Production and Radiochemical Separation of the Auger Electron Emitter ^{140}Nd

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Among the Auger electron emitters, the radiolanthanide ^{140}Nd has some unique nuclear properties with potential for endoradiotherapeutic applications. In the present study, ^{140}Nd was produced via the ^{140}Ce(^{3}He,3n) nuclear process at the FZ Jülich CV28 cyclotron, irradiating CeO_2 with ^{3}He particles of 36 MeV primary energy. Yields of about 5 MBq ^{140}Nd per μAh were experimentally obtained. Batch yields of >100 MBq ^{140}Nd were reached. ^{140}Nd was separated in $75 \pm 5\%$ radiochemical yield using a two-step process, first by extracting the bulk of the target material according to a $Ce^{(IV)}/Nd^{(III)}$ separation, then by final ion exchange purification.

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Effective endoradiotherapy (ERT) of soft tissue tumours and small metastases with labelled complexes, particles, peptides, monoclonal antibodies or fragments requires the appropriate selection of a suitable radionuclide. Radiopharmaceuticals labelled with β^--emitting nuclides such as ^{90}Y, ^{153}Sm or ^{186,188}Re are commonly used for the treatment of medium-sized tumours, but also for small tumours or metastases. Nevertheless, for small-size tumours, β^--emitting nuclides with lower β^--energy or nuclides emitting α-particles or Auger electrons seem to be adequate. These particles generally offer a shorter range as well as a higher linear energy transfer (LET) in tissue.

Among the Auger electron emitters, the radiolanthanide ^{140}Nd has some unique nuclear properties:

- The ^{140}Nd itself exclusively emits Auger electrons, not accompanied by high-energy γ-radiation. Additional photons, and Auger electrons, however, originate from the decay of its short-lived daughter ^{140}Pr.
- The ^{140}Nd half-life of 3.37 d seems to be suitable for most of the usual treatments in ERT. It allows a significant tumour to blood activity ratio to be reached and it is, therefore particularly useful for the application of larger molecules with relatively long biological kinetics.
- The Auger electron emission rates are 0.079 for the K-shell, and 0.94, 0.876 and 0.875 for the L-shells (L_1, L_2, L_3). These emission rates are thus comparable with those for the, usually, in vitro used Auger electron emitter ^{125}I (0.116 and 0.956, 0.921, 0.921, respectively) (1, 2).
- There are groups of Auger electrons emitted per decay, creating a positively charged residual atom. On averaging the Gaussian distribution, the corresponding charges are +7 to +9 with maximum values up to +20 to +30 (3). On the whole, the therapeutic efficacy of one decay of ^{140}Nd parallels the number of the emitted Auger electrons.
- The mean energy of the Auger electrons emitted amounts to 6 keV, with the dominating fraction of the LXY emission of 4 keV (compared to 17.9 keV for ^{125}I; (2)), thus concentrating the ^{140}Nd Auger electron radiation on several cell dimensions exclusively. Surrounding healthy tissue is effectively saved.

^{140}Nd produces the short-lived intermediate isotope ^{140}Pr ($T_{1/2} = 3.39$ min). This daughter isotope decays via positron emission (51% β^+, $E_{max} = 2.3$ MeV) to the stable ^{140}Ce (cf. Fig. 1). While the contribution of the decay of the daughter to the total dosimetry needs to be studied in detail, it is obvious that the decay of ^{140}Pr offers the possibility of using positron emission tomography (PET) to determine quantitatively the uptake kinetics and radiation doses of the ^{140}Nd-labelled radiotherapeuticals. First

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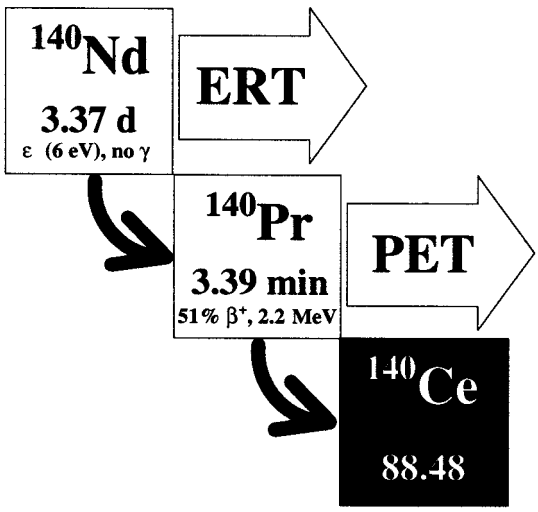

Fig. 1. Principal decay scheme of the Auger electron emitter ^{140}Nd via the short-lived positron emitter ^{140}Pr to stable ^{140}Ce.

