5 From Radiochemistry of the Lanthanides to ^{225}Ac and the Interference with Richard Baum

Gerd Juergen Beyer

5.1 Personal Introduction

In 1990, Heinz Schelbert, one of the pioneers of PET, has been asked during an invited lecture at the ZfK Rossendorf, why it happens that few newly created PET centers have significant success and others do not have at all. His answer was simple and clear: institutions where physicians accept scientists, for instance radio-chemists and physicists as equal partners and where they collaborate truly together, there the progress is programmed. In my scientific carrier, I have been privileged to have those fruitful collaborations, for instance with Prof. W. G. Franke, Clinic of Nuclear Medicine of the Medical Academy Dresden in the late 70-th–end 80-th and further at the end of my carrier with Richard Baum. He is one of those distinguished nuclear medical physicians, he is not only just collaborating with experts in different scientific disciplines (biochemistry, radiochemistry, physics, and others), he is promoting those close collaboration and has created a network around the world independent on political and economic situation in countries like Cuba, China, South Africa, and others. His strong engagement is motivating us in developing new techniques making new radionuclides available toward personalized nuclear medicine. In this contribution, I try to give a historical overview over the related research work that has been performed in Dresden, Dubna, and Geneva starting from the methodical developments for nuclear physics basic research in the late 60-th until the recent input especially with the Tb-isotopes to the Bad Berka activities guided by Richard Baum.

It was around 1954/1955: The International conference on peaceful use of nuclear technology in Geneva induced the foundation of national nuclear research centers all over the world, for instance CERN, JINR Dubna, KFK, Jülich, ZfK Rossendorf, etc. Nuclear technology became a fundamental part of the academic education programs. In the former GDR, the Faculty of Nuclear Technology at the Technical University Dresden was created including the chair "Radiochemistry". The new technology did fascinate me and with the age of 15 years, I decided that "Radiochemistry" should be the direction for my future professional carrier. The study in Radiochemistry at TU Dresden began in 1960 at TU Dresden. The Faculty of Nuclear Technology was closed down again in 1962, however direction Radiochemistry continued under the umbrella of inorganic chemistry. My first radioactive preparation I received in 1963 that was produced from Uranium-fission at the Rossendorf Research Reactor by Gerhard Wagner under the supervision of Prof. R. Muenze. G. Wagner finished his Radiochemistry study in Dresden 2

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years earlier. Since that time, we kept close professional relations over a historical period of 55 years.

In this contribution, I try to give a historical overview of the developments of new radiochemical separation techniques which are relevant for making available special radionuclides for biomedical research and nuclear medical application and which have been performed in Dresden (Germany), Dubna (Russia), Geneva and CERN (Switzerland). It starts from the methodical developments for nuclear physics basic research in the late 60-th until the recent input especially with the Tb-isotopes to the Bad Berka activities guided by Richard Baum. Statements and conclusions are essentially strongly influenced by own experiences and a subjective point of view and should not be seen as a general scientific review.

A three-year research fellow ship position at the Joint Institute for nuclear research (JINR) Dubna was offered to me before finishing my diploma. Between the Radiochemistry at the TU Dresden and the Department of Nuclear Spectroscopy and Radiochemistry at the Laboratory of Nuclear Problems in Dubna very close relationships were already established. E. Herrmann (also absolvent of Radiochemistry, TU Dresden in 1963) was already delegated to Dubna and had introduced there a new extraction chromatographic process for separating short-lived light lanthanide isotopes from a very massive lanthanide target [1, 2] (see further below). This task is very similar to the task today: separating ^{177}Lu from massive Yb-targets. It was foreseen to replace E. Herrmann Dubna, since his three-year period was ending. After diploma 1965 and after about 1 year as scientific assistant position at the TU Dresden my scientific activity as radiochemist in Dubna started on 11 January 1967.

5.2 Situation of Nuclear Medicine in the 60-th

In the 60-th the Nuclear medicine was in the process switching from using rectilinear scanners to the planar scintillation camera. The number of available suitable isotopes was very limited. Intense R&D was going on to develop approaches for using ^{99m}Tc as radiotracer for different imaging protocols. The breakthrough was found in 1969 with the introduction of Sn^{2+} as reducing agent for pertechnetate [TcO_4^-] by R. Dreyer and R. Muenze. This invention opened the door to the cold KIT era [3, 4] and induced an enormous increase of the demand in ^{99}Mo/^{99m}Tc-generators.

In the beginning of the 60-th the atomic physicists were highly motivated to study short-lived nuclides far away from the line of beta-stability generally. In this concern, the region of lanthanides was of special interest because of a nuclear deformation in the lanthanide region. This nuclear deformation is also responsible for the alpha decay of several radionuclides in the middle of the lanthanide group (^{149}Tb!). Two international research projects were initiated at that time: ISOLDE at CERN (ISOLDE stays for Isotope Separation On Line Device) [5] and YASNAPP at the Joint Institute for Nuclear Research (JINR) Dubna (YASNAPP stays for **ya**dernaya **s**pectroscopia **na** **p**rotonom **p**utschke) [6]. The Idea for the ISOLDE Facility was born already in 1960 and the on-line separator went into operation in 1967 at CERN. After the shut-down of the synchrocyclotron (SC) at CERN in 1990 the new ISOLDE-2 facility was constructed and connected to the proton beam delivered from the CERN BOOSTER, the heart of the CERN accelerator cascade.

An off-line mass separator for the YASNAPP project in Dubna was proposed in 1967 and became operational in 1969. The semi-on-line system YASNAPP-1 went into full operation in 1971. It consisted of the isotope separator itself, a newly developed surface ionization ion source [7], a self-made fast rabbit system for transporting the irradiated targets to the separator, and a dedicated radiochemical laboratory nearby for fast separation of carrier-free nuclear reaction products from massive irradiated targets.

5.3 How to Make Sort-lived Nuclides Far from Beta Stability

High-energy proton-induced reaction (Spallation reaction) is an unspecific but very powerful and universal tool for producing radionuclides. The

spallation process generates neutron-deficient nuclides of elements left from the target element; fragmentation gives n-rich nuclides of the light elements and fission generates neutron-rich nuclides of elements in the middle. As shown in Fig. 5.1 the higher the proton energy the higher the cross sections of the products far away from Z of the target element. With one heavy Z target element, we can produce practically all nuclides of the whole chart of nuclides. It was and is still a challenge for radiochemists and physicists to pick out one single nuclide from those very complex mixtures (Fig. 5.1).

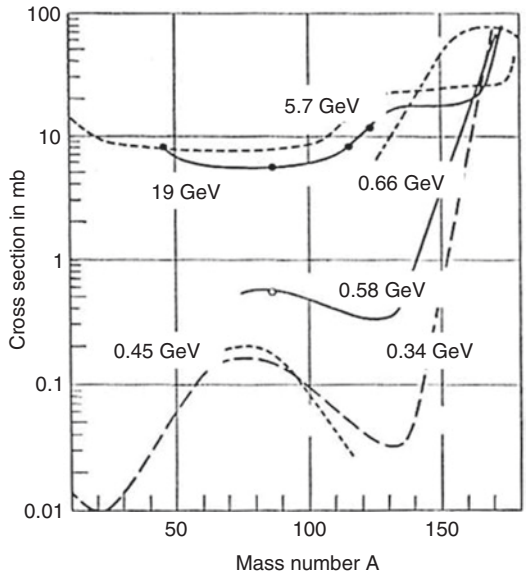

Fig. 5.1 Cross section for the formation of nuclides in interaction of high-energy protons with Ta-target (taken from [8])

Proton beams: The general difference between the two research projects highlighted in (Fig. 5.2) is the following: ISOLDE worked from the very beginning on-line, meaning an integrated unit of a target-ion source is directly connected to the analyzing magnet that separates the radioactive ion beams directly according to their atomic mass. A chemical separation one could make after mass separation, if required. The YASNAPP-1 project in Dubna started in reverse order: first, the radiochemical separation was done and thereafter the mass separation off-line.

In order to meet the physics interest to study the short-lived lanthanide isotopes new innovative separation techniques for lanthanides were developed in Dubna. In the following chapters, only few technologies for fast separations in the lanthanide region will be explained. A general overview one can find in [9].

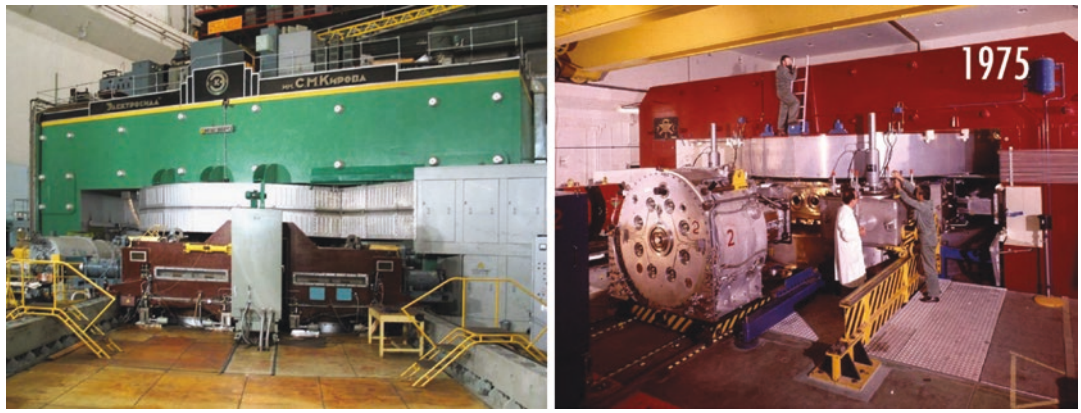

Fig. 5.2 (Left) Synchrocyclotron in Dubna (1984 reconstructed to a phasotron) providing a 660 MeV proton beam, this accelerator became operational in Dec1949 and was the largest accelerator at that time. (Right) the synchrocyclotron at CERN, that delivered 600 MeV protons, operated from 1954 to 1990

5.4 Optimized Extraction Chromatography

From Fig. 5.1 we learned that when using 660 MeV protons as initial reacting particle interacting with a Ta-target the yield for nuclear reaction products (nuclides of the lanthanides) drops down relatively fast when we move away from Z of Ta. Consequently, there was the pressure to use massive lanthanides itself as target for producing strong sources of carrier-free short-lived radionuclides of the lanthanides. Figure 5.3 shows the radio-chromatogram for the separation of the carrier-free light lanthanides from a massive irradiated Er matrix. The point is that when loading the chromatographic column with macroscopic quantities of a lanthanide we find a very sharp front of the elution profile of the macroscopic component. This break-through point can be identified nicely and calibrated. In front of this break-through point the lighter lanthanides are eluted with high yield in carrier-free form, as long as the target material is not contaminated with lighter lanthanides. For cation exchange chromatography exist similar conditions, which can be used today for separating ^{177}Lu from massive Yb-targets for instance for shortening the separation time significantly.

