

# International Year of the Periodic Table 2019: Elements important for Life Sciences

Division of Medicinal Chemistry and Chemical Biology

A Division of the Swiss Chemical Society

## Matched Pair Theranostics

Andreas Türlér\*

\*Correspondence: Prof. Dr. A. Türlér, Universität Bern, Departement Chemie und Biochemie, Freiestr. 3, CH-3012 Bern, E-mail: andreas.tuerler@dcb.unibe.ch

**Keywords:** Photo nuclear reactions · Positron emission tomography · Radionuclide therapy · Theranostics

The principles of personalized medicine, companion diagnostics or theranostics can be almost ideally realized in the field of nuclear medicine. Radionuclides coupled to a specific vector, which can be a small molecule such as glucose or a peptide, or a large molecule, such as an antibody or antibody fragment, can be used to first image and thus diagnose a patient. It is the intent of the diagnosis to make biochemical processes visible in the organism without interference. If the vector is labelled with a therapeutic radionuclide of the same element as the diagnostic one, the biological behavior can be assumed to be nearly identical, as different isotopes of an element exhibit nearly the same kinetics and chemical reactivity. With therapy, one would like to kill tumor cells without side effects. Therefore, in the future, it should be possible to predict the therapeutic response of a patient to an applied radiation dose based on data from nuclear imaging. Furthermore, by imaging the patient after a radionuclide therapy, the progress of the treatment can be assessed, and, if needed, a second or third therapy cycle administered. Follow-up diagnosis allows monitoring of the progression-free survival.

Inspection of the chart of nuclides reveals very few cases of true theranostic pairs if applying the following criteria: the diagnostic radionuclide should be a low-energy positron emitter suitable for Positron Emission Tomography / Computed Tomography (PET/CT) or Positron Emission Tomography / Magnetic Resonance Imaging (PET/MRI) with a half-life in the range of 2 to 24 h. The positron branching should be high and the number of accompanying gamma-rays should be low. Furthermore, its production should be easily accomplished with good yield at a low energy particle accelerator, such as a medical cyclotron in no-carrier added form. Its therapeutic counterpart should be a beta minus – and/or Auger electron emitter with a half-life in the range of 2 to 10 days, again featuring no or only low energy, low intensity accompanying gamma-rays. The production of the radionuclide must be accomplished in large quantities, *i.e.* TBq per production run in no-carrier added quality. Very advantageous is furthermore an already established labelling chemistry using thermodynamically and kinetically very stable chelators, such as the DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) chelator.

The available radionuclide pairs are illustrated in Fig. 1 together with some other commonly used diagnostic and therapeutic radionuclides. To reach the goal of theranostics, new radionuclides with optimum decay characteristics and chemical properties are essential. Their availability is presently very limited, especially in Switzerland, which is entirely lacking adequate production facilities for therapeutic radionuclides, such as  $^{177}\text{Lu}$  or  $^{131}\text{I}$  to name a few. A stable and sustainable supply of radionuclides in quantity and quality suitable for medical applications represents a major effort and remains a scientific challenge.

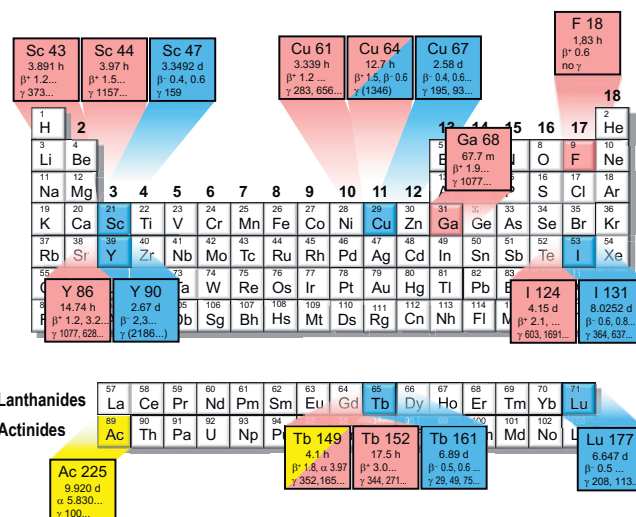


Fig. 1. Periodic table of the elements highlighting diagnostic radionuclides suitable for PET and therapeutic radionuclides, as well as true theranostic pairs.

