Research Article

Journal of Labelled Compounds and Radiopharmaceuticals

Received 8 September 2011, Revised 6 January 2012, Accepted 10 January 2012 Published online in 16 February 2012 Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jlcr.2906

Recoil and conversion electron implications to be taken into account in the design of therapeutic radiopharmaceuticals utilising *in vivo* generators

Jan Rijn Zeevaart,[a]* Zoltan Szucs,[b,c] Sandor Takacs,[c] Johann van Rooyen,[d] and David Jansen[b]

The use of radionuclides as potential therapeutic radiopharmaceuticals is increasingly investigated. An important aspect is the delivery of the radionuclide to the target, in which the radionuclide is not lost from the chelating agent. For *in vivo* generators, not only the log *K* of complexation between the metal ion and the chelator is important but also whether the daughter radionuclide stays inside the chelator after decay of the parent radionuclide. In our previous work, we showed that the classical recoil effect for β-decay only applies to decays with a *Q* value higher than 0.6 MeV (for the atomic mass range around 100). However, the published result for ^{140}Nd/^{140}Pr (*Q* = 0.222 MeV) indicated that >95% of the daughter (^{140}Pr) was lost by a DOTA chelator upon decay of ^{140}Nd. The experiment was repeated with the ^{166}Dy/^{166}Ho generator (*Q* = 0.486 MeV) and the ^{90}Sr/^{90}Y generator (*Q* = 0.546 MeV), which resembles an *in vivo* chelator system where the transition via the Auger process is absent. It was found that 72% of the daughter (^{166}Ho) was liberated from the DOTA chelator, in contrast to our recoil calculations. It was also found that this ratio of the ^{166}Ho released corresponds to the ratio of transition of holmium atoms via the Auger process (immediately after decay of ^{166}Dy). For the pure β ^{90}Sr/^{90}Y generator, a 1% release from the DOTA chelator was recorded. On theoretical grounds, an electron ejected with an energy above 0.36 MeV (for atomic number = 90) is expected to cause recoil of the daughter atom out of a DOTA chelator, if the chemical bond is 3 eV. From the β-continuum spectrum of ^{90}Sr, an estimated 10.2% of β particles have an energy exceeding 0.36 MeV. For the ^{166}Dy/^{166}Ho generator, the matching ratio of experimental release versus Auger transition is explained by the fragmentation of the chelator by Auger electron thereby releasing the holmium atoms. For the ^{90}Sr/^{90}Y generator, the calculated and measured percentage release is in the same order of magnitude, proving the equation suitable to describe the classical recoil effect for pure β emission. The discrepancy between the experimental and theoretically calculated release can be explained by a correction of the chemical bond energy to 4.4 eV.

Keywords: ^{103}Pd/^{103m}Rh; ^{90}Sr/^{90}Y; ^{166}Dy/^{166}Ho; *in vivo* generators

Introduction

The use of radionuclides as potential therapeutic radiopharmaceuticals is increasingly investigated. An important aspect is the delivery of the radionuclide to the target, in which the radionuclide is not lost from the chelating agent.[1–4] The well-established use of ^{125}I and ^{111}In Auger-emitting radioisotopes has also stimulated the search for other Auger emitters that may be more practical to use in terms of availability, physical half-life and cost. Recently, the potential of ^{103m}Rh ($t_{½}$ = 56.12 min) as an Auger emitter in combination with ^{103}Pd ($t_{½}$ = 16.96 days), in the form of an *in vivo* generator system, has been proposed.[1,4]

$$^{103}_{46}\mathrm{Pd} \xrightarrow[\text{EC branching ratio 99.974\%}]{} {}^{103m}_{45}\mathrm{Rh} \xrightarrow[\gamma\text{-emision}]{} {}^{103}_{45}\mathrm{Rh}$$

As both these short range nuclides are interesting from a cancer treatment point of view, a combination into one radiopharmaceutical is an option to consider, although the recoil of the parent nuclide from the carrier molecule should be prevented to ensure that the daughter nuclide decays in the target organ/cell. The concept is not new and is an inherent problem for α-emitters, which often decay via a decay chain in a short time. For instance, the decay of ^{225}Ac to ^{209}Bi forms five