The first ~150 ml eluate that contained the wanted short-lived carrier-free radionuclides of the light lanthanides was evaporated and the products were thereafter separated into the different lanthanide fractions using a small separation column. The overall time for the isolation of a Tb-fraction from a 2 g Er target was about 45 min. In order to be faster one can make use of the mechanical recoil effect during the irradiation. G. Pfrepper proposed to irradiate suspension of very fine grain powders of insoluble materials (for instance phosphates of Lanthanides, Ta_2O_5, WO_3) as suspension in diluted mineral acid. After a simple filtration process, one can harvest up to 40% of the nuclear reaction products in the filtrate [10].

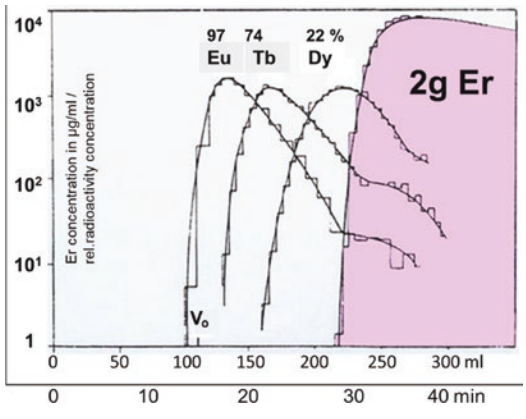

Fig. 5.3 Separation of lighter radio-lanthanides from massive Er-target by extraction chromatography: Column: 100 g silicagel, 26 × 410 mm (0.6 g HDEHP/1 g silicagel), elution with 2.68 M HCl, 7 ml/min at 40 °C (see [1, 2, 9])

5.5 Separations Based on Szilard-Chalmers Effect

The 60-th was the high time of hot atom chemistry or recoil chemistry. My task for the research program in Dubna was to look after the potential using Szilard-Chalmers effects for preparative separations in the lanthanide region. The focus were complex compounds of the Lanthanides with complexions (polyamino-polycarboxylic acids) like EDTA or DTPA. First systematic isotope exchange studies were performed and the obtained results can be summarized as follows [11]:

The isotope exchange rate R in the system Ce^{3+}/[CeEDTA]$^-$ does not depend on the Ce^{3+} concentration.

The isotope exchange rate R depends linear on the H^+-concentration in the EDTA system (see Fig. 5.4 left).

The rate constant k_1 for the isotope exchange process is directly proportional to the stability constant β_{LnY} of the complex.

The exchange rate is generally low in neutral pH regions. This pH region is suitable to study the chemical effects of radioactive decay processes (see Fig. 5.4 right).

As a first conclusion of these results crystalline complex salts of the composition $(NH_4)_2$[Ln DTPA] x 2 H_2O were synthesized with a well-defined excess (0.1 Mol-%) of free Ln^{3+} (Ln = Er, Dy, Gd, Eu). About 1 g of those and material was

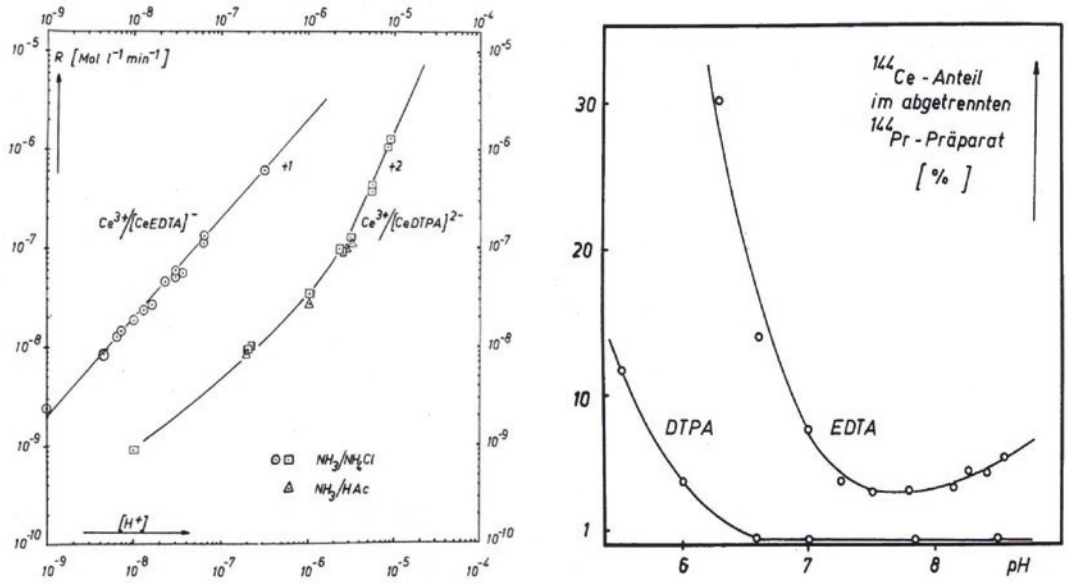

Fig. 5.4 Influence of the pH on the isotope exchange between Ce^{+3}-ions and complexed $[CeY]^{n+}$-ions, where Y is EDTA and DTPA. The isotope exchange is significantly smaller for the DTPA system ([11] for more details see text)

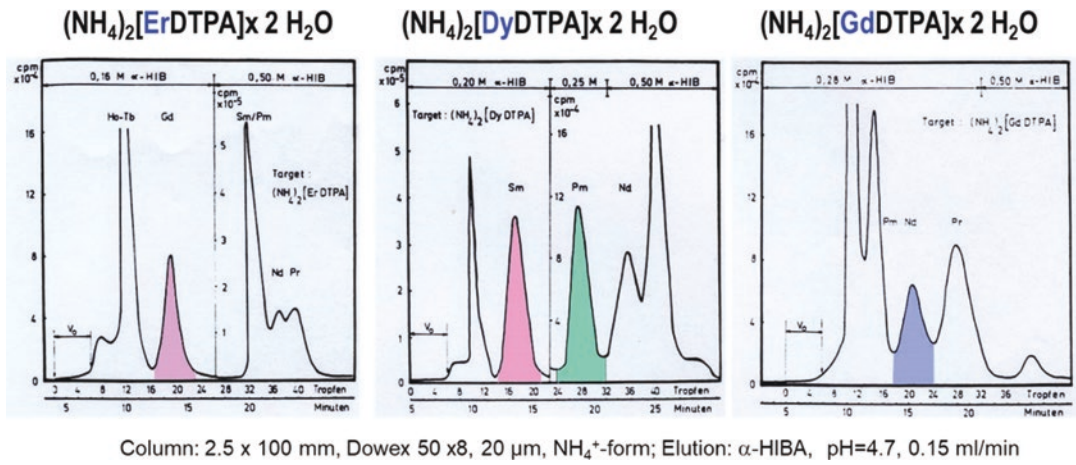

Fig. 5.5 Radio-chromatograms of preparative separation of short-lived radio lanthanides obtained in bombardment of different lanthanide DTPA complex compounds with 660 MeV protons

then irradiated with 660 MeV protons at the Dubna synchrocyclotron, thereafter dissolved in 5–8 ml H_2O that contained ~10 mg of a fine grain cation exchange resin (first we used "self-made" very fine resin, later on suitable resins became available on the market: Aminex A5). The nuclear reaction products stabilize as free ionic Ln^{3+}-ions. Because of the very low isotope exchange rate, we are able to collect the wanted short-lived nuclides at the cation exchange resin within less than a minute and transfer this resin with the adsorbed products to a small cation exchange resin column for fast chromatographic separation [12]. Figure 5.5 shows those fast chromatographic separations for three different target complexes. The reader needs to consider that the radionuclides are short-lived and consequently during the separation process we generate daugh-

ter nuclides of neighboring elements. The fraction peaks look by far not that sharp as usual. The time needed for obtaining a clean fraction of a wanted lanthanide element took about 15 min; the total volume of one fraction was between 3–5 drops (~150 µl). The fastest separation was 8 minutes (for ^{144}Gd, half-life 4.5 min).

It was 1970 when P. Gregers Hansen, Prof. of Physics University of Aarhus (Denmark) and one of the Danish initiators of the ISOLDE program, visited the JINR Dubna. He was very much impressed by the obtained results of the fast radiochemical separation techniques for the Lanthanides and he invited me for a half-year fellowship position in his Institute of Physics in Aarhus (DK). His former radiochemist in that position (Helge Ravn) has been delegated to the ISOLDE project to CERN. I mention this because this was the real start of a close, continuous, and fruitful collaboration with CERN ISOLDE.

In Aarhus, I studied in detail the chemical effects of different radioactive decay processes. The Lanthanide group is indeed ideal for this kind of study; this group contains a complete range of radioisotopes having as complete a diversity of types of radiation and energy of radiation and half-life one would wish. Consequently, one could study the behavior of any decay mode without changing the basic chelating ligand. The different decay modes were: beta decay accompanied with gamma radiation with ignorable low (^{172}Er), medium (^{144}Ce) and high inner conversion rate (^{143}Ce), EC-decay mode (^{134}Ce, ^{135}Ce), isomeric decay with high inner conversion rate (^{137m}Ce). For producing the needed different radiotracers continuous access to the research reactor in Risö was assured (this research reactor has been shut down unfortunately since long time).