Commonly, diagnostic radionuclides are either derived from a generator system, *i.e.* from a  $^{99}\text{Mo}$  generator for  $^{99\text{m}}\text{Tc}$ -labelled products used for diagnosis with single photon emission computed tomography (SPECT), or a  $^{68}\text{Ge}$ -generator for  $^{68}\text{Ga}$ -labelled products for diagnosis by PET. Quite often, PET diagnostic radionuclides, such as the most common  $^{18}\text{F}$  (but also  $^{11}\text{C}$ , and rarely  $^{13}\text{N}$ ,  $^{15}\text{O}$ ,  $^{64}\text{Cu}$  or  $^{89}\text{Zr}$ ), are produced by medical cyclotrons hosted by hospitals or industrial production sites.

Therapeutic radionuclides, which are administered in much higher doses with respect to diagnostic ones, are usually produced in nuclear research reactors. Prominent examples are  $^{131}\text{I}$ ,  $^{177}\text{Lu}$  or  $^{153}\text{Sm}$ , while  $^{90}\text{Y}$  is derived from a  $^{90}\text{Sr}$  generator system.

Currently so-called ‘matched pairs’ are in use to perform theranostics. In this case, not true isotopic pairs are being used, but chemically very similar elements are combined, *i.e.* making use of the very good stability of the DOTA chelator with elements in the +3 oxidation state, such as Ga, Sc, Y, Lu, Tb or Ac. Currently,  $^{68}\text{Ga}$ -labelled compounds for PET diagnostics are combined with their  $^{177}\text{Lu}$ -labelled counterpart for radionuclide therapy, where routinely a standard dose between 5.55–7.4 GBq is administered.<sup>[1]</sup> An example are PET diagnostic interventions with  $^{68}\text{Ga}$ -labelled compounds such as [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC (DOTA<sup>0</sup>,Tyr<sup>3</sup>-octreotide) or [ $^{68}\text{Ga}$ ]Ga-DOTA-TATE (DOTA<sup>0</sup>,Tyr<sup>3</sup>,Thr<sup>8</sup>-octreotide)<sup>[2]</sup> for the diagnosis of metastasized neuroendocrine tumors. Recently, diagnosis with [ $^{68}\text{Ga}$ ]Ga-PSMA-11<sup>[3]</sup> for metastasized prostate cancer was followed successfully by treatment with the alpha-particle emitter  $^{225}\text{Ac}$  in the form of [ $^{225}\text{Ac}$ ]Ac-PSMA-617 (Fig. 2).<sup>[4]</sup>

The decisive factor to enable future true theranostics lies in the everyday and year-round availability of the respective radionuclides. The following promising candidates contained in Fig. 1 are discussed in more detail.

## The Theranostic Pair $^{43,44g}\text{Sc}/^{47}\text{Sc}$

The positron emitter  $^{43}\text{Sc}$  has a high positron branching of 88.1%, a lower mean beta-plus energy ( $E_{\beta^+ \text{ avg}}$ ) than  $^{44g}\text{Sc}$ , and