[a]*CARST, Mafikeng Campus, North-West University, Private Bag X2046, Mmabatho 2735, South Africa*

[b]*Radiochemistry, Necsa (South African Nuclear Energy Corporation Ltd.), PO Box 582, Pretoria 0001, South Africa*

[c]*Institute of Nuclear Research of the Hungarian Academy of Sciences, Atomki, H4026 Debrecen, Hungary*

[d]*Radiation and Reactor Theory, Necsa (South African Nuclear Energy Corporation Ltd.), PO Box 582, Pretoria 0001, South Africa*

**Correspondence to: Jan Rijn Zeevaart, CARST, North-West University, Mmabatho 2735, South Africa.*
E-mail: zeevaart@necsa.co.za

intermediates and produces four α particles and two β particles. The release of these decay products from the original carrier molecule and their migration out of target cells are well documented.[5] For example, the reason for the release of one of these intermediates, ^{221}Fr (monovalent cation and mimicking K^+, an alkali metal ion), is, firstly, that it requires significantly different chelation chemistry from actinium and, secondly, that the recoil energy of ^{221}Fr after the α-particle emission (0.1 MeV) is much greater than the chemical binding energy of the ^{225}Ac conjugate. The change from Pd to Rh is not expected to be very significant because they are both part of the Pt group of metals. However, the recoil is also a cause of concern for the proposed ^{103}Pd/^{103m}Rh *in vivo* generator, although the recoil energy from Pd to Rh is expected to be significantly lower. In order to investigate the likelihood of recoil taking place in the ^{103}Pd/^{103m}Rh *in vivo* generator, which can initiate the release of the daughter nucleus ^{103m}Rh as well as others, a fully relativistic equation has been derived for calculating the kinetic energy of the recoiling nucleus (E_N).[1]

$$E_N = \sqrt{\left(M_N^2c^4 + E_p^2 + 2m_pc^2E_p\right)} - M_Nc^2 \qquad (1)$$

where E_N is the kinetic energy of the recoiling nucleus, M_N is the mass of the recoiling nucleus, E_p is the kinetic energy of the emitted particle, and m_p is the mass of the emitted particle.

Briefly, Eqn 1 is a general, fully relativistic expression that holds true for non-zero and zero rest-mass particles. The term $2m_pc^2E_p$ will be zero for photon emission because the rest-mass of a photon is zero; the term $2m_pc^2E_p$ will be negligibly small for neutrino emission because the rest-mass of the neutrino is at present estimated to be of the order of 30 (meV), which is about 3×10^{-11} a.m.u. For heavier emitted particles, such as α and β particles, the term $2m_pc^2E_p$ will dominate and lead to great recoil energies.

When a nucleus de-excites by the emission of a γ-photon, $m_p = 0$ in Eqn 1. It is seen that Eqn 1 holds true for all emitted particles irrespective of whether they have a non-zero or zero mass.

It was further estimated that the bond strength in a chelate-complex molecule, typically through DOTA complexes, often used in radiopharmacy, is in the order of 3 eV.[6] Therefore, a radionuclide that is calculated to have an E_N kinetic energy below 3 eV is assumed not to recoil out of its chemical environment upon decay.[1] From this, Table 1 has been compiled[4], which gives the upper limits for the energy of the emitted photons or particles of the different atomic masses that will exhibit the recoil effect. This table is useful in determining whether recoil is expected upon decay of any radionuclide, by comparing the recoil threshold with the *Q* value energy of the decay for a particular atomic mass.