The result of this systematic studies can be summarized as follows [13]: The recoil energy of the beta decay is usually lower than the chemical binding energy, thus if we observe a bound brake this must be independent from the decay energy. Pure beta decay leads to 20 % bond brake due to

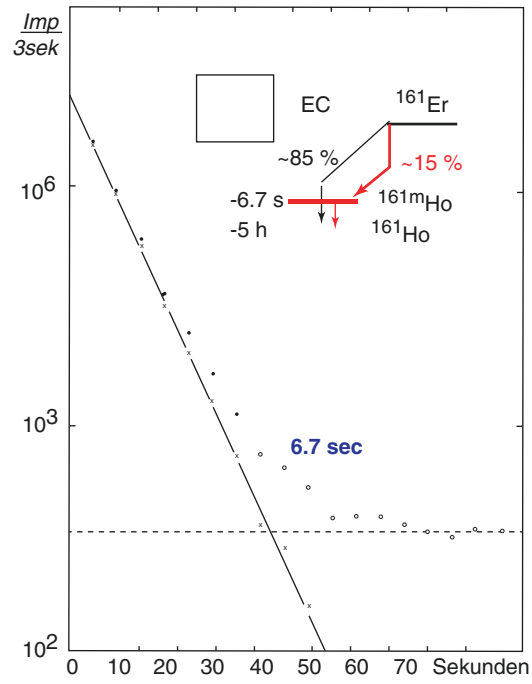

Fig. 5.6 New type of radionuclide generator based on chemical effects after radioactive decay. The mother nuclide ^{161}Er is been adsorbed as [^{161}Er DTPA]$^{2-}$-ion at a small anion-exchange column, the daughter products were eluted with a neutral 10^{-5}M Er^{3+}-solution [13, 14]

so-called electron shake-off effect. EC decay mode leads to 100% brake of any chemical binding due to Auger effect, independent on the decay energy. Same concerns all inner conversion processes. For alpha decay one has to consider very high recoil energies that cause in any case a complete destruction of the surrounding molecular environment.

These effects in combination with the knowledge of the isotope exchange kinetic allowed designing a completely new principle for radionuclide generators that are based on nuclear effects and not on chemical effects as usual. As an example in Fig. 5.6 the decay curve is shown for the 6.7 s half-life ^{161m}Ho. The mother nuclide ^{161}Er decays with ~15 % via EC to ^{161m}Ho and with ~85% the ground state of ^{161g}Ho. The ^{161}Er has been chelated with DTPA and fixed as [^{161}Er DTPA]$^{2-}$-ion at a

small anion-exchange column, the daughter products were eluted with a neutral 10^{-5}M Er^{3+}-solution. F. Rösch [15] replaced the chelator DTPA later on by the macrocyclic chelator DOTA, which made the generator principle significantly more reliable.

1971 marked a significant milestone in the nuclear spectroscopy of short-lived lanthanide isotopes: the introduction of the surface ionization ion source developed in Dubna under the leadership of V. I. Raiko and H. Tyrroff [7]. With this new technique, we studied the ionization efficiencies for the different Lanthanides showing, that one can separate these isotopes with up to 80% efficiency within few minutes. The same research program we expanded to study the ionization efficiency for the Actinides. And 1991 is the time, when ^{225}Ac first time showed up in our research program. In [16] we describe a method to separate ^{225}Ac from irradiated Th-metal targets combining anion-exchange with the standard cation-exchange chromatography. In the same paper, we documented that the yield for the mass separation of Ac-radionuclides reached a value of 80%. This aspect since we will see later that one can use this technique to clean up ^{225}Ac from the unwonted side product ^{227}Ac. Similar separation yields we measured for some trans-Uranium elements, which we produced in heavy ion induced reaction at the heavy ion cyclotron U-300 of the Flerov Laboratory in Dubna.

A semi-on-line approach by inserting an unprocessed irradiated role of 15 mm × 2.5 mm × 100 μm Zr-Nb alloy foil target directly into the newly developed ion source was demonstrated first time for the identification of the ^{78}Rb [17]. We expected advantages for releasing the Rb from metal matrix because of the significant higher vapor pressure compared to that of the yttrium or lanthanides. This was the usually accepted hypothesis at that time. Later we will see that this hypothesis should be revised. However, with this Rb-experiment we initiated a serious program to study the transport of nuclear reaction products inside refractory metals with focus on the radio-lanthanides.

5.6 High-temperature Release Studies of Radio-lanthanides from Refractory Metals

For obtaining mono-isotope preparations directly from irradiated targets off-line or even on-line, the different radionuclides need to pass the following transport steps:

- Diffusion from the inner target matrix to the surface
- Desorption from the metal surface
- Effusion to the ionizer and finally
- Ionization

For the investigation of the transport processes a special experimental setup has been designed, which used the construction principles of the new Dubna surface ionization ion source. With this special furnace we were able to heat up small target samples within one minute from room temperature to ~3000 °C in vacuum (Fig. 5.7).

The temperature of the samples was controlled by two different techniques: first a W/W-Re thermocouple was inserted into a “black hole” in the bottom of each of the crucibles. Second, the vacuum furnace was tightened on top with a polished quartz plate that allowed measuring the temperature of the sample with a pyrometer. The temperature was adjusted by electron bombardment heating. The 1 mm thick W-winding is heated by few 100 A current to emit electrons, which are accelerated by an adjustable high-tension between 100 and 1000 V for bombarding the crucible. We could heat the small crucibles with up to 1 kW (1 A at 1000 V) power. Small samples of irradiated foils (660 MeV protons) of the following metals with different thicknesses were annealed at different temperatures for different periods: Ti, Zr, Nb, Hf, Ta, W, and Re. The results of these studies are published for each target element (e.g., Ta [18]) and summarized in [19]. Out of the large data set of our experimental results, only few aspects with relevance to the later bio-medical application are discussed later on.

Figure 5.8 illustrates that when heating the irradiated Zr-sample to only 1000 °C first the Y-nuclides are released from the sample and Sr

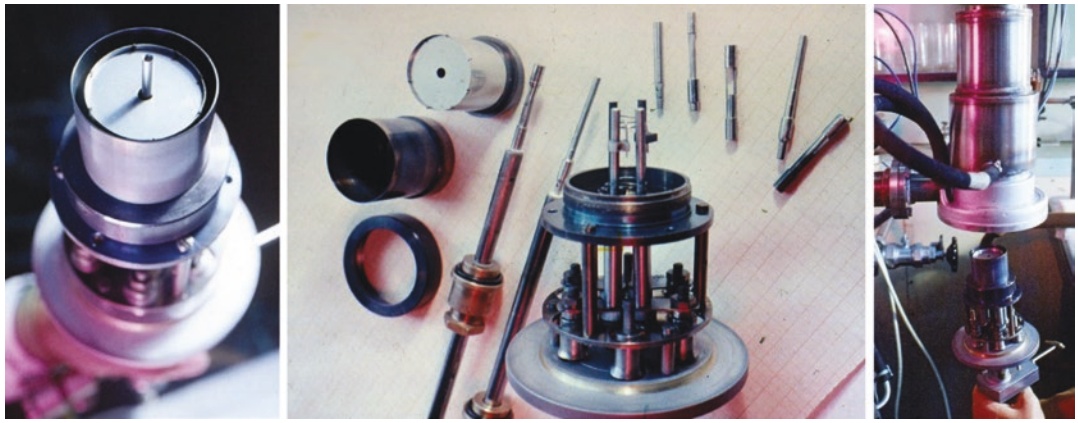

Fig. 5.7 Experimental vacuum-furnace for the study of high-temperature release of radio-lanthanides from irradiated refractory metal foils. Electron bombardment heating allowed heating up samples within one minute up to 3000 °C. **Left**: Insert with heat screens and an eight cm long conical Mo-crucible for thermo-chromatographic separation of radio-lanthanides. **Middle**: details of the furnace: heat screens, different configurations of crucibles and isolated holder for the crucibles. **Right**: Insertion of the furnace into the chilled vacuum stand

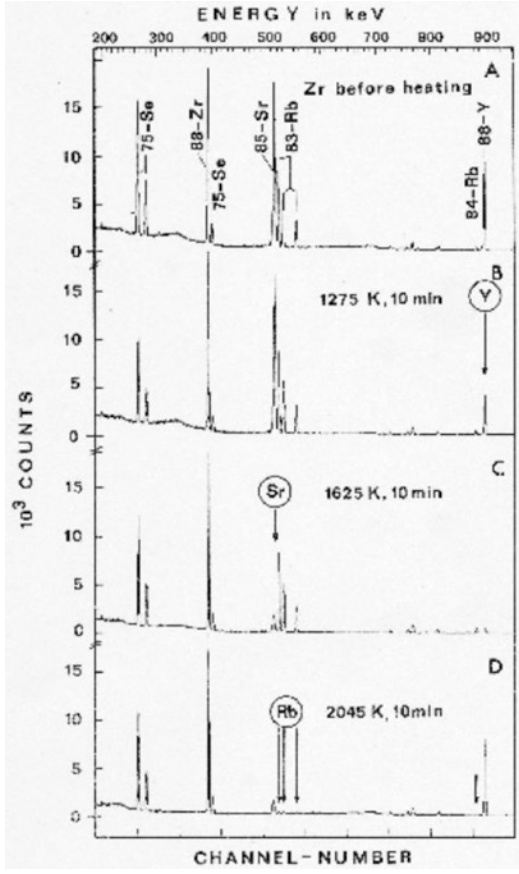

Fig. 5.8 Segments of gamma spectra of Zr-foil samples, irradiated with 660 MeV p (**a**) Zr-sample before heating, (**b**) same Zr-Sample after 10 min heating at 1000 °C, (**c**) after heating at 1340 °C, (**d**) after heating at 1760 °C

und Rb remain practically quantitatively inside the Zr sample. Sr is released only after heating to significant higher temperature (Fig. 5.8c) and Rb evaporates only closer to the melting point of Zr. Quantitatively we obtain a clear linear relationship between the radius of the diffusing specie and diffusion coefficient shown in Fig. 5.9 for two different metal target Zr and Ta.