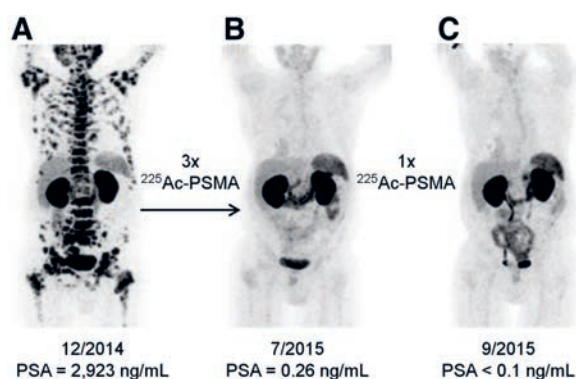


Fig. 2.  $^{68}\text{Ga}$ -PSMA-11 PET/CT scans of a patient. Pretherapeutic tumor spread (A), restaging 2 mo after third cycle of  $^{225}\text{Ac}$ -PSMA-617 (B), and restaging 2 mo after one additional consolidation therapy (C). This research was originally published in JNM.<sup>[4]</sup> © SNMMI

an accompanying gamma-ray of 372.9 keV (22.5%), which lies below the 511 keV annihilation radiation of the positron and does thus not interfere with detection and position reconstruction, while exhibiting an almost ideal nuclear half-life of 3.89 h, similar to  $^{44}\text{gSc}$ . This nuclide can be produced with high radionuclidic purity at a 18 MeV medical proton cyclotron in the reaction  $^{46}\text{Ti}(p,\alpha)^{43}\text{Sc}$  or at a cyclotron equipped with a deuteron source (9 MeV) in the reaction  $^{42}\text{Ca}(d,n)^{43}\text{Sc}$ . The reaction  $^{43}\text{Ca}(p,n)^{43}\text{Sc}$  is challenging.<sup>[5]</sup>  $^{44}\text{gSc}$  can easily be produced in good yield from  $^{44}\text{Ca}$  targets<sup>[5]</sup> or from a  $^{44}\text{Ti}/^{44}\text{gSc}$ -generator system<sup>[6]</sup> and has been successfully applied in first human patients.<sup>[6,7]</sup>  $^{43}\text{Sc}$  has been tested only preclinically.<sup>[8]</sup> However, the co-emission of a high-energy gamma-ray of 1157 keV with every positron requires additional shielding for the hospital personnel compared to regular  $^{18}\text{F}$ . Nevertheless, for first clinical trials  $^{44}\text{Sc}$  is very suitable and can be replaced by  $^{43}\text{Sc}$  later on.

The companion  $^{47}\text{Sc}$  was identified some time ago as a useful therapeutic radionuclide. It combines a similarly favorable mean beta-minus decay energy  $E_{\beta, \text{avg}}^- = 0.162$  MeV as compared with  $^{177}\text{Lu}$  ( $E_{\beta, \text{avg}}^- = 0.134$  MeV) with the ideal half-life of 3.35 d, similar to  $^{90}\text{Y}$  ( $T_{1/2} = 2.67$  d). The emitted gamma-ray of 159.4 keV can be ideally used for SPECT, although its relatively large intensity of 68.3% may be considered as less advantageous. However, the production of large activities of  $^{47}\text{Sc}$  in no-carrier-added form (nca), suitable for therapeutic interventions, so far was confronted with significant obstacles.<sup>[8]</sup>

A completely new approach to production of  $^{47}\text{Sc}$  presents the use of so-called photonuclear reactions. Several companies have developed powerful electron accelerators in the energy range from 35–40 MeV and made them commercially available. The intense electron beam is directed at a high density converter target producing Bremsstrahlung. The high-energy part of the gamma-ray spectrum above about 10 MeV can be used to induce photonuclear reactions on selected target materials. It was shown that  $^{47}\text{Sc}$  can be produced in the photonuclear reaction  $^{48}\text{Ti}(\gamma,p)^{47}\text{Sc}$ .<sup>[9]</sup> Using a sufficiently intense electron beam will enable the production of several hundred GBq per day!

