

RADIOACTIVE ION BEAMS FOR BIO-MEDICAL RESEARCH AND NUCLEAR MEDICAL APPLICATION

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The ISOLDE facility at CERN is the world leading on On-Line Isotope Separator installation. The main aspects which makes ISOLDE produced radio-isotopes such valuable for use in bio-medical research are: *the availability of exotic or uncommon radio-isotopes, the high purity and the ion beam quality.*

A short overview on research strategies, on experimental work and application of ISOLDE produced radionuclides used in the field of bio-medicine over a period of more than 2 decades will be given. Special attention will be directed to the radio-lanthanides, because they can be seen as one single element providing the unique possibility to study systematically relationships between molecule parameters and a biological response without changes in the basic tracer molecule. Among those radionuclides we find any radiation properties we wish (single photon emission suitable for SPECT, positron emission suitable for positron emission tomography (PET), α -, β - and Auger electron emission. The radioactive isotopes obtained at ISOLDE are primary singly charged ions of 60 keV energy, very suitable for a new principle for a radionuclide generator system: the implantation type of the $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$ -generator for in vivo use and useful for new labelling procedures.

1 Introduction

The most important aspects in the field of nuclear medicine today are to increase of specificity of functional imaging, the quantification of medical imaging techniques based on PET and SPECT and the development of new high specific radiotherapeutics for systemic therapy. All aspects can be significantly supported by using radioactive ion beams (RIB) produced at RIB facilities or ISOLDE, the world leading isotope separator on line, which is located at CERN [1, 2].

There are three main aspects which make ISOLDE produced radio-isotopes such valuable for use in bio-medical research and nuclear medical application:

- i. availability of exotic or uncommon radio-isotopes
- ii. the unprecedented high purity (isotopically separated and carrier-free) and
- iii. the ion beam quality of the radionuclides.

Spallation reaction makes available a complete range of isotopes having as complete a diversity of types and energies of radiation, of half-life, and of chemical properties as one would wish. Again, of special interest is the simultaneous availability of the full range radio-lanthanides from just two standard ISOLDE target systems.

2 Production techniques of radio-lanthanides using ISOLDE

In the interaction of high-energy protons with a suitable target material the radionuclides are formed unspecifically in three different main pathways:

fragmentation, fission and spallation. The low energy loss of 1 GeV protons while passing through a solid material allows us to use very thick and heavy targets (the normal target is 20 cm long). From Tab.1 in [6] we learn that 3 target ion source systems are most useful for the production of the wanted isotopes: the uranium-carbide is suitable for the production of the $^{225}\text{Ra}/^{225}\text{Ac}$ via spallation and for the production of the neutron-rich isotopes of the light lanthanides (^{141}Ce , or ^{153}Sm) from fission. The neutron deficient nuclides of the lanthanides are best obtained using the tantalum foil target. In a similar way, the radio-yttrium is produced from a niobium foil target. In all cases a surface-ionization ion source is applied similar to the design described in [3].

In practice we produce our radio-lanthanide preparations in the following way: the 1.0 or 1.4 GeV proton beam (typically 3.3×10^{13} protons per pulse, corresponding to 1 - 2 μA integrated beam current) from the CERN PS booster interacts with a $112 \text{ g}\cdot\text{cm}^{-2}$ Ta foil target kept at a temperature of $2200 \text{ }^\circ\text{C}$. Under these conditions the radiolanthanides produced in the spallation process are released very fast from the target material [4] and migrate to the ion source where they are ionized by surface ionization on a W - surface kept at $2500 \text{ }^\circ\text{C}$ [2]. The singly charged positive lanthanide ions are then extracted from the target ion source unit by a 60 keV extraction electrode. The ions are separated according to mass-to-charge ratio in an electromagnetic separator with a resolution of $M/\Delta M = 2400$ (GPS = General Purpose Separator). Any desired radioactive ion beam can then be selected and transported to a collection point through a beam transport line. Details of the radiochemical separation process are described in [5]. We collected our

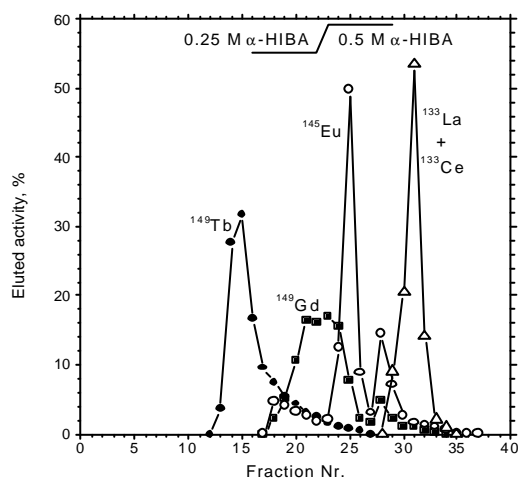


Figure 1
Separation of the $A = 149$ isobars obtained in the on line isotope separation process at ISOLDE by using cation exchange chromatography. Column: Aminex A 5 in NH_4^+ form, $3 \times 60 \text{ mm}^2$, eluent: α -HIBA, elution speed: $100 \mu\text{l}/\text{min}$, (one drop = one fraction). The isotopic content of each fraction has been determined by high-resolution gamma ray spectrometry [5].