Interesting is that we did not "lose" the Y (Fig. 5.8). The released Y-fraction was adsorbed quantitatively at the Ta-foil used as an envelope to protect the Zr-sample. The same effect was seen for the release of Sc from irradiated Ti and for the lanthanides released from Hf. We can expect to use this adsorption effect for a new separation technology for producing ^{225}Ac from irradiated Th. Furthermore, since the ^{225}Ra will remain in the Th-matrix we can use the thermic selective release of Ac as a kind of ^{225}Ra—^{225}Ac generator, providing "clean" ^{225}Ac (without ^{227}Ac—that is generated as contamination in the spallation process).

The adsorption enthalpies of the lanthanide nuclides at Ta-surface have been studied using the same vacuum furnace shown in Fig. 5.7 [20]. The adsorption enthalpies increase in the following order: Yb, Eu < Nd < Sc, Ce, Pm, La, Tm. < Gd < Lu, Y << Zr, Hf. The differences in the adsorption enthalpies can be used to separate the corresponding radio-lanthanides as shown in Fig. 5.10.

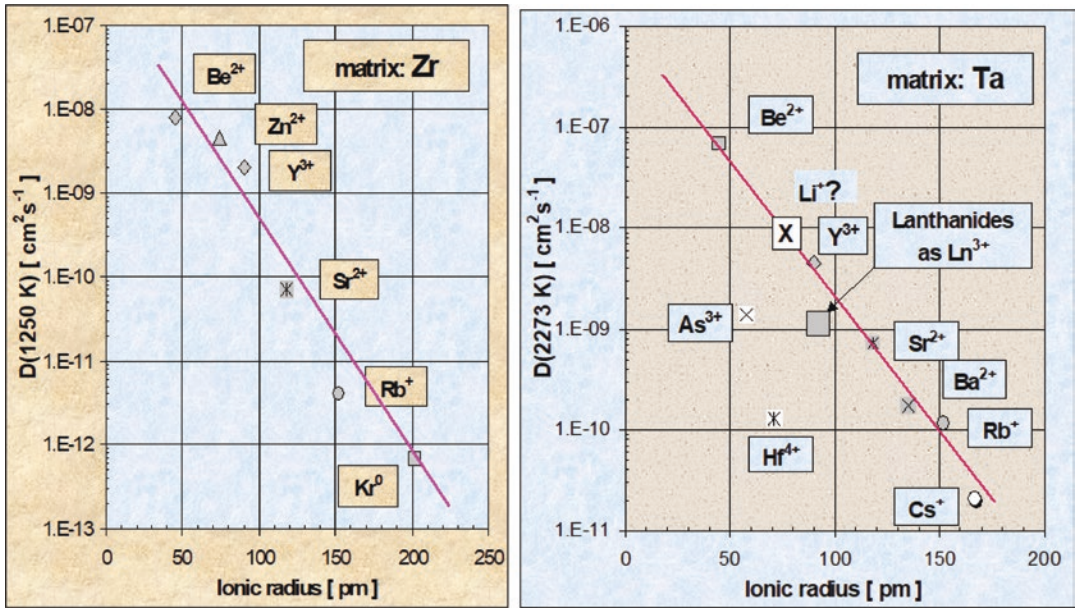

Fig. 5.9 Function of the diffusion coefficient of different nuclear reaction products in Zr (left) for 977 °C and Ta (right) for 2000 °C on the ionic radius of diffusing species. The samples were irradiated with 660 MeV protons at the Dubna synchrocyclotron

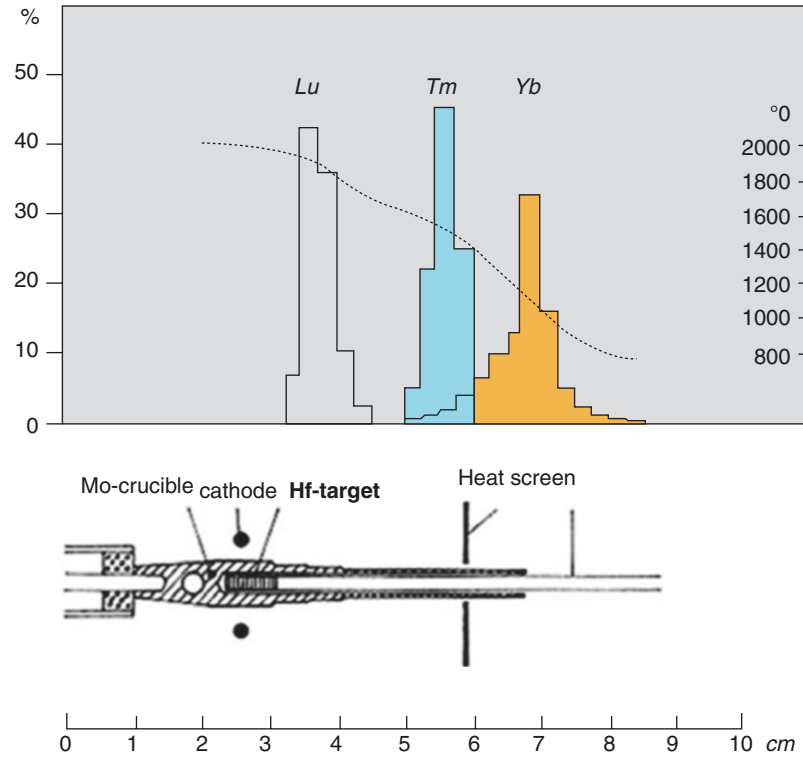

Fig. 5.10 Thermochromatographic separation of radiolanthanides (details see text)

An irradiated Hf-foil target (660 MeV protons, Dubna Synchrocyclotron) has been inserted into the conical-shaped long Mo-crucible shown in Fig. 5.7. A Ta-tube has been inserted into that Mo-crucible as well. The conical shape of the Mo-crucible and the configuration of the heat screens allowed the formation of a temperature gradient along the crucible until the end of the Ta-tube from about ~2200 °C down to 600 °C. When heating the Hf-target by electron bombardment slightly above 2000 °C the lanthanide nuclides evaporate quantitatively from the Hf into the vacuum and then they are distributed along the Ta-tube according to their adsorption enthalpies, generating this nice vacuum-thermochromatogram. The same picture we obtained for Gd–Eu–Sm. The whole process took just 5 min.

5.7 ISOLDE and the On-line Production Lanthanide Nuclides

The above-discussed aspects of diffusion and adsorption of the spallation-produced radionuclides are finally implemented into the ISOLDE technology. Here we will concentrate only on the production of radionuclides of the lanthanides (Fig. 5.11).

By variation of the temperature-distribution in the target-ion source unit and variating the target configuration (foil thickness and grain size of powder), we can strongly influence the chemical selectivity of the extracted lanthanide element. This ISOL technique is a powerful tool to make also longer-lived radionuclides available for biomedical research and nuclear medical application.

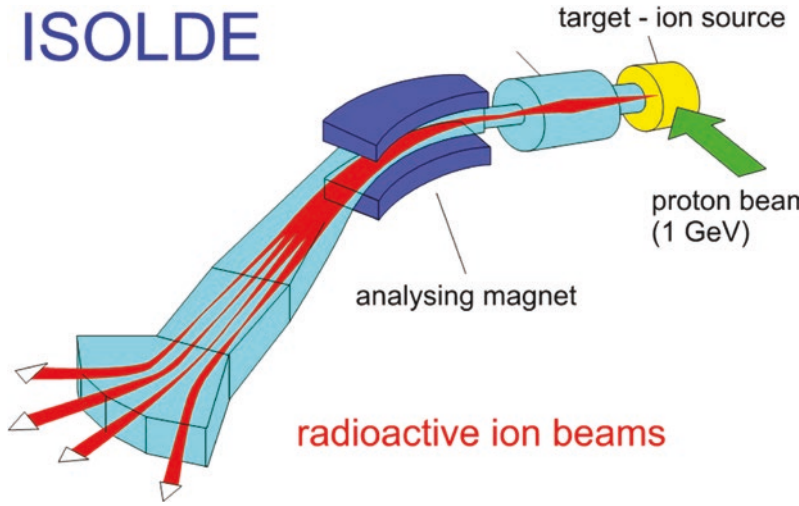

Fig. 5.11 ISOLDE principle: the high-energy proton beam hits a Ta-target, heated to ~2000 °C. The nuclear reaction products (mainly radio-lanthanides) releases from the target matrix by diffusion and desorption from the Ta-surface, effuse to the ionizing surface heated to about 2800 °C, they becomes ionized by surface ionization and the single charged ions are extracted from the target ion source system with 60 kV. The radioactive ion beam is passing the analyzing magnet where they are separated according to the atomic mass number A

