Research outputs:

**Half-lives of $^{132}_{\text{La}}$ and $^{135}_{\text{La}}$**

The half-lives of $^{132}_{\text{La}}$ and $^{132}_{\text{La}}$ were determined via serial gamma spectroscopy, and the half-life of $^{135}_{\text{La}}$ was further determined by a high-precision ionization-chamber measurement. The results are 18.91(2) hr for $^{132}_{\text{La}}$ and 4.59(4) hr for $^{132}_{\text{La}}$ compared with the previously compiled values of 19.5(2) hr and 4.8(2) hr, respectively. These lanthanum isotopes comprise a medically interesting system with positron emitter $^{132}_{\text{La}}$ and Auger-electron emitter $^{135}_{\text{La}}$ forming a theranostic pair for internal diagnostics and therapeutics. The precise half-lives are necessary for proper evaluation of their value in medicine and for a more representative tabulation of nuclear data.

**General information**

Publication status: Published
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory, Michigan State University, University of Wisconsin-Madison
Contributors: Abel, E. P., Clause, H. K., Fonslet, J., Nickles, R. J., Severin, G. W.
Number of pages: 5
Publication date: 2018
Peer-reviewed: Yes

**Publication information**

Journal: Physical Review C (Nuclear Physics)
Volume: 97
Issue number: 3
Article number: 034312
ISSN (Print): 2469-9985
Ratings:
  - BFI (2018): BFI-level 1
  - Scopus rating (2018): CiteScore 3.14 SJR 1.502 SNIP 1.372
  - Web of Science (2018): Impact factor 3.132
  - Web of Science (2018): Indexed yes
Original language: English
Electronic versions:
  - Untitled.pdf
DOIs:
  - 10.1103/PhysRevC.97.034312

**Bibliographical note**

©2018 American Physical Society
Liquid–liquid extraction in flow of the radioisotope titanium-45 for positron emission tomography applications

A continuous liquid–liquid extraction of natTi and its PET radioisotope 45Ti into an organic phase from 12 M HCl is described. The extraction is completely selective with respect to Sc, which is commonly used as a cyclotron target for 45Ti production. A membrane-based separator with integrated pressure control allowed for efficient, reproducible, and robust aqueous/organic phase separation in flow. Optimization studies established a guaiacol–anisole 9/1 (v/v) mixture and a flow rate ratio of 1/3 (aq. to org.), with a residence time of 13.7 s as the optimal extraction conditions. 90.3 ± 1.1% of natTi was consistently extracted from a 0.01 M solution of natTiCl4 and ScCl3, while 84.8 ± 2.4% of 45Ti was extracted from 0.03–0.13 M ScCl3 containing picomolar amounts of the 45Ti radionuclide, without extracting any Sc from either system. The organic phase can be directly used for 45Ti-radiolabelling as demonstrated by the efficient radiosynthesis of the 45Ti-radiolabeled antineoplastic [45Ti]IJsalan)TiIJdipic). This development opens a pathway to achieve continuous and efficient 45Ti recovery and processing using an automated micro or millifluidics setup.

General information
Publication status: Published
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory, Massachusetts Institute of Technology
Corresponding author: Zhuravlev, F.
Pages: 898-904
Publication date: 2018
Peer-reviewed: Yes

Publication information
Journal: Reaction Chemistry and Engineering
Volume: 3
Issue number: 6
ISSN (Print): 2058-9883
Ratings:
Scopus rating (2018): CiteScore 3.77 SJR 1.216 SNIP 0.921
Web of Science (2018): Impact factor 3.935
Web of Science (2018): Indexed yes
Original language: English
DOIs:
10.1039/C8RE00175H
Source: FindIt
Source ID: 2440262736

Manganese-52: applications in cell radiolabelling and liposomal nanomedicine PET imaging using oxine (8-hydroxyquinoline) as an ionophore