This was a theoretical calculation and therefore warrants experimental proof. A paper by Zhernosekov *et al.*[2] reported that the authors studied the proposed ^{140}Nd/^{140}Pr *in vivo* generator and determined the release of the ^{140}Pr from a DOTA chelator. It was found that >95% of the ^{140}Pr could be washed from a C-18 column containing DOTATOC (DOTA^0-Phe^1-Tyr^3-octreotide) labelled with ^{140}Nd with 10^{-3} M DTPA (diethylene triamine pentaacetic acid). The authors referred to this phenomenon as a 'post-effect'. In terms of our calculations, this was also surprising. From Table 1, the threshold is 0.51 MeV for a.m.u. = 140, while the *Q* value energy for ^{140}Nd/^{140}Pr is only 0.222 MeV.[7] According to the calculations, no recoil can be expected. This discrepancy led to the experiments with the ^{166}Dy/^{166}Ho generator[3] and ^{90}Sr/^{90}Y generator described herein.

Table 1. Calculated limit for the emitted recoil energy of the nuclides of different atomic mass (a.m.u.), if the chemical bond is less than 3 eV

Mass, recoiling nucleus (a.m.u.)	Limiting electron energy (MeV)	Limiting neutrino or photon energy (MeV)
10	0.05	0.24
20	0.10	0.33
30	0.14	0.41
40	0.19	0.47
50	0.22	0.53
60	0.26	0.58
70	0.30	0.63
80	0.33	0.67
90	0.36	0.71
100	0.40	0.75
110	0.43	0.78
120	0.45	0.82
130	0.48	0.85
140	0.51	0.89
150	0.54	0.92
160	0.56	0.95
170	0.59	0.98
180	0.62	1.00
190	0.64	1.03
200	0.66	1.06
210	0.69	1.08
220	0.71	1.11
230	0.73	1.13
240	0.76	1.16

Results

Establishment of the generators

The establishment of the ^{166}Dy/^{166}Ho generator was already reported by Zeevaart *et al.*[3], and only the main results thereof will be repeated here for the sake of completeness.

The column (as ^{90}Sr/^{90}Y generator) was successfully established with 8.6 MBq of ^{90}Sr-DOTATATE and 16.5 MBq ^{90}Y-DOTATATE. Although DOTA is known to have a preference for the trivalent Y over the divalent Sr, at equilibrium in the ^{90}Sr/^{90}Y generator, the ratio of ^{90}Sr atoms to ^{90}Y is 3900, allowing 99.9% of the Sr atoms to be complexed to DOTA.

The activity of both radio isotopes was determined from the activity of the loaded and washed-out fraction. The ratio of the isotopes in the fraction was measured by means of the highly effective TLC separation, followed by LSC measurements.

The percentage of residual ^{90}Sr in the ^{90}Y chromatographic section was determined by repeat scintillation counting after 30 days, after which the original ^{90}Y would have decayed. The amount of ^{90}Sr was below the detection limit; it must therefore be less than 0.015% of the activity of ^{90}Y.

The percentage of residual ^{90}Y in the ^{90}Sr chromatographic section was determined by repeat scintillation counting after 30 days, after which the original ^{90}Y would have decayed. Twice the original value (at equilibrium, an equal amount of new ^{90}Y

has grown in) minus the original value reveals the ^{90}Y amount to be 1.1%.

Up to the elutions performed after 96 days of loading, it was demonstrated that intact ^{90}Sr/^{90}Y-DOTATATE was eluted in addition to recoiled ^{90}Sr. This was measured to be 10% of ^{90}Sr by comparing with the eluted activity. Only after 136 days did the column start to degrade due to radiation damage.

Corrections based on the last three aspects were made to all measurements to ensure a true reflection of the amount of ^{90}Y in the eluate.

Elution of the generators

The elution curve for the ^{166}Dy/^{166}Ho generator as reported by Zeevaart *et al.*,[3] where the number of atoms versus time is plotted, is presented in Figure 1. The top dotted line indicates the decay of only ^{166}Dy. The bottom curve represents the decay of only ^{166}Ho. The middle dashed line shows the decay of ^{166}Dy and ^{166}Ho in equilibrium (no washing). The solid triangles indicate the measured ^{166}Ho amount before and after elution, while the circles indicate the result of a simple model calculation. The solid line represents the calculated washing curve. If no release from DOTA had been experienced by the ^{166}Dy nuclei during decay, the solid line should have mimicked the dashed line. If almost all ^{166}Dy nuclei had experienced release from DOTA upon decay, the solid line would be expected to return to the bottom curve after each elution. As can be seen from Figure 1, it is neither. The average amount of ^{166}Ho that remained on the columns in all the elutions was 28 ± 5% of the total amount of ^{166}Ho. (30 ± 4%, if the first column is excluded, as it has a high standard deviation for the individual elutions). This means that 72% of the ^{166}Dy nuclei were released from DOTA upon decay to form ^{166}Ho found outside the DOTA ring and were therefore eluted from the column. This result does not match the calculations derived from Eqn 1.