5.8 Isotopes in Medicine: Situation in the 60-th

The early pioneering time of Nuclear Medicine was characterized by using "naked" radionuclides like ^{131}I or ^{89}Sr for nuclear medical application. With the introduction of the ^{99m}Tc-generator the radiochemists were occupied to search for useful reducing agents to bring the pertechnetate ion into an oxidation stage suitable for labelling of newly designed organic molecules. The general break through was reached 1969 with the introduction of Sn^{2+} as reducing agent by R. Dreyer and R. Münze [3], which marked the beginning of the cold KIT era around 1970 [4]. In that time, "new" isotopes were introduced into the nuclear medical practice: ^{67}Ga by C.L. Edwards in 1969 and 1973 the introduction of ^{123}I, ^{201}Tl, and ^{111}In. The first [^{18}F] FDG study was performed in around 1978. At this time of radio-isotope application in nuclear medicine (1975 I returned from Dubna to the ZfK Rossendorf and changed from the radiochemistry for nuclear physics basic research to the radiochemistry for medical isotope production. In a simple formless discussion in 1975 with Prof. R. Münze—in that time Head of the Radio-Isotope Department of the ZfK—he told me: "Look, there over we have this Russian cyclotron (U-120), they do something for nuclear medicine (^{85}Sr). Look after, there shall outcome something more". In a second similar discussion, he said: "Here are some Japanese papers about lanthanide application in nuclear medicine, look what is behind". This was the stile in that time to transfer research tasks and induce initiative, essentially without further formalities, but also without providing additional resources. These little moments determined my later occupation and activities. It was a great pleasure supervising thereafter a small but powerful research group: F. Rösch, J. Steinbach, R. Bergmann, M. Kretzschmar, K. Schomäker, G. Kampf, G. Pimentel-Gonzales (Cuba) and others. Within a short time ^{67}Ga and ^{123}I were introduced into the nuclear medical practice of East Germany, ^{81}Rb/^{81m}Kr-generators and ^{111}In followed. ^{211}At became the main subject with a strong internationally well-recognized research group at the TU Dresden. Starting around 1980 the development for introduction of PET in the former GDR became the main research direction of our group. The second main research subject remained the radio-lanthanides for medicine. This was also the time for the interference with Richard Baum; our systematic studies of the bio-kinetic behavior of radio-lanthanides and actinium in tumor-bearing mice and rats and the developments to get access to longer-lived positron emitting metallic radionuclides together with F. Rösch played further on a dominant role in Richard Baum's carrier.

Initiated by the Japanese research on the bio-kinetic behavior of ^{169}Yb and ^{167}Tm (see for instance [21]) we confirmed in [22] that radio-lanthanides (e.g., ^{167}Tm) show the dramatic faster blood clearance compared to ^{67}Ga (Figs. 5.12 and 5.13).

The complete bio-kinetic study of ^{167}Tm was highlighted with the first planar scintigraphy patient study in 1978 in Dresden, Fig. 5.13 [22, 23].

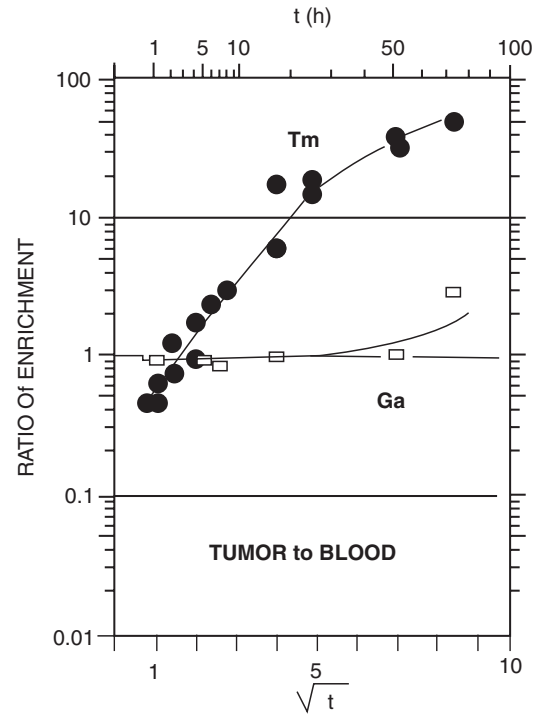

Fig. 5.12 Comparison of the blood clearance between ^{167}Tm and ^{67}Ga simultaneously injected as Citrate in tumor-bearing rats [22]

Fig. 5.13 First planar scintigraphy of a lymphoma patient 5 h p.i. 2 mCi ^{167}TmCit produced at CERN-ISOLDE

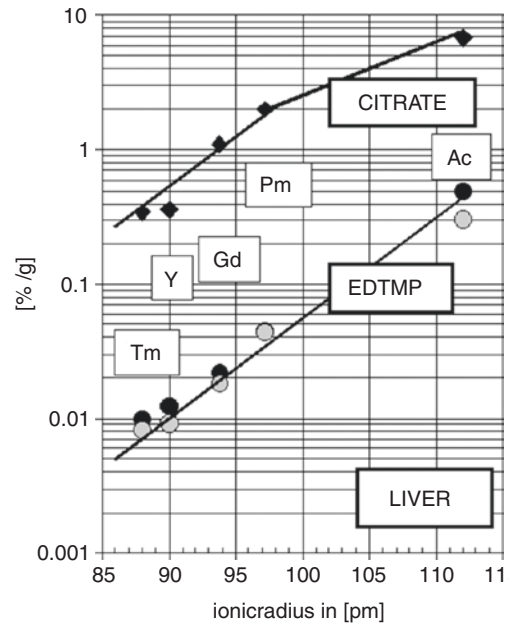

Fig. 5.14 Comparison of the bio-distribution of simultaneously injected radio-lanthanides and ^{225}Ac in Citrate and EDTMP solutions at 5 h p.i. in tumor-bearing rats [24, 26, 27]

In the following years, we collected bio-kinetic data for simultaneously injected cocktails of different radio-lanthanides, yttrium, and Ac in combination with different chelating ligands as citrate, EDTA, DTPA, NTA, and EDTMP. All radionuclide preparations were produced either in Dubna or at CERN ISOLDE as described above. From a stock of suitable long-lived radio-nuclides cocktails were mixed in a way that gamma spectroscopic technique allowed a clear data evaluation of the individual radio-tracer based on their characteristic gamma signals obtained from individual organ measurements. Few of the collected results will be presented here. For more details see [23–25].

Figure 5.14 illustrates two important results: The liver uptake of radio-lanthanides and Ac is strongly determined by the ionic radius of the Lanthanide nuclide. A liver uptake of ~0.01 %/g 2–5 h p.i. is accepted for nuclear medical in-vivo application. These low uptake values are obtained for the heavy Lanthanides and Y. For ^{67}Ga these values are reached only after ~48 h. The light lanthanides and Ac however show unacceptable high liver uptake because of the higher ionic radius. The second message is that when changing from Citrate to EDTMP ligand the liver uptake is reduced by a factor ~50. In further systematic experiments, we studied the influence of the EDTMP-ligand concentration (Fig. 5.15) [25].

In Fig. 5.15 we visualize clearly the competition between the two main excretion pathways: via kidney or liver: with increasing EDTMP concentration the excretion pathways for the individual lanthanides and Ac changes in favor of the urinary excretion. On the other hand, over a large range of EDTMP-concentration there is only little influence on the uptake in tumor and bone. Please note that the highest EDTMP-concentration used in this study was 30 mM, which is nearly three times the isotonicity. In this concern it should be mentioned, that there is no need to inject ^{153}SmEDTMP as such in palliative therapy of bone metastases. We have identical bio-distribution of the radio-lanthanides, if unlabeled EDTMP solution is injected first followed by the radio-tracer-injection thereafter independent on the chemical form: citrate complex or naked cation [28]. Due to these findings the author is convinced, that the main task of ETDMP in this kind of therapy is protecting the liver and not to link the radio-lanthanides into the bone

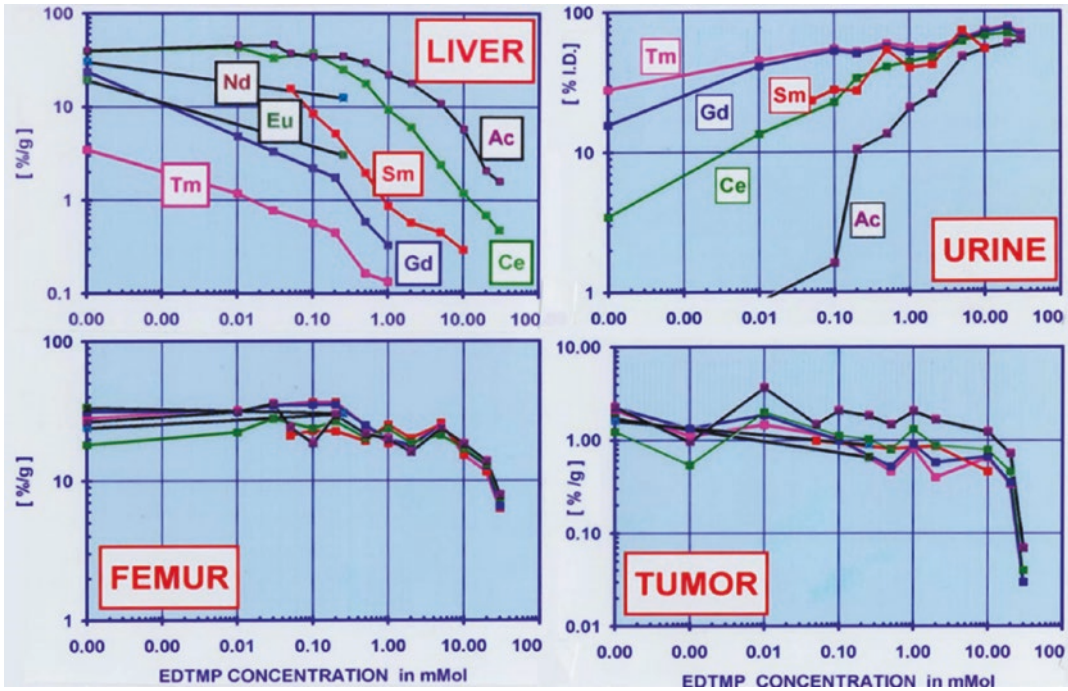

Fig. 5.15 Influence of the EDTMP concentration on the bio-kinetic behavior of radio-lanthanides and ^{225}Ac in tumor-bearing rats [25]

metastasis. The conclusion is, that we can practically use EDTMP as cold KIT in the same way as it is practiced for ^{99m}Tc.