### The Theranostic Pair $^{61,64}\text{Cu}/^{67}\text{Cu}$

Another very interesting pair for theranostics is the combination  $^{61}\text{Cu}/^{67}\text{Cu}$  or  $^{64}\text{Cu}/^{67}\text{Cu}$ .<sup>[10]</sup> The positron emitter  $^{64}\text{Cu}$  is produced by proton irradiation of an enriched nickel target following the nuclear reaction  $^{64}\text{Ni}(p,n)^{64}\text{Cu}$  at a medical cyclotron with a cross section maximum at 11 MeV.  $^{64}\text{Cu}$  with a half-life of 12.7 hours decays 17.6% by positron emission, 38.5% by  $\beta^-$ -emission, and 43.9% by electron capture and can be used for both imaging and therapeutic applications. Furthermore, only one accompanying gamma-ray with rather low intensity is observed ( $E_{\gamma} = 1345.8$  keV; 0.5%). A number of institutions are currently supplying  $^{64}\text{Cu}$

on a routine basis for clinical trials. However, no  $^{64}\text{Cu}$  radiopharmaceutical with a marketing authorization is currently available. The relatively low positron branch of 17.6% may be considered as less favorable, as the patient receives an additional dose from the associated  $\beta^-$ -emission and electron capture decay.

Although there is significant interest in  $^{67}\text{Cu}$ , its use is restricted by its low availability. Similarly to  $^{47}\text{Sc}$ ,  $^{67}\text{Cu}$  has a half-life of 2.6 d, which, in many cases, fits with the biological half-lives of many pharmaceutical compounds. The mean beta-decay energy  $E_{\beta, \text{avg}}^- = 0.141$  MeV is similar to that of  $^{177}\text{Lu}$ . Similar to  $^{47}\text{Sc}$ , the gamma-rays of 184.6 keV, 93.1 keV and 91.3 keV can be used for SPECT imaging. Also, the gamma-ray intensities are comparable. Review articles describe the production, separation, and use of  $^{67}\text{Cu}$  for radioimmunotherapy.<sup>[10,11]</sup> Attempts to produce  $^{67}\text{Cu}$  in the (p,2p) reaction on natural Zn resulted in  $^{67}\text{Cu}$  with relatively low specific activity due to the co-production of stable Cu isotopes in significant quantities.<sup>[12]</sup> Significantly better results were obtained using enriched  $^{68}\text{Zn}$  targets.<sup>[13]</sup>

Again, as in the case of  $^{47}\text{Sc}$ , the use of photonuclear reactions will enable the production of very clean, no-carrier added  $^{67}\text{Cu}$  in the reaction  $^{68}\text{Zn}(\gamma,p)^{67}\text{Cu}$ . First batches of  $^{67}\text{Cu}$  are available through the US Department of Energy.<sup>[14]</sup> Future facilities should be able to produce several hundred GBq per day of irradiation.

### The Theranostic Pair $^{152}\text{Tb}/^{161}\text{Tb}$ and $^{149}\text{Tb}$

The therapeutic radionuclide  $^{161}\text{Tb}$  has very similar decay properties as  $^{177}\text{Lu}$  concerning half-life and beta-decay energy. However, its decay is accompanied by the emission of additional Auger- and conversion electrons. Calculations have shown that  $^{161}\text{Tb}$  delivers up to 4.1 times higher dose to a cell-sized sphere of 10  $\mu\text{m}$  diameter compared to that from  $^{67}\text{Cu}$  and 8.1 times that from  $^{47}\text{Sc}$ .<sup>[15,16]</sup> Tb can be produced in nca form by neutron irradiation of  $^{160}\text{Gd}$  in a nuclear reactor.<sup>[16]</sup> A perfect diagnostic match was found in the form of  $^{152}\text{Tb}$ , which was produced *via* a spallation process followed by mass separation at ISOLDE, CERN. A first-in-human PET/CT with [ $^{152}\text{Tb}$ ]-Tb-DOTA-TOC was successfully performed at Zentralklinik Bad Berka in Germany.<sup>[17]</sup> However, the very limited availability of  $^{152}\text{Tb}$  due to the required use of a mass separator will be a major obstacle for further widespread applications. Another very interesting radionuclide that comprises both diagnostic and therapeutic functions by exhibiting positron- as well as alpha particle emission is  $^{149}\text{Tb}$  with a half-life of 4 h. Likewise,  $^{149}\text{Tb}$  was produced *via* a spallation process followed by mass separation at ISOLDE, CERN and evaluated in pre-clinical work.<sup>[18]</sup> In summary, the use of  $^{161}\text{Tb}$  for therapeutic applications appears very promising and feasible in the near future, while  $^{149}\text{Tb}$  and  $^{152}\text{Tb}$  are currently more of academic interest.