wanted radiolanthanide by implanting the ions of the desired mass number into a thin layer of KNO_3 , which was molten on Al-backings. The sample size was 8 mm in diameter with about 0.2 mm thickness, which amounts to 20 mg of KNO_3 . A typical radio-chromatogram, obtained is shown in Fig.1. The Tb-fraction was combined and evaporated to dryness on a PTFE backing. By further heating the eluting agent (α -HIBA) is completely released. The same technique has been adapted to any other isotope of the radio-lanthanides. The remaining radioactivity was taken up in 100 μl of 50 mM HCl solution and used as stock for the different systematic in vivo studies for labeling of different bio-active molecules. The production yields for the radio-lanthanides range from $1 \cdot 10^9 - 2 \cdot 10^{10}$ ions per second, depending on mass number, ionization efficiency and release properties. Thus, we can produce batches of radio-lanthanides at the ISOLDE facility of the order of 4 GBq for the shorter-lived ^{142}Sm , of 1 GBq ^{149}Tb , or of 10 MBq of the long-lived ^{143}Pm for example.

3 Systematic bio-kinetic studies with radio-lanthanides

The radio-lanthanides are of special interest for bio-medical research: they are three-valent metallic radionuclides which show any radiation properties we wish. Using high resolution gamma spectroscopy we measured simultaneously the biodistribution of carrier-free radionuclides of several rare earth elements ($^{87,88}\text{Y}$, ^{141}Ce , ^{147}Nd , ^{143}Pm , ^{145}Sm , ^{147}Eu , $^{149,153}\text{Gd}$, ^{155}Tb , ^{159}Dy , ^{167}Tm , ^{169}Yb) and ^{225}Ac in tumor bearing nude mice and Wistar rats. The radionuclides were injected as free chelates (citrate, EDTMP and others) or bound to DTPA-conjugated monoclonal antibodies and peptides (review in [6], see Fig.2).

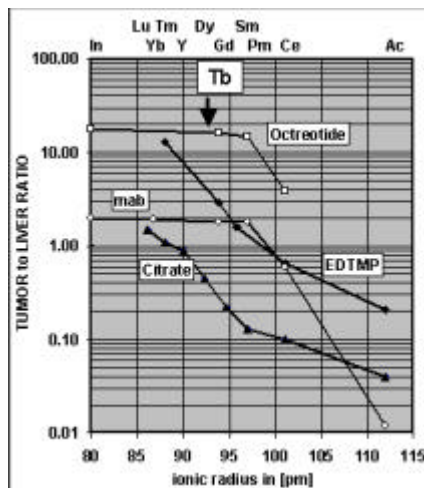


Figure 2. Comparison of the bio-distribution of different tumor seeking radio-tracers labeled with radio-lanthanides, ^{225}Ac and ^{111}In . The ratio of radioactivity uptake in tumor to liver tissue is plotted versus the ionic radius of the radio-metal [6]. Mice and rats bearing different tumors were used in this experiments. For the citrate system the T/L ratio is decreasing from about 1 for the heavy lanthanides with increasing ionic radius down to 0.04 for Ac. The same tendency is seen for the EDTMP system ([EDTMP] = 2 mMol, injected volume 0.5 ml per rat), however the values are one order of magnitude higher due to the reduction of liver uptake. In case of monoclonal antibodies no difference were observed for In and the heavy lanthanides down to Pm. With higher ionic radius the T/L ratio decreases, reaching a value of 0.01 for Ac. Highest values for the T/L ratio are obtained with Octreotides. The stability constant of the Pm-DTPA complex ($\log \beta = 22$) seems to be the threshold, below which the in vivo stability of the metal-ligand complex becomes insufficient.

The liver uptake is very strong influenced from the ionic radius of the radio-lanthanides in case of the free chelates [7]. The release half-time of radiolanthanides from tumor tissue was determined to be of the order of 7 days [9]. The EDTMP-ligand concentration plays an important role for the biokinetic behavior [8]. In case of conjugated antibodies and peptides (back-bone DTPA linker) no differences in the biokinetic behavior were found for Pm and higher Z lanthanides [9]. For the lanthanides with larger ionic radius the tumor to liver uptake ratio drops slowly down. ^{225}Ac -labeled antibodies show by far insufficient in vivo stability. This powerful technique for the simultaneously study of biokinetic behaviour is now being recognized and supported within the EU-COST program [11].