In the 90-th we also started using chelated antibodies (DTPA-RITUXIMAB) and chelated peptides (Octreotide) (Fig. 5.16). In all cases, cocktails of radio-lanthanides and ^{225}Ac were used, meaning the radiotracers were injected simultaneously.

A combined summary of a large data matrix on our bio-kinetic studies performed over several years is presented in Fig. 5.16. For the citrate system, the T/L ratio is dramatically decreasing from about 1 for the heavy lanthanides down to 0.04 for Ac. The same tendency is seen for the EDTMP system (injected volume 0.5 ml per rat with a ligand concentration [EDTMP] = 2 mMol), however the T/L-ratios were about one order of magnitude better due to the reduced liver uptake in case of EDTMP compared to Citrate. In case of the DTPA-conjugated monoclonal antibodies no differences 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. The in-vivo stability is far below the requirement. Best values of the T/L ratio were obtained with Octreotides. The stability constant of the Pm-DTPA-mab complex ($pK_{ß}$ ~ 22) seems to be a threshold: for lower complex stability the in vivo stability of the metal-ligand complex becomes insufficient. Today we know that by changing the conjugated chelator DTPA by a macrocycle chelators like DOTA we increase the in vivo stability in a way, that there are no differences anymore between the different lanthanides. Even Ac can be used without changing of the tracer molecule. This was a great breakthrough into the direction of personalized nuclear medicine. Today we can use one basic bio-specific compound without any changes for any radionuclide of this group of elements independent on the decay mode and mode of application: for SPECT, PET, or therapy. A great step towards precision oncology.

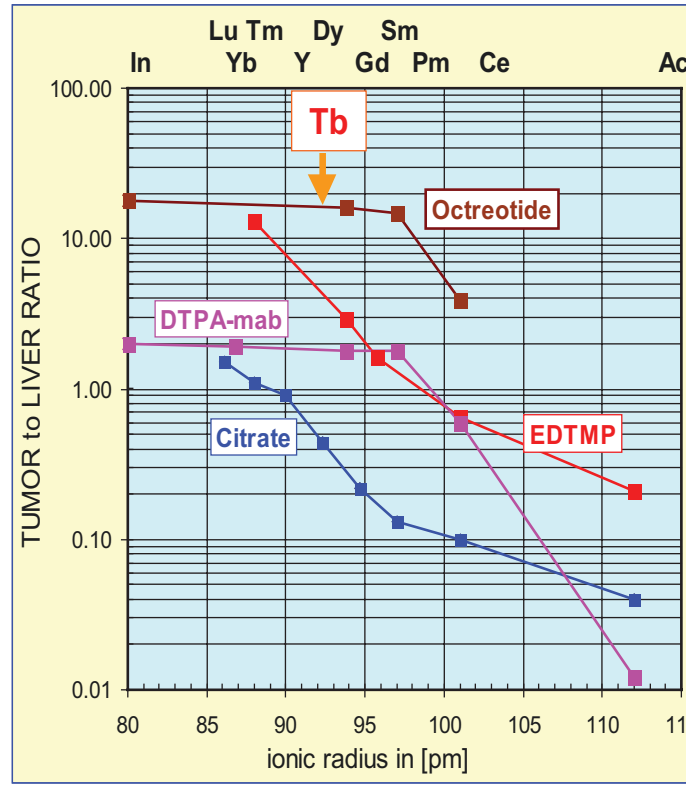

Fig. 5.16 Comparison of the bio-distribution of different tumor seeking radio-tracers labeled with radio-lanthanides, ^{225}Ac and ^{111}In. The ratio of radioactivity uptake in tumor to liver tissue is plotted versus the ionic radius of the radio-metal [26, 27]. For more details see text

5.9 Metallic Positron Emitters

In the later 80-th we started in Rossendorf together with F. Rösch to think about metallic positron emitters for PET [29]. The list of potential candidates contained ^{44}Sc, ^{68}Ga, ^{86}Y, the positron emitters of the lanthanides, and others. This new direction became later on the dominant scientific field of F. Rösch with great impact in the activities of R. Baum especially when bringing the theranostic pair ^{68}Ga /^{177}Lu to the clinical routine. In the early 90-th we performed in Geneva several PET-phantom studies with the prototype of the rotating PET scanner (RPT 1), designed by David Townsend. This was the first PET scanner in Geneva. In Sept.1994 we performed a PET scan with a normal rabbit injecting the beautiful positron emitter ^{142}Sm (72 min), produced at ISOLDE [30], aiming to use this as tool **for *individual in-vivo dosimetry*** for the treatment with ^{153}SmEDTMP. The industrial producer of the ^{153}Sm EDTMP radiopharmaceutical for palliative treatment of bone metastases rejected the related proposal. Anyhow, this PET image of the rabbit done in 1994 was selected to beautify the cover page of the CERN Grey Book 1994 [31]. The time was simply not ready to understand the importance of the quantification, the terminus "Theranostica" was not yet born. PET scans with the mentioned RPT-1 scanner have been performed with other positron emitters of the lanthanides: ^{138}Nd/^{138}Pr, ^{134}Ce/^{134}La, ^{140}Nd/^{140}Pr, and 1996 also with ^{152}Tb and ^{149}Tb. In Fig. 5.17 fragments of all those PET-scans are presented. With this only RPT-1 PET scanner, the images for ^{152}Tb were acceptable while for ^{149}Tb the quality was poor.

At the EANM congress 1998 in Berlin we presented a summary of the bio-kinetic studies with the focus on the alpha emitter ^{149}Tb asking the question: "Is ^{152}Tb suitable to monitor tissue doses in alpha therapy with ^{149}Tb using PET?" We also presented the table of the four interesting Tb-isotopes (Fig. 5.18) illustrating the unique

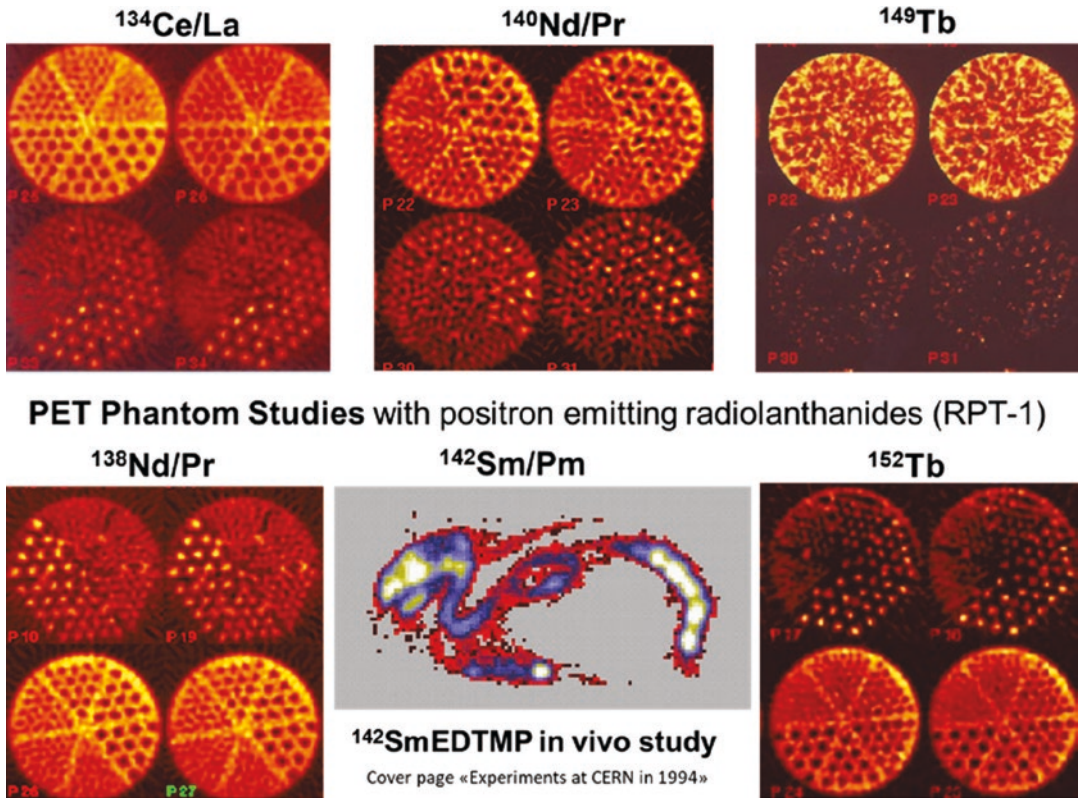

Fig. 5.17 PET phantom studies with the Rotating Pet scanner at the University Hospital of Geneva using ISOLDE produced positron-emitting radionuclides of the lanthanides performed 1900–1995

Fig. 5.18 The four Tb isotopes with nuclear medical relevance for α- and β-therapy, PET, and SPECT [32, 33]

isotope $T_{1/2}$	decay mode	energy [keV]	branching [%]	production route
^{161}Tb 6.9 d	β^- max mean photons	590 195 48.9 74.6	100 14.8 9.8	^{160}Gd (n,γ) → ^{161}Gd → $\beta^-_{(3.6\ min)}$ ^{161}Tb
^{155}Tb 5.32 d	EC photons	 **86.2** **105.3**	100 **31.8** **24.9**	Ta (p,spallation) ISOLDE diverse cyciotron reactions **^{155}Gd (p,n) ^{155}Tb**
^{152}Tb 17.5 h	β^+ max EC photons	2800	**20** 80 diverse	Ta (p,spallation) ISOLDE diverse cyciotron reactions
^{149}Tb 4.1 h	α β^+ max EC photons	**3970** 1800	**17** **7** 75 diverse	Ta (p,spallation) ISOLDE **^{142}Nd (^{12}C,4n) ^{149}Db** **^{152}Gd (p,4n) ^{149}Tb** other HI reactions

properties of terbium, combining all main decay modes suitable for specific nuclear medical applications: beta-therapy (^{161}Tb), SPECT imaging (^{155}Tb), PET-imaging (^{152}Tb), and finally alpha therapy (^{149}Tb) [32, 33]). Tb is the only element, which provides these unique universal possibili-