The ionophore 8-hydroxyquinoline (oxine) has been used to radiolabel cells and liposomal medicines with 111In and, more recently, 89Zr, for medical nuclear imaging applications. Oxine has also shown promising ionophore activity for the positron-emitting radionuclide 52Mn that should allow imaging of labelled cells and nanomedicines for long periods of time (>14 days). However, to date, the radiometal complex formed and its full labelling capabilities have not been fully characterised. Here, we provide supporting evidence of the formation of [52Mn]Mn(oxinate)_2 as the metastable complex responsible for its ionophore activity. The cell labelling properties of [52Mn]Mn(oxinate)_2 were investigated with various cell lines. The liposomal nanomedicine, DOXIL® (Caelyx) was also labelled with [52Mn]Mn(oxinate)_2 and imaged in vivo using PET imaging. [52Mn]Mn(oxinate)_2 was able to label various cell lines with moderate efficiency (15-53%), however low cellular retention of 52Mn (21-25% after 24 h) was observed which was shown not to be due to cell death. PET imaging of [52Mn]Mn-DOXIL at 1 h and 24 h post-injection showed the expected pharmacokinetics and biodistribution of this stealth liposome, but at 72 h post-injection showed a profile matching that of free 52Mn, consistent with drug release. We conclude that oxine is an effective ionophore for 52Mn, but high cellular efflux of the isotope limits its use for prolonged cell tracking. [52Mn]Mn(oxinate)_2 is effective for labelling and tracking DOXIL in vivo. The release of free radionuclide after liposome extravasation could provide a non-invasive method to monitor drug release in vivo.

General information
Publication status: Published
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory, King's College London, GlaxoSmithKline, Hebrew University of Jerusalem, Imperial College London
Corresponding author: de Rosales, R. T.
135La as an auger-electron emitter for targeted internal radiotherapy

Introduction: 135La has favorable nuclear and chemical properties for Auger-based targeted internal radiotherapy. Here we present detailed investigations of the production, emissions, imaging characteristics, and dosimetry related to 135La therapy. Methods and Results: 135La was produced by 16.5 MeV proton irradiation of metallic natBa on a medical cyclotron, and was isolated and purified by trap-and-release on weak cation-exchange resin. The average production rate was 407 ± 19 MBq/µA (saturation activity, n = 3), and the radionuclidic purity was 98% at 20 h post irradiation. Chemical separation recovered > 98 % of the 135La with an effective molar activity of 70 ± 20 GBq/µmol. To better assess cellular and organ dosimetry of this nuclide, we have recalculated the X-ray and Auger emission spectra using a Monte Carlo model accounting for effects of multiple vacancies during the Auger cascade. The generated Auger spectrum was used to recalculate cellular S-factors. Conclusion: 135La was produced with high specific activity, reactivity, radionuclidic purity, and yield. The emission spectrum and the dosimetry are favorable for internal radionuclide therapy.
Imaging neuronal pathways with 52 Mn PET in rats

General information
Publication status: Published
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory, Eberhard-Karls-Universität Tübingen
Pages: 149
Publication date: 2017
Peer-reviewed: Yes

Publication information
Journal: Journal of Cerebral Blood Flow and Metabolism
Volume: 37
Issue number: Suppl. 1
Article number: PS01-083
ISSN (Print): 0271-678X
Ratings:
- BFI (2017): BFI-level 1
- Scopus rating (2017): CiteScore 5.07 SJR 2.558 SNIP 1.532
- Web of Science (2017): Impact factor 6.045
- Web of Science (2017): Indexed yes

Original language: English
Electronic versions:
- SG_JCBJ170031_98..pdf
Source: FindIt
Source ID: 2358787881
Research output: Contribution to journal › Conference abstract in journal – Annual report year: 2017 › Research › peer-review

Imaging neuronal pathways with 52 Mn PET: Toxicity evaluation in rats

Manganese in its divalent state (Mn²⁺) has features that make it a unique tool for tracing neuronal pathways. It is taken up and transported by neurons in an activity dependent manner and it can cross synapses. It also acts as a contrast agent for magnetic resonance imaging (MRI) enabling visualization of neuronal tracts. However, due to the limited sensitivity of MRI systems relatively high Mn²⁺ doses are required. This is undesirable, especially in long-term studies, because of the known toxicity of the metal. In order to overcome this limitation, we propose ⁵²Mn as a positron emission tomography (PET) neuronal tract tracer. We used ⁵²Mn for imaging dopaminergic pathways after a unilateral injection into the ventral tegmental area (VTA), as well as the striatonigral pathway after an injection into the dorsal striatum (STR) in rats. Furthermore, we tested potentially noxious effects of the radioactivity dose with a behavioral test and histological staining. 24 h after ⁵²Mn administration, the neuronal tracts were clearly visible in PET images and statistical analysis confirmed the observed distribution of the tracer. We noticed a behavioral impairment in some animals treated with 170 kBq of ⁵²Mn, most likely caused by dysfunction of dopaminergic cells. Moreover, there was a substantial DNA damage in the brain tissue after applying 150 kBq of the tracer. However, all those effects were completely eliminated by reducing the ⁵²Mn dose to 20-30 kBq. Crucially, the reduced dose was still sufficient for PET imaging.

General information
Publication status: Published