PET images of a ^{140}Nd (^{140}Pr) phantom have been acquired (4). ERT and PET are thus being bridged inherently and might allow quantitative validations as described for ^{90}Y (ERT) and ^{86}Y (PET) (5–7).

As a trivalent lanthanide, ^{140}Nd should provide an excellent chemical potential for use either as ^{140}Nd ligand complexes alone or as conjugates being coupled to various compounds via bifunctional chelators. This might be of particular interest, for example, to label octreotide derivatives similar to the ^{111}In-, ^{68}Ga- or ^{90,86}Y-analogs.

MATERIAL AND METHODS

Production of ^{140}Nd

There are three principal routes to producing ^{140}Nd at cyclotrons, namely (i) the spallation reactions with $E_p >$ 100 MeV on Ta, W or lanthanide targets, (ii) the bombardment of ^{141}Pr with protons or deuterons, i.e. the ^{141}Pr(p,2n)- or ^{141}Pr(d,3n)-reactions (8), and (iii) the α- or ^{3}He-induced nuclear reactions on ^{140}Ce, i.e. the ^{140}Ce(^{3}He,3n)- or ^{140}Ce(^{4}He,4n) processes. In the present study, the ^{140}Ce(^{3}He,3n) route was used. Targets consisted of 500 mg CeO_2 of high chemical purity (99.9999%, Sigma, Aldrich), which was compressed into pellets. These targets were irradiated with ^{3}He-particles of 36 MeV primary energy at the CV28 cyclotron of the Forschungszentrum Jülich.

Radiochemical separation

^{140}Nd was radiochemically separated using a two-step process, first extracting the bulk of the target material according to a $Ce^{(IV)}/Nd^{(III)}$ separation, followed by final ion exchange purification. For systematic experiments, ^{141}Ce and ^{147}Nd were used as tracers and were produced via the ^{140}Ce(n,γ)- and ^{146}Nd(n,γ)-reactions at the TRIGA research reactor Mainz.

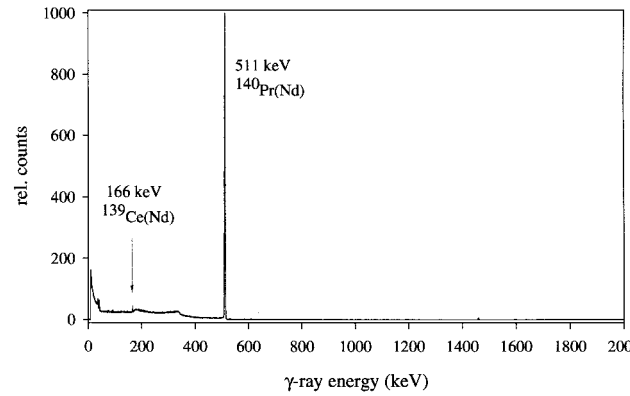

Fig. 2. γ-ray spectrum of ^{140}Nd (^{140}Pr).

The irradiated CeO_2 was dissolved in concentrated HNO_3 containing traces of HF. The bulk of $Ce^{(IV)}$ was then extracted into n-heptane using HDEHP (Di-2-ethylhexyl-o-phosphonic acid) (9). $KBrO_3$ was added for complete oxidation of Ce before the next extraction cycle. The no-carrier-added (nca) ^{140}Nd was subsequently isolated from the aqueous solution and subjected to cation exchange chromatography. ^{140}Nd was selectively eluted from a small Aminex A6 column using α-hydroxyisobutyrate.