### The Alpha Particle Emitter $^{225}\text{Ac}$ and its Production

The radionuclide  $^{225}\text{Ac}$  has been in the focus of attention for many years and recent clinical applications hold great promise (Fig. 2).<sup>[4]</sup> However, the world-wide availability of this radionuclide is extremely limited. The best radionuclidic purity  $^{225}\text{Ac}$  is available by milking from a  $^{229}\text{Th}$  generator every 50 days. However, the supply of the mother nuclide  $^{229}\text{Th}$ , which is a decay product of  $^{233}\text{U}$  is very limited, as  $^{233}\text{U}$  is nuclear weapons grade material managed under stock-pile stewardship. Limited amounts of  $^{225}\text{Ac}$  were produced at a low energy cyclotron in the nuclear reaction  $^{226}\text{Ra}(p,2n)$  first at Institute for Transuranium Elements, Karlsruhe<sup>[19]</sup> and later at Technical University Munich. Both sites have ceased production of  $^{225}\text{Ac}$  more than 10 years ago.  $^{225}\text{Ac}$  is currently available through the US Department of Energy, where  $^{225}\text{Ac}$  is produced *via* spallation from massive  $^{232}\text{Th}$  targets.<sup>[14]</sup> This material, however, contains traces of  $^{227}\text{Ac}$  impurities.  $^{227}\text{Ac}$  is currently the nuclide with the lowest authorization limit in the

Swiss Radiation Protection Ordinance with 1 LA corresponding to only 8 Bq.

Again, a very interesting alternative for the production of  $^{225}\text{Ac}$  are photonuclear reactions.<sup>[20]</sup> By irradiation of  $^{226}\text{Ra}$  with high-energy gamma-rays the nuclide  $^{225}\text{Ra}$  is formed in ( $\gamma, n$ )-reactions, which in turn decays to  $^{225}\text{Ac}$  via  $\beta^-$  decay. First calculations show that a future facility would be able to produce hundreds of patient doses of  $^{225}\text{Ac}$  per day of irradiation, with  $^{225}\text{Ac}$  being virtually free of the  $^{227}\text{Ac}$  contaminant.<sup>[20]</sup>

University of Bern and the Federal Institute of Metrology (METAS) are currently engaged in a Sinergia project named PHotonuclear Reactions (PHOR): Breakthrough Research in Radionuclides for Theranostics funded by the Swiss National Science Foundation (SNSF). Both, METAS with its 22 MeV electron microtron and the Bern Cyclotron Laboratory, with its 18 MeV proton cyclotron, being equipped with a solid target station and an automatic delivery system, are well suited for this task. It is the goal of this interdisciplinary project to lay the scientific foundation for a future theranostic center involving cyclotrons and high-power electron accelerators for radionuclide production in Switzerland.