For the ^{90}Sr/^{90}Y generator, no curve was drawn up, as only a small percentage of ^{90}Y was recorded in the eluate. Over the eight elutions, 0.95 ± 0.13% was found in the EDTA eluate, while 0.016 ± 0.006% was found in the water wash. As indicated before, corrections were made to all measurements to ensure a true reflection of the amount of ^{90}Y in the eluate. After each elution, it is assumed that the column has been 'reset', as all recoiled ^{90}Y atoms have been washed out. The new in-growth was calculated from this instant for the next elution.

On the basis of Eqn 1, an electron ejected with an energy above 0.36 MeV is expected to cause recoil of the daughter atom out of a DOTA chelator for atomic mass = 90, when the chemical bond energy is 3 eV. From the β-continuum spectrum of ^{90}Sr recorded (Figure 2) directly after separation from ^{90}Y (before any ^{90}Y in-growth could occur), an estimated 10.2% of β particles are emitted with energy greater than 0.36 MeV. This agrees with the literature value of 8% by Kriss *et al.*,[8] as well as with the ICRP data of 12.3%.[9]

Discussion

The 72% release measured for the ^{166}Dy/^{166}Ho generator was surprising, but was not a complete release as found by Zhernosekov *et al.*[2] for ^{140}Nd/^{140}Pr. Upon close examination of the decay process of ^{166}Dy to ^{166}Ho, we found that, after the β-decay of ^{166}Dy to ^{166}Ho*, the excitation energy of the ^{166}Ho* was removed by the emitted gamma photons. The rearrangement of the electron shell configuration that the newly formed

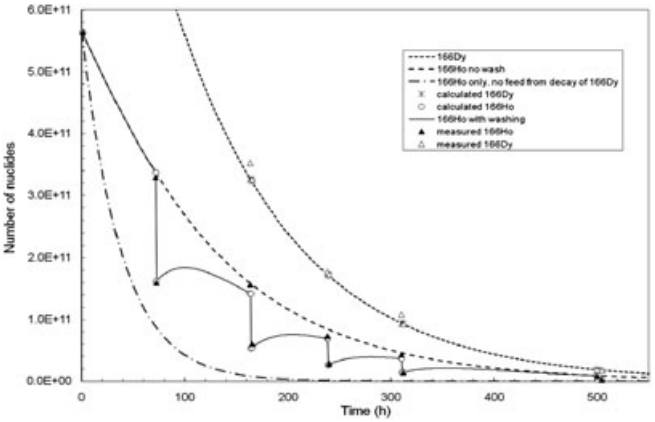

Figure 1. Elution curve for the ^{166}Dy/^{166}Ho column, expressed per number of atoms. Top dotted line indicates the decay of only ^{166}Dy. Bottom curve represents the decay of only ^{166}Ho. Middle dashed line shows the decay of ^{166}Dy and ^{166}Ho in equilibrium (no washing). Solid triangles indicate the measured ^{166}Ho amount before elution, and circles, after elution. Solid line represents the fitted washing curve.