RESULTS

Through the irradiation of 500 mg CeO_2, yields of about 5 MBq ^{140}Nd per μAh were experimentally obtained. Using ^{3}He beam currents of 5 μA and irradiation periods of >5 h, batch yields of >100 MBq ^{140}Nd were reached. Owing to the comparatively short half-lives of the co-produced Nd isotopes ^{139}Nd ($T_{1/2} = 5.5$ h) and ^{141}Nd ($T_{1/2} = 2.5$ h), the isotopic purity of ^{140}Nd approaches 100% at the time of its application. The γ-ray spectrum of a highly purified ^{140}Nd sample as measured at an HPGe detector is presented in Fig. 2.

Extraction

The irradiated CeO_2 was dissolved in concentrated HNO_3 containing traces of HF. After neutralization, the first extraction was performed into n-heptane/25% HDEHP. About 95% of ^{140}Nd and >95% Ce were extracted. Subsequently, ^{140}Nd was re-extracted using 8 N HNO_3 with 80% yield. $KBrO_3$ in a 6 : 1 stoichiometry with respect to the remaining amount of ≤ 10% of the macroscopic $Ce^{(III)}$ was added for complete oxidation of Ce and removed by extraction twice with n-heptane/25% HDEHP. About 2 ± 1 mg of the Ce target material remained in the solution, corresponding to about 0.5% of the initial target mass. The nca ^{140}Nd was subsequently co-precipitated from the aqueous solution as the hydroxide by adding NH_3. After centrifugation, the hydroxide was washed and finally dissoved in 0.5 ml of conc. HCl.

Table 1

Comparison of Ce contaminations for the overall ^{140}Nd separation process for different concentrations of the eluent α-HIB applied in the ion exchange purification

^{140}Nd fraction considered	Ce contamination			
	0.25 M α-HIB		0.22 M α-HIB	
95%	0.02%	0.4 µg*	–	–*
99%	0.05%	1.0 µg*	<0.01%	<0.2 µg*

* Starting from overall 500 mg irradiated CeO_2 and ≤2 mg $Ce^{(III)}$ before ion exchange purification.

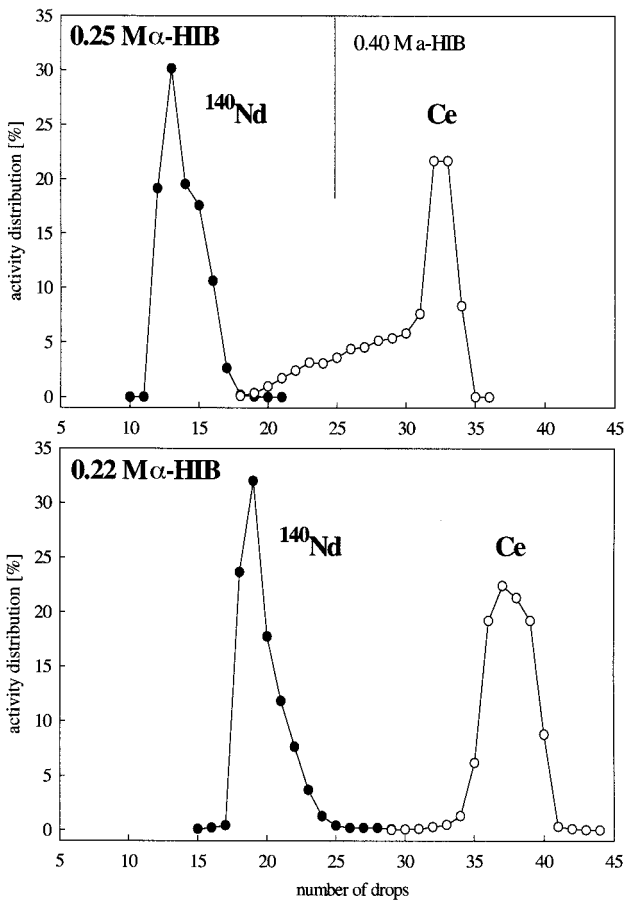

Fig. 3. Typical elution profiles for the separation of nca ^{140}Nd and about 2 µg Ce on an Aminex A6 column (50× 3 mm).