4 Exotic radionuclides of the rare earth elements for systemic radionuclide therapy and in vivo dosimetry

Using the ISOLDE Facility we have access to radio-lanthanides, which have a potential in systemic radionuclide therapy or positron emission tomography in carrierfree quality. Consequently, the RIB-technology would allow to study in detail the relationship between the specific activity of a given tracer and the biological response; or in addition to that relationships between the type of emitted particles (alpha, beta, conversion and Auger electrons), the particle energy and the related biological response. This kind of basic research will contribute to an optimization of systemic radionuclide therapy. Most interesting in this concern is the availability of an 4.1 hour partial alpha emitting metallic radionuclide (^{149}Tb) which showed excellent radiotoxic properties in combination with bioconjugated monoclonal antibodies [12]. The labeling yield of our CHX-DTPA mab with the alpha emitting ^{149}Tb was instantaneously better than 95 % and a specific activity of 250 MBq/mg mab was obtained [10].

The individual in vivo dosimetry will be an integrated component in the protocols for systemic radionuclide therapy. First clinical studies demonstrated clearly, that the presently applied approach to perform the dosimetry for ^{90}Y DOTATOC patients via the corresponding ^{111}In DOTATOC SPECT provides wrong results [13]. Only quantitative PET imaging using the same tracer molecule labeled with a homologue positron emitting radionuclide would provide objective dosimetric information. Essentially, the positron emitting ^{86}Y would be an ideal isotope for the individual in vivo dosimetry for the therapy with ^{90}Y [14]. The RIB-technology provides the access to any of the metallic positron emitters of this interesting group of elements, including the ^{85}Y , ^{44}Sc and several lanthanides. The positron emitters $^{134}\text{Ce/La}$, $^{138}\text{Nd/Pr}$, $^{140}\text{Nd/Pr}$ and $^{142}\text{Sm/Pm}$ provide excellent PET images [15] (see Fig.3). In vivo studies have been performed with the shortest lived isotope of this class, with $^{142}\text{Sm}/^{142}\text{Pm}$ [16,17] (Fig.4). In all these cases we have to deal with generator nuclides, the positrons are emitted from the daughter nuclides, which are very short lived. The mother isotopes provides the longer half life suitable for the labeling and imaging protocols. There are two aspects to consider:

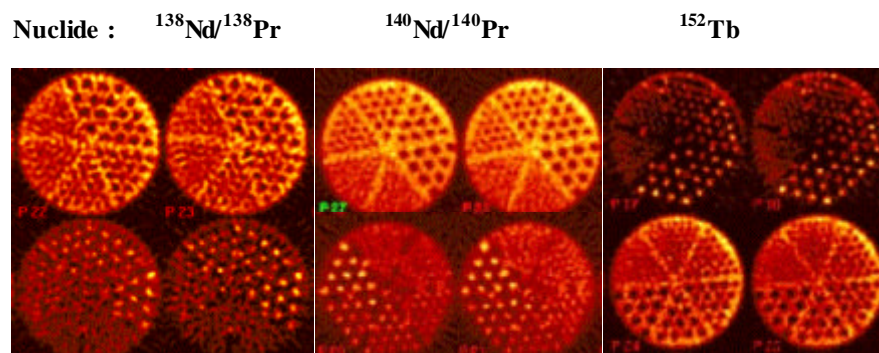


Figure 3. PET images performed with the JASZCZAK phantom and positron emitting lanthanides produced at ISOLDE facility at CERN [15]. For details see text.

the first is that these isotopes have very good radiation properties, which means high positron branching rate and no or only very little gamma contribution. Secondly, the daughter isotopes are released from the original tracer molecule due to the EC process. In an earlier study it has been demonstrated that the EC process leads unavoidable to a 100 % bond rupture, while in case of beta decay 80 % of the daughter atoms can stay in the original tracer molecule [18]. From our systematic biokinetic in vivo studies (see chapter 3) we learnt, that once the lanthanide is trapped in a certain tissue, it stays there quite stable [9].