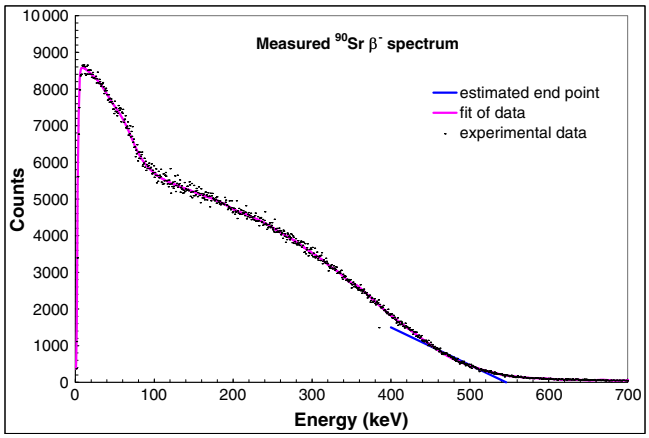

Figure 2. The β-continuum for ^{90}Sr as recorded on the Perkin Elmer TriCarb 2800.

holmium atom went through in different processes quickly resulted in emission of a series of Auger electrons (see Table 2). It is known that, in the Auger process, high numbers of electrons can be ejected by the atom (as high as 31 electrons for ^{195m}Pt). The resulting highly charged ion then acts as an electron sink that will seek surrounding electrons. If these are binding electrons, the surrounding molecules will be destroyed. The cytotoxicity of the well-known Auger emitter ^{125}I in cells is well documented,[10] as well as the single- and double-strand DNA breaks caused by its decay. The total ratio of Auger electron emission is 72% in case of holmium atoms, which matches the releasing percentage measured experimentally.

Table 2. The release of the excitation energy of the newly formed ^{166}Ho* via Auger electron emission to reach ^{166}Ho (ground state)

Energy (keV)	Intensity (%)	Decay
38.4	3	E AU K
5.33	69	E AU L
Total	72	

It is therefore postulated that the transition of $^{166}Ho^{*}$ atoms via Auger emission is responsible for the partial or full destruction of the DOTA chelator, which makes it possible for DTPA (or any other chelator) to complex and elute the ^{166}Ho atoms. This is in agreement with the report of Nash *et al.*[11] that fragmentation of the surrounding molecules occurs predominantly due to charge neutralisation, whereby electrons from neighbouring molecules flow to the highly charged atom that remains after Auger emission. Only molecules that contain a large number of delocalised π-electrons can survive such a process and do not fragment. (DOTA complexes do not possess delocalised π-electrons.)

Because the release of the ^{166}Ho from the DOTA complex matches the expected fragmentation following Auger emission, no recoil of the decaying nucleus was measured, which is in agreement with Eqn 1, which predicted no recoil escape for the β-decay of ^{166}Dy to $^{166}Ho^{*}$. The results of Zhernosekov *et al.*[2] indicated a more than 95% release of ^{140}Pr from the DOTA chelator for $^{140}Nd/^{140}Pr$, where ^{140}Nd decays 100% via electron capture, with subsequent emission of Auger electrons in 81.3% of cases.

For the pure β-emitter ^{90}Sr, no fragmentation via an Auger process can occur. This therefore permits the experimental verification of Eqn 1. As 10.2% of the emitted β particles have energy above the theoretical threshold for atomic mass = 90, it gives an even better test of the theoretical calculations, as a small recoil percentage has to be calculated. The 0.95% recoil found is in the same order of magnitude, confirming the above, and indicating that the theoretical recoil equations[1,4] are correct. This is further strengthened when considering that the 3-eV chemical bond energy was merely assumed. Table 3 compares the expected recoil percentage for the $^{90}Sr/^{90}Y$ generator with the chemical bond energy. For the ~1% recoil, a bond energy of 4.4 eV can be calculated, implying that a ^{90}Y atom that is formed by β^{-} electron emission with an energy higher than 489 keV will recoil from the DOTA chelator. The study of the recoil percentage of a generator can therefore be used to estimate the chemical bond energy of the chelator with the radionuclide and even covalent bonds.