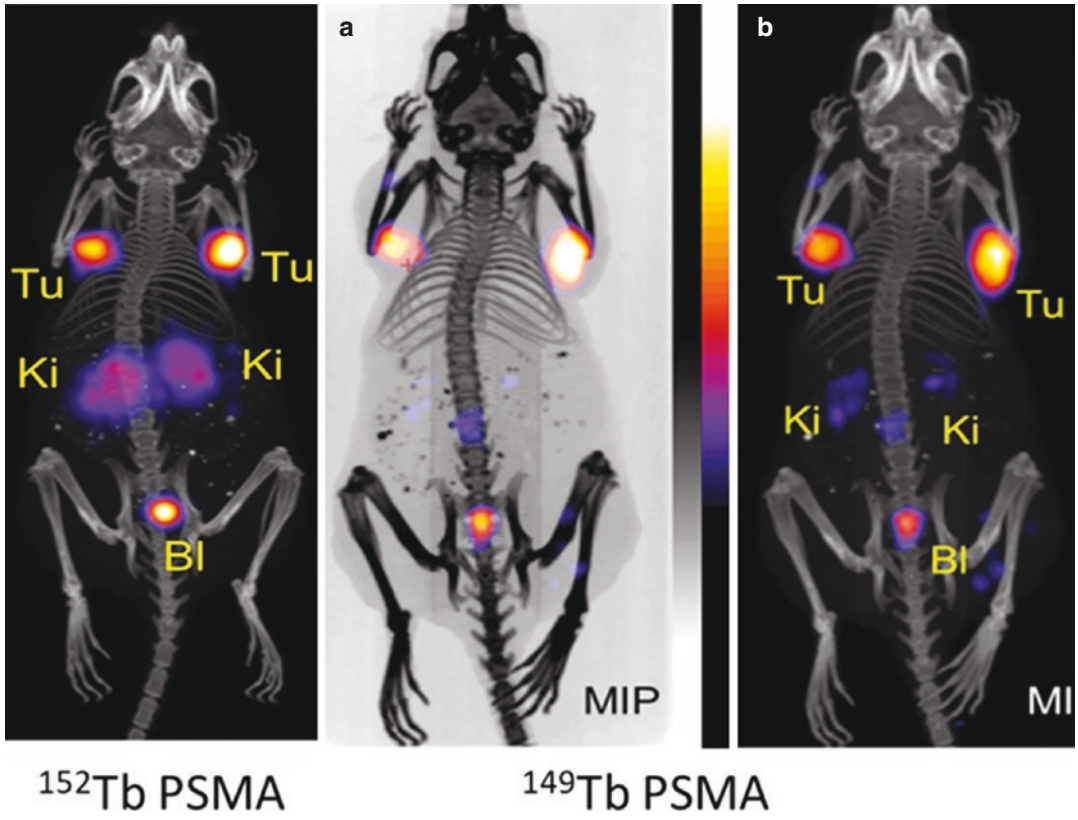

Fig. 5.19 PET/CT images of mice with ^{152}Tb PSMA (left) and ^{149}Tb PMSA (right) performed at PSI [25, 34]

ties. It is a great pleasure to see today, that great progress has been achieved due to the initiative of R. Baum together with his enthusiastic partners from PSI Ch. Mueller, Nick van der Meulen, and others [34, 35]. The latest highlight in this concern is the first PET/CT study of a patient using ^{152}Tb DOTATOC [36], where the ^{152}Tb was produced at CERN ISOLDE based on the technology described above (Fig. 5.19).

5.10 The Alpha Emitters ^{149}Tb and ^{225}Ac

In the Habil-Thesis 1978 (Beyer/Herrmann) [37] one can read at page 334, Vol 2, the following note: "*…Neben diesen für die nuklearmedizinische Diagnostik interessanten Nukliden sind mit den vorgestellten Targetvarianten auch weiche kurzlebige α-Strahler der Seltenen Erden zugänglich, die für die Therapie in der Nuklearmedizin Bedeutung erlangen könnten (*^{153}*Dy,* ^{151}*Tb,* ^{150}*Tb und* ^{149}***Tb****)*".

Over nearly 20 years I had completely forgotten about ^{149}Tb, lost it out of my field of view. Mid 1990-th it was Barry Allen (Australia) who waked me up. He was in Geneva and we discussed the Targeted Alpha Therapy (TAT) with lanthanides—with ^{149}Tb! Next day we met in the hospital, I brought an old Dubna-prepring from 1971 with me about our spectroscopic studies of Tb-isomeres [38] showing that we had 1971 already serious activities of this interesting isotope ^{149}Tb in our hands. The ISOLDE schedule was changed immediately (fortunately ISOLDE had just the Ta-target in operation) and few days later we had a collection of mass number A = 149 in our lab in the hospital and made the chromatographic separation and we had around 400 MBq of ^{149}Tb in our hand. This was a real breakthrough: Barry Allen delegated one of his technicians to Geneva and we were starting to

work on the Tb-isotopes, documented in several publications related to ^{152}Tb and ^{149}Tb see for example [39–41]. Since then the α-emitter ^{149}Tb became the focus of our lanthanide work. In [42] we described our very complex study about the evidence for single cell kill effect using ^{149}Tb RITUXIMAB. The conjugated antibody Rituximab we obtained from S. Larson (NY). The experiment with nude mice was designed by M.Miederer (Munich), the daudi cells came from Lausanne, cell cultivation and animal service was done in the Institute of Bio-Chemistry, Geneva University (Dir. Prof. R. Offord). The cell labeling was done by S. Vranješ from Belgrade, operation of the ISOLDE facility and the collection of A = 149 was done by J. Comor from Belgrade, the radiochemical purification of the ^{149}Tb, the labeling of the RITUXIMAB and QC as well as the gamma-spectroscopic data evaluation of the organ measurements of all animals was the job of G. Beyer. It was a real surprise and great pleasure learning, that in three independent experimental runs 90 % of the animals that received the ^{149}Tb injection survived four months (until the moment when the financing was exhausted). We lost only one mice; G.Künzi said later on that he remembers, that the injection of the ^{149}Tb RITUXIMAB in one of the nude mice was not perfect (meaning not completely i.v.). Thus, terbium with his distinguished isotope ^{149}Tb and in his shadow the other three sisters (^{152}Tb, ^{155}Tb, and ^{161}Tb) advanced to the most distinguished theranostic element. There is no other element in the periodic table, that combine all the four decay modes needed in nuclear medicine: β^- and β^+, α and suitable photon radiation (note: ^{165}Er is the only pure Auger electron emitter in the lanthanide group). CERN-people named the ^{149}Tb later on the Swiss knife (Fig. 5.20).

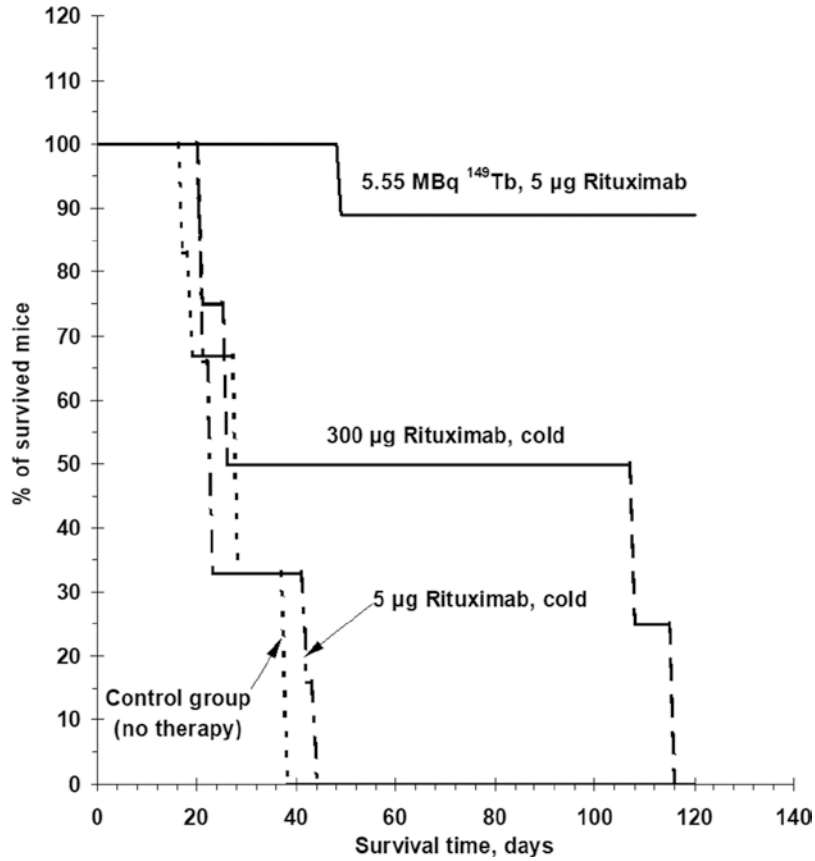

Fig. 5.20 Surviving study with ^{149}Tb-RITUXIMAB in scid mice [42]

5.11 From "Radioactive Ion Beams for Bio-Medical Research" Until CERN Medicis: A New Facility

After the reunification of Germany (1991) I continued working directly at ISOLDE CERN (1991–1993) and thereafter until retirement in 2005 at the University Hospital of Geneva setting up the Geneva Cyclotron Unit for PET together with Ch. Morel. The main task at CERN was to study the potential of radioactive Ion beams for bio-medical research and nuclear medical application. Together with H. L. Ravn, U. Köster (both CERN at that time), and T. Ruth (Vancouver) we were fighting for acceptance of this technological approach (see for instance [43]). At that time our related proposal to CERN from 2005 [44, 45] did not yet find the required resonance by the CERN DG, because LHC had priority in all activities at CERN. A patent application has been formulated with the CERN Technology Transfer section [46]. Finally, with a delay of about 10 years the MEDICIS Project became a reality in 2014 [47] mainly based on the new initiative of Thierry Stora. A bright future can be expected for this pioneering system.