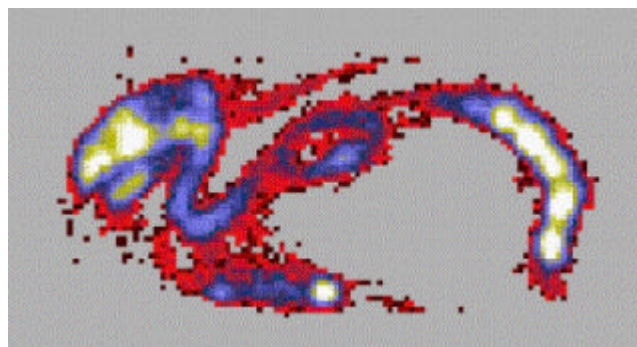


Figure 4. The image represents a 3 mm sagittal slice of a positron emission tomogram of a young rabbit 60 minutes p.i. of a solution containing EDTMP as chelating ligand and 30 MBq ^{142}Sm as the positron emitting isotope. The PET image was recorded using the rotating prototype PET scanner of the Division of Nuclear Medicine of the Geneva University Hospital [16,17]. The isotope ^{142}Sm was produced at the CERN ISOLDE facility. PET in combination with ^{142}Sm provides a quantitative measurement of radioactivity uptake in tissue regions of interest allowing the dose applied using ^{153}Sm treatment to be monitored precisely in order to optimize the therapy (individual in vivo dosimetry).

5 Implantation techniques open new possibilities

When ions with a certain energy are implanted into metals the plastic material, than the implantation channels are burned out and remain open. This effect is used in practice for producing nuclear filters. In a previous paper we proposed to apply this effect for a new approach of a $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$ generator for use in nuclear medicine [19, 20]. The ^{81}Rb -ions produced at ISOLDE carry an energy of 60 keV. If we implant these 60 keV $^{81}\text{Rb}^+$ -ion in plastic foils (Mylar or Kapton for example) the ions are finally located on the bottom of the implantation channel and the daughter product, $^{81\text{m}}\text{Kr}$, which is formed in the radioactive decay process is allowed and able to diffuse out through the channel to the surface where it can be carried away by any eluting media. As eluting media one can use any gas (air for example) or any liquid (water or saline solution). Most exciting is the new possibility to configure the generator in the form of a catheter. From our experimental studies we learnt that if we implant the ^{81}Rb with a density of up to 10^{13} ions per cm^2 , the elution yield of the daughter $^{81\text{m}}\text{Kr}$ is close to 100 %, while the ^{81}Rb is not released. At higher implantation densities the surface of the implantation material loses its configuration, becomes amorphous, with the consequence that we wash out large fractions of the implanted ^{81}Rb . At very high implantation densities the heat deposition causes a destruction of the material by melting, causing zero release of daughter activity and no wash-out of ^{81}Rb .

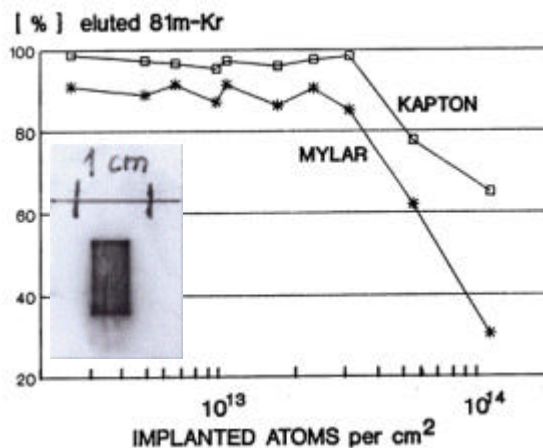


Figure 5. Yield of $^{81\text{m}}\text{Kr}$ eluted from the implantation type $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$ generator over the implantation density. The beam of mass separated $^{81}\text{Rb}^+$ -ions has been swapped over a surface of 0.5 cm^2 (insert shows an autoradiogram of a sample). The elution yield is nearly quantitative for the more temperature resistant Kapton material at implantation densities of around 10^{13} $^{81}\text{Rb}^+$ -ions per cm^2 . For Mylar foils the elution yield is only slightly lower. One can use air or any liquid (water, saline solution, plasma or even blood) as eluting agents. At high implantation densities the surface becomes destroyed, the elution yield drops down dramatically [20].

In Fig. 5 we present some experimental results. A surface of 1 cm^2 can carry $37\text{ MBq }^{81}\text{Rb}$ (corresponding to $8 \cdot 10^{12}$ Rb-atoms). It is not a technical problem to implant these amount of ^{81}Rb activity into the tip of a 3 mm diameter catheter (1 cm implantation length is required). This catheter is really an “in-vivo generator”. One can bring the tip of the catheter to any place in a patient, where one would like to image the perfusion. It has been shown in the mean time that these technology works perfectly [21].

In a similar way ion implantation techniques is applied to label stands with ^{32}P (for use in cardiovascular brachytherapy) [21]. One can assume that this way of implantation may open a new approach for labeling of macromolecules, macro-aggregates or microspheres. The problem will be the radiation damage, since the implantation energy is high. On the other hand, today exists possibilities to decelerate the ions dawn to very low energies making normal chemical labeling of sensitive molecules (monoclonal antibodies for example) possible as well.

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