Materials and methods

Establishment of the $^{90}Sr/^{90}Y$ generator

$^{90}Sr/^{90}Y$ (188 MBq; in 1 M HCl) was acquired from NTP Radioisotopes Pty. Ltd. from their ^{90}Y-production line. After receipt, the $^{90}Sr/^{90}Y$ was left for 30 days to ensure full equilibrium (^{90}Sr, $t_{½} = 28.5$ years; ^{90}Y, $t_{½} = 64.1$ h). After 10 times dilution, 100 µl (1 M HCl) containing 18.7 MBq ^{90}Sr and ^{90}Y was taken, with the pH of the solution adjusted with 1 M NaOH to about 6, and added to a 1-ml vial in which 0.65 mg of DOTATATE ($DOTA^{0}$-Tyr^{3}-octreotate, Bachem, Switzerland) was weighed; the mixture was diluted with 100 µl of water and then heated to 58 °C for 1.25 h. A standard procedure[12] was followed for the preparation of the ^{90}Sr-DOTATATE and ^{90}Y-DOTATATE complexes. Briefly, 8.6 MBq of ^{90}Sr-DOTATATE and 16.5 MBq of ^{90}Y-DOTATATE were loaded on a C-18 cartridge, Phenomenex Strata-X minicolumn (30 mg/ml), while the uncomplexed ^{90}Sr and ^{90}Y were washed from the column with the first wash that 'reset' the column for the experiment. The cartridge was conditioned by pre-equilibrating and washing with 5 ml of methanol and 1 ml of water consecutively. The cartridge itself became the column of the radionuclide generator system, which could be operated with standard single-use syringes. The ratio of ^{90}Sr-DOTATATE and ^{90}Y-DOTATATE was determined, after their TLC separation, by liquid scintillation counter.

Table 3. Theoretically calculated recoil percentages and threshold energy for chosen chemical bond energies of ^{90}Y

Chemical bond energy (eV)	Threshold energy of β-electron emission (keV)	Recoiled ^{90}Y (%)
2.0	263	26.02
2.5	310	17.46
3.0	356	10.70
3.5	403	5.62
4.0	449	2.46
4.5	496	0.78
5.0	542	0.04

Elution of the $^{90}Sr/^{90}Y$ generator

It is known that DOTA-conjugated peptides (e.g. DOTATATE) can be adsorbed on a solid reversed phase column from aqueous solutions with a high distribution coefficient, while free metal cations and metal DTPA or EDTA complexes can be eluted. The peptide is bound to the C-18 cartridge. Due to the high thermodynamic stability and kinetic inertness of metal-DOTA type complexes, the release of the parent radionuclide ^{90}Sr is inhibited. If recoil of the daughter nuclide (during the decay) or a 'post-effect' takes place, on the other hand, it leads to the release of the daughter radionuclide ^{90}Y. As an eluent system, aqueous solutions of 10^{-3} M EDTA were used, as no difference was observed between DTPA and EDTA.[3] All further elutions were carried out with 2 ml of 10^{-3} M EDTA, except for the first elution of the excess ^{90}Sr and ^{90}Y that were removed by washing the cartridge with 5 ml of 10^{-3} M DTPA. After the elution, the column was washed with 1 ml of water to remove residual activity (this fraction was also collected and counted). Between successive elutions, the generator was kept in pure water. Elutions were carried out successively after 5, 3, 4, 3, 7, 6, 8 and 6 days of in-growth periods. Accurately pipetted 10-µl portions of the eluents (and wash water) were added to the liquid scintillation cocktail (Ultima Gold), and the total β-activity was counted on a Perkin Elmer TriCarb 2800.

The relative amounts of ^{90}Sr and ^{90}Y in a sample were determined by using the method of Pandey *et al.*[13] Briefly, a Whatman #1 chromatography paper was cut into 12 × 1 cm strips. Then ~10 µl of KSM-17 (PC88A oil) was applied at the origin of the paper chromatography strips and allowed to air-dry. The chromatography technique involves the spotting of 5 µl of the test solution over the dried spot of KSM-17, allowing it to dry, and developing the paper in 0.9% saline solution by ascending mode. After movement of the solvent front to the top of the paper, the paper was removed, dried and cut into halves. The paper was immersed in liquid scintillation and counted on a Perkin Elmer TriCarb 2800. The front half contained the ^{90}Sr and the origin half contained the ^{90}Y. After 30 days, all samples were recounted to determine residual ^{90}Sr in the ^{90}Y half and residual ^{90}Y in the ^{90}Sr half.