5.12 The ^{225}Ac Story

First time we made ^{225}Ac in 1971 by irradiating Th-metal with 660 MeV protons, separating the Ac by anion and cation exchange chromatography [16]. At that time we simply studied the ionization efficiency together with other actinide elements with our new surface ionization ion source. The Th-irradiation with protons was already a routine in Dubna especially for producing high purity ^{211}At from the decay of ^{211}Rn [48]. Our interest in ^{225}Ac appeared already in the 80-th when we studied the biokinetic behavior of the radio-lanthanides. The ^{225}Ac we produced ourselves either with the ISOLDE facility at CERN or by irradiating Th (or U) in Dubna. Our radiochemical separation schemes for separating ^{225}Ac from irradiated Th are described in [16] and for U_3O_8 in [49]: 27 g U_3O_8 were irradiated with 650 MeV protons at the Dubna phasotron. After three days of decay time the target was dissolved in 5M HNO_3. The U was separated by anion exchange chromatography using a Dowex 1 × 8 column. From the U-free solution the radio-lanthanides, Ac and Ra were coprecipitated with 100 mg Ba-carrier as $BaSO_4$ which was thereafter converted to $BaCO_3$. This sample containing the radio-lanthanides, Y, Ac, and Ra was shipped to Rossendorf for the final separation and purification [49].

For the first time, we used ^{225}Ac to label monoclonal antibodies in 1995 [50]. In that time the mab were still conjugated with DTPA, this conjugation one has to pay with one carboxylic group of the DTPA ending up with a chelator similar to EDTA only. The chelated mab labeled with ^{111}In and the heavy lanthanides showed practically identical and satisfactory biodistribution, however the complex stability for ^{225}Ac was significantly too low and consequently the in vivo stability was by far insufficient: Ac was trapped in the liver. After presenting those dates at a seminar at Sloan Kettering Hospital NY in 1995 Scheinberg asked, why you used ^{225}Ac and not ^{213}Bi. At Sloan Kettering Hospital they pioneered the TAT with ^{213}Bi which is obtained from an ^{225}Ac/^{213}Bi generator. The aim of our study was different, we simply wanted to compare the biokinetic behavior of Ac with the "golden" standard at that time (^{111}In) and with the lanthanides. But definitely this study initiated the motivation using the ^{225}Ac directly. The direct use of ^{225}Ac became possible in the moment when macrocycle chelators (like DOTA for example) replaced the former used DTPA and provided for Ac the same in vivo stability as for In or the lanthanides. H. Mäcke conjugated different peptides with different macrocycle chelators, which is the basis of the grandiose recent progress in radionuclide therapy. The beauty is that with this class of ligands we can use all the radionuclides of the group III of the periodic table (Ga and Sc, Y, lanthanides, and actinides) independent on their decay properties. This is a universal theranostic approach. Because of this development already at the beginning of the twenty-first century the quest for ^{225}Ac has grown significantly.

5.13 Where the ^{225}Ac Comes From

Until about 2003 the only source for ^{225}Ac in Germany or Europe was a nearly 1 kg stock of Th that is "contaminated" with about 1.5 GBq ^{229}Th and located at the Institut of Transuranium Elements (ITU Karlsruhe) and for the US about 5 GBq ^{229}Th stock at Oakridge (US). In Russia, a small fraction of the existing stock of ^{233}U has been processed making another source of ~0.5 GBq ^{225}Ac available [51]. Based on our Dubna experiences Shuikov initiated a program (around 2005) at the Troitzk LINAC for producing ^{225}Ac via the process Th(p;spall)^{225}Ac [52]. Since few years the US Department of isotopes is offering frequently ^{225}Ac products along this spallation process. The drawback of this process is that we have to consider a side production of ^{227}Ac that disturb the direct in-vivo application of the ^{225}Ac preparation.

In the scheme Fig. 5.21 the possible production routes for ^{225}Ac or ^{225}Ra are presented [53]. There are in principle three main strategies to access ^{225}Ac: the indirect production routes via ^{229}Th, the indirect production routes via ^{225}Ra and the direct production routes via spallation or ^{226}Ra (p,2n)^{225}Ac process. The problem with the process ^{226}Ra (p,2n)^{225}Ac is simply the fact that the normal reaction of protons with an energy higher than ~16 MeV is the fission process according to ^{226}Ra (p,f) FP. In order to avoid fission and for obtaining a relatively undisturbed ^{226}Ra(p,2n) ^{225}Ac process one needs to reduce the p-energy down to ~16 MeV. This means that one could run this process in principle with a classical PET cyclotron. However, we just scratch the excitation function and consequently the productivity is low. The licensing procedure and safety regulations related to alpha laboratories are other important issues. A small alpha workshop was

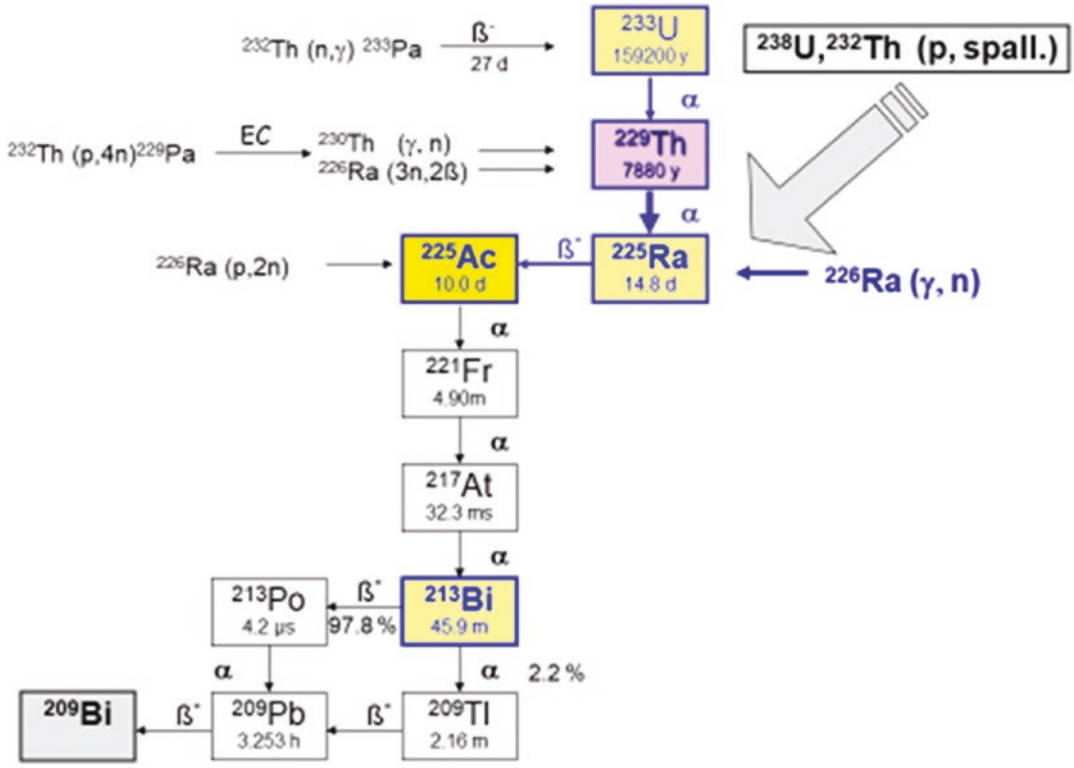

Fig. 5.21 The decay chain of ^{233}U and the potential production routes for ^{225}Ac [53]

organized in Dubna in 2003 with the participation of US representatives from the DOE, ROSATOM Authorities and mainly the Russian researchers. The interest of the US representatives was clearly to get access to the Russian resources for making ^{225}Ra and ^{225}Ac. With the Canadian firm Alpha IICH we started to organize a regular supply of small ^{225}Ac-preparations for R&D to the European market and succeeded to obtain four test samples of 18.5 MBq ^{225}Ac in 2004 from Russia (produced with the ^{229}Th/^{225}Ac generator principle described in [51]. The quality of these test samples was o.k. It took further about 15 years until a reliable supply of around 0.5 GBq ^{225}Ac from Russia is achieved now. By far the today's fast-growing demand in ^{225}Ac cannot be met with the existing resources. Today the discussion for project ideas for industrial scale ^{225}Ac production facilities continues at the platform of the regular TAT-workshops and conferences, last one being the TAT 11 Conference Ottawa (Canada) 2019 [54]. https://www.tat11.com/. Most promising seems to be the photonuclear process ^{226}Ra (γ, n) ^{225}Ra, a technology that has been proposed since long time. The needed high-power electron accelerators exists, the required quantities of ^{226}Ra are available. The bottleneck is that the investors are most likely not yet 100% convinced that the ^{225}Ac will play a serious role in future alpha therapy that justifies the high investment today. However, R. Baum's activities clearly demonstrated that ^{225}Ac will definitely play a dominant role in the future for treating cancer generally and effectively, within the International Centres for Precision Oncology ICPO. It is high time to establish a reliable industrial scale ^{225}Ac supply.

5.14 Summarizing

This contribution is a trial to draw the historical development of radiopharmaceuticals restricted to the radionuclides of the rare earth elements from the early beginning using them as naked metallic cation via chelates like Citrate or EDTMP and with labeled DTPA-conjugated mab's and -peptides until the modern radiopharmaceuticals based on peptides linked with macrocyclic chelators and further starting from simple scintigraphic imaging for diagnosis through quantitative PET imaging to the theranostic approaches of personalized nuclear medicine. The initial radiochemical and physicochemical developments in the field of rare earth elements definitely contributed to the progress in nuclear medicine, from diagnosis to precision oncology. R. Baum is one of the most distinguished medical specialists for precision oncology who understood the importance of scientific disciplines like radiochemistry, nuclear physics, or biochemistry as being unavoidable for success in the fight against cancer.

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