Cation exchange chromatography

The solution was transferred to a small Aminex A6 column (50× 3 mm). ^{140}Nd was quantitatively absorbed on the resin. After washing the resin with NH_4Cl and water, ^{140}Nd was selectively eluted using 0.25 or 0.22 M α-hydroxyisobutyrate (α-HIB), pH 4.7. Elution fractions were collected and every drop was measured γ-spectrometrically on an HPGe detector. Optimum separation between ^{140}Nd and 2 ± 1 mg Ce was obtained at a concentration of 0.22 M α-HIB (cf. Fig. 3). The overall radiochemical separation yield of ^{140}Nd amounts to $70 \pm 5\%$.

The final radiochemical purity of ^{140}Nd depends on the percentage of the ^{140}Nd elution fraction considered; i.e. the more complete the ^{140}Nd fraction, the higher the overlap with the Ce elution fraction. Even a 99% consideration of the ^{140}Nd fraction results in a contamination of <0.2 µg Ce (cf. Table). However, in the case of 95% of the ^{140}Nd fraction considered for subsequent labelling reactions, no detectable amount of Ce was found for 0.22 M α-HIB concentration.

CONCLUSION

The Auger electron emitter ^{140}Nd is of significant interest for the synthesis of endoradiotherapeuticals. The radiolanthanide ^{140}Nd can be produced via the ^{140}Ce(^{3}He,3n) nuclear process in yields of about 5 MBq ^{140}Nd per µAh and in high radionuclidic and radiochemical purity. It is thus available for further investigation of its labelling to molecules relevant to nuclear medicine and the investigation of their endoradiotherapeutic potential. Its particular advantage is the combination of the local Auger effect for endoradiotherapy and the in situ generation of a β^+ emission for simultaneous detection using PET. The therapeutic components of the Auger effect as well as of the latter positron and 511 keV γ-radiation require further investigation.

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REFERENCES

1. Bambynek W, Crasemann B, Fink RW, et al. X-ray fluorescence yields, Auger, and Coster-Kronig transition probabilities. Rev Modern Phys 1972; 44: 716–67.
2. Firestone RB, Shirley VS, (eds). Table of isotopes. 8th ed. New York: John Wiley & Sons, Inc, 1996.
3. Metag V, Habs D, Specht HJ. Spectroscopic properties of fission isomers. Physics Report 1980; 65: 1–41.
4. Rösch F, Brockmann J, Lebedev NA, Qaim SM. The Auger electron emitter ^{140}Nd: production and radiochemical separation. J Labelled Cpd Radiopharm 1999; 42 (Suppl. 1): S927–9. Abstracts from St. Louis, 13th Int Symp on Radiopharm Chem, June 27–July 1, 1999.

5. Herzog H, Rösch F, Stöcklin G, Lueders C, Qaim SM, Feinendegen LE. Measurement of pharmacokinetics of yttrium-86 radiopharmaceuticals with PET and radiation dose calculation of analogous yttrium-90 radiotherapeutics. J Nucl Med 1993; 34: 2222–6.
6. Rösch F, Herzog H, Plag C, et al. Radiation doses of yttrium-90 citrate and yttrium-90 EDTMP as determined via analogous yttrium-86 complexes and positron emission tomography. Eur J Nucl Med 1996; 23: 958–66.
7. Rösch F, Herzog H, Brockmann J, et al. Quantitative evaluation of the in vivo stability, uptake kinetics and radiation doses of the somatostatin receptor ligand (^{86}Y)DOTA-DPhe^{1}-Tyr^{3}-octreotide using positron emission tomography in non-human primates. Eur J Nucl Med 1999; 26: 358–66.
8. Zeisler S, Becker D. Production of the ^{140}Nd/^{140}Pr radionuclide generator for biomedical studies. J Labelled Cpd Radiopharm 1999; 42 (Suppl. 1): S921–3. Abstracts from St. Louis, 13th Int Symp on Radiopharm Chem, June 27–July 1, 1999.
9. Pierce TB, Peck PF. The extraction of the lanthanide elements from perchloric acid by di-(2-ethylhexyl) hydrogen phosphate. Analyst 1963; 88 (1044): 217–21.