Conclusion

For the $^{90}Sr/^{90}Y$system, the theoretical equations to calculate the recoil energy of a daughter nuclide in an *in vivo* generator can be experimentally verified. However, it is concluded that for the $^{166}Dy/^{166}Ho$ system, the low recoil energy of the daughter nucleus ^{166}Ho is not a sufficient reason to rule out the release of the nuclide from chelators. This can happen via the transition of Ho atoms through the Auger process, which fragments the chelator. The combination of these two aspects provides a valuable tool in predicting the fate of an *in vivo* generator through an *in silico* process.

Acknowledgements

The authors wish to thank Necsa for permission to publish this work and the National Research Foundation (NRF) for funding via the SA-Hungary bilateral (UID 68768). A word of thanks to Deon Kotze for assistance with the recording of the β spectra and interpretation thereof and to Nguyen Thi Thu (Vietnam) for supplying the PC88A used for separating ^{90}Sr and ^{90}Y. Thanks to NTP Radioisotopes (Pty) Ltd. for supplying the $^{90}Sr/^{90}Y$.

Conflict of Interest

The authors did not report any conflict of interest.

References

[1] J. Van Rooyen, Z. Szucs, J. R. Zeevaart. A possible *in vivo* generator $^{103}Pd/^{103m}Rh$—recoil considerations. *Appl. Rad. Isot.* **2008**, *66*, 1346–1349.

[2] K. P. Zhernosekov, D. Filoofov, S. M. Qaim, F. Rosch. A Nd-140/Pr-140 radionuclide generator based on physicochemical transitions in Pr-140 complexes after electron capture decay of Nd-140-DOTA. *Radiochim. Acta* **2007**, *95*, 319–327.

[3] J. R. Zeevaart, Z. Szucs, S. Takacs, N. V. Jarvis, D. R. Jansen. Recoil and conversion electron considerations of the $^{166}Dy/^{166}Ho$ *in vivo* generator. *Radiochim. Acta* **2011**, *99*, 1–5.

[4] Z. Szucs, T. J. Van Rooyen, J. R. Zeevaart. Recoil effects on β-decaying *in vivo* generators, interpreted for $^{103}Pd/^{103}Rh$. *Appl. Rad. Isot.* **2009**, *67*, 1401–1404.

[5] S. Hassfjell, M. W. Brechbiel. The development of the α-particle emitting radionuclides ^{212}Bi, and ^{213}Bi for therapeutic applications. *Chem. Rev.* **2001**, *101*, 2019–2036.

[6] NIST. Standard Reference Database 46, Version 8.0. In: Martell AE, Smith RM (Eds.) Gaithersburg, MD 20899 USA; **2007**.

[7] NUDATdata files. National Nuclear Data Center, Brookhaven National Laboratory, U.S. Department of Energy; **1997**.

[8] A. A. Kriss, D. M. Hamby. Beta-spectroscopy with a large-area avalanche photodiode module and a plastic scintillator. *Nucl. Instrum. Methods Phys. Res., Sect. A* **2004**, *525*, 553–559.

[9] ICRP. Nuclear Decay Data for Dosimetric Calculations. ICRP Publication 107. *Ann. ICRP* **2008**, *38*(3).

[10] KSR Sastry. Biological effect of the Auger emitter I-125—a review. Report no. 1 of AAPM Nuclear Medicine Task group No. 6. *Med. Phys.* **1992**, *19*, 1361–1383.

[11] A. Nash, M. J. Prushan, G. J. Gilbert. Can super-excited molecules survive fragmentation? *J. Radioanal. Nucl. Chem.* **2001**, *247*, 589–591.

[12] M. S. Cooper, E. Sabbah, S. Mather. Conjugation of chelating agents to proteins and radiolabelling with trivalent metallic isotopes. *Nature Prot.* **2006**, *1*, 314–316.

[13] U. Pandey, P. S. Dhami, P. Jagesia, M. Venkatesh, M. R. A. Pillai. Extraction paper chromatography technique for the radionuclidic purity evaluation of ^{90}Y for clinical use. *Anal. Chem.* **2008**, *80*, 801–807.