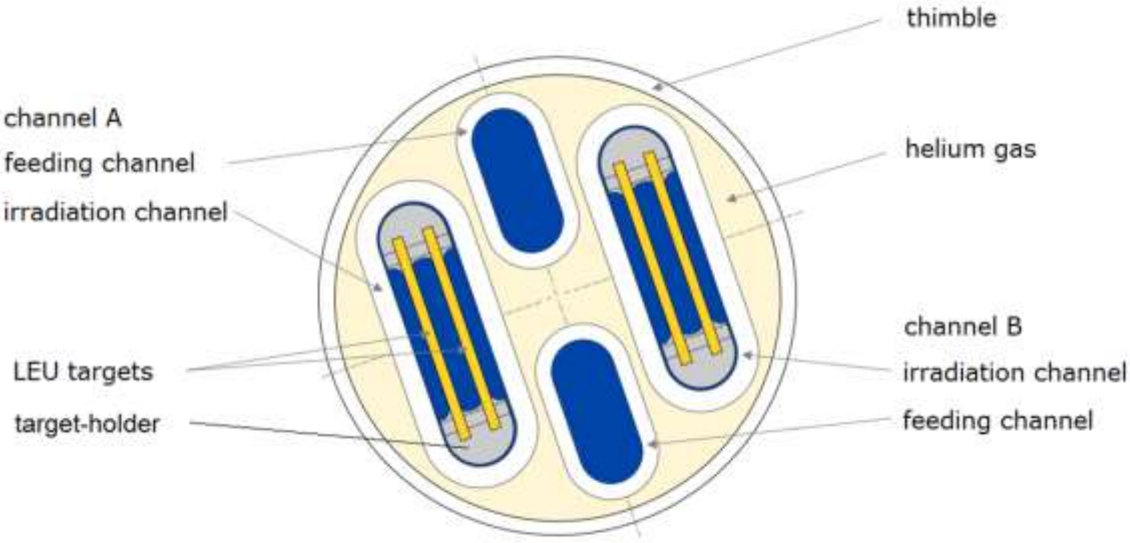
A typical therapy dose requires approximately 12 GBq Ho-166. For this purpose 600 mg of sample material including 20% of Ho-165 are to be irradiated for about 1 h in order to an activity of 25 GBq at the end of exposure. A time close to one half-life (26.8 h) is allowed for the transportation of the irradiated vial from Munich to the hospital in Rotterdam where the treatment is carried out and the preparation of the microspheres for clinical use.

For the mid-term future it is foreseen to establish a laboratory close to the reactor site in Garching for the post irradiation preparation of the microspheres. The rapid processing of the freshly irradiated microspheres is highly desirable in particular with respect to the possible extension of the Ho-radioembolization method for the treatment of liver metastases to hospitals in the South German region. The concentration of the entire production chain in the same region will minimize the decay losses during transportation and correspondingly allow reducing the exposure time of the vials and will also help to preserve the microspheres from an unnecessary high mechanical damage.

3.3 Production of Mo-99/Tc-99m

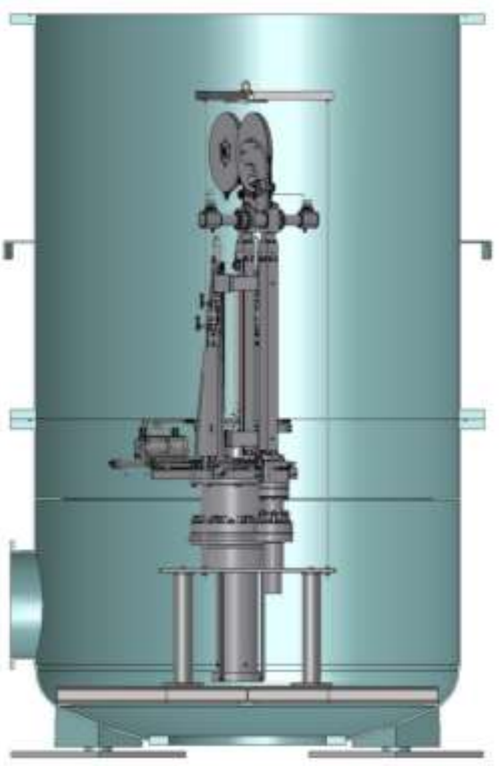
Tc-99m is still the most widely used radioisotope in nuclear medicine. As a pure γ-emitter with a short half-life of only 6.02 h and a low γ-energy of 141 keV it offers ideal parameters for nuclear-medical diagnostics at a minimum radiation related risk for the patient. The most efficient way for its production requires the irradiation and fission of uranium in a nuclear research reactor generating its mother isotope Mo-99 with a yield of approximately 6.2%. Due to the still increasing demand for Mo-99/Tc-99m and the ageing or even shut-down of suitable high-flux research reactors for the production of those isotopes it was decided to equip FRM II with a dedicated irradiation facility for the irradiation of LEU (19.75% in U-235) targets.

After completion of feasibility studies the formal application for “Installation and Operation of an Irradiation Facility dedicated to the Production of Mo-99” was launched at the regulatory authority. The safety case was handed over in May 2017. The inspection of the safety by an independent experts-organization working on behalf of the regulatory body is still in progress.



An irradiation position has been identified within the moderator tank that provides a thermal neutron flux density of $\Phi_{th} \approx 2E14\ cm^{-2}s^{-1}$ i.e. the highest one available at FRM II. The facility will be made up of 2 independent irradiation channels with a capacity to expose up to 16 standard plate-like targets in parallel. A light water coolant stream of ≥ 5kg/s is provided for the release of the thermal power of about 400 kW being generated by the fission processes in the targets. The irradiation channels will be separated from the heavy water by means of a vertical thimble in order to facilitate the loading and unloading of U-targets during reactor operation (see fig.).

FRM II is a research reactor in operation. Consequently access to the future installation and operation position of the Mo-99 facility is limited to maintenance periods only. In order to overcome this difficulty to the extent possible a full size mock-up of the central components was built and installed in a neighboring laboratory building. In order to simulate the original operating conditions within FRM II as realistic as possible the trials using the mock-up were done under water in a large drum. The experiments gained from these test experiments will for sure help to reduce drastically the time required for the installation and commissioning of the original facility in the reactor pool.



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