Received: October 7, 2019

- [1] J. J. Zaknun, L. Bodei, J. Mueller-Brand, M. E. Pavel, R. P. Baum, D. Hörsch, M. S. O'Dorisio, T. M. O'Dorisiol, J. R. Howe, M. Cremonesi, D. J. Kwakkeboom, *Eur. J. Nucl. Med. Mol. Imaging* **2013**, *40*, 800, DOI 10.1007/s00259-012-2330-6.
- [2] I. Velikyan, *Theranostics* **2014**, *4*, 47.
- [3] A. Afshar-Oromieh, A. Malcher, M. Eder, M. Eisenhut, H. G. Linhart, B. A. Hadaschik, T. Holland-Letz, F. L. Giesel, C. Kratochwil, S. Haufe, U. Haberkorn, C. M. Zechmann, *Eur. J. Nucl. Med. Mol. Imaging* **2013**, *40*, 486.
- [4] C. Kratochwil, F. Bruchertseifer, F. L. Giesel, M. Weis, F.A. Verburg, F. Mottaghy, K. Kopka, C. Apostolidis, U. Haberkorn, A. Morgenstern, *J. Nucl. Med.* **2016**, *57*, 1941.
- [5] T. S. Carzaniga, M. Auger, S. Braccini, M. Bunka, A. Ereditato, K. P. Nesteruk, P. Scampoli, A. Türlér, N. van der Meulen, *Appl. Radiat. Isot.* **2017**, *32*, 124.
- [6] F. Rösch, R. P. Baum, *Dalton Trans.* **2011**, *40*, 6104.
- [7] A. Singh, N. P. van der Meulen, C. Müller, I. Klette, H. R. Kulkarni, A. Türlér, R. Schibli, R. P. Baum, *Cancer Biotherapy and Radiopharmaceuticals* **2017**, *32*, 124.
- [8] K. A. Domnanich, R. Eichler, C. Müller, S. Jordi, V. Yakusheva, S. Braccini, M. Behe, R. Schibli, A. Türlér, N. P. van der Meulen, *EJNMMI Radiopharm. Chem.* **2017**, *2*, 14.
- [9] M. Mamtamin, F. Harmon, V. N. Starovoitova, *Appl. Radiat. Isot.* **2015**, *102*, 1.
- [10] C. S. Cutler, H. M. Hennkens, N. Sisay, S. Huclier-Markai, S. S. Jurisson, *Chem. Rev.* **2013**, *113*, 858.
- [11] N. A. Smith, D. L. Bowers, D. A. Ehst, *Appl. Radiat. Isot.* **2012**, *70*, 2377.
- [12] S. C. Srivastava, *Semin. Nucl. Med.* **2012**, *42*, 151.
- [13] D. G. Medvedev, L. F. Mausner, G. E. Meinken, S.O. Kurczak, H. Schnakenberg, C.J. Dodge, E.M. Korach, S. C. Srivastava, *Appl. Radiat. Isot.* **2012**, *70*, 423.
- [14] <https://isotopes.gov/news/notices.html> Notice #102 – December 21, **2018**.
- [15] C. Champion, M. A. Quinto, C. Morgat, P. Zanotti-Fregonara, E. Hindíe, *Theranostics* **2016**, *6*, 1611.
- [16] S. Lehenberger, C. Barkhausen, S. Cohrs, E. Fischer, J. Grünberg, A. Hohn, U. Köster, R. Schibli, A. Türlér, K. Zernosekov, *Nucl. Med. Biol.* **2011**, *38*, 917.
- [17] R. P. Baum, A. Singh, M. Benešová, C. Vermeulen, S. Gnesin, U. Köster, K. Johnston, D. Müller, S. Senftleben, H. R. Kulkarni, A. Türlér, R. Schibli, J. O. Prior, N.P. van der Meulen, C. Müller, *Dalton Trans.* **2017**, *46*, 14638.
- [18] C. Müller, K. Zernosekov, U. Köster, K. Johnston, H. Dorrer, A. Hohn, N. T. van der Walt, A. Türlér, R. Schibli, *J. Nucl. Med.* **2012**, *53*, 1951.
- [19] C. Apostolidis, R. Molinet, J. McGinley, K. Abbas, J. Möllenbeck, A. Morgenstern, *Appl. Radiat. Isot.* **2005**, *62*, 383.
- [20] O. D. Maslov, A. V. Sabel'nikov, S. N. Dmitriev, *Radiochem.* **2006**, *48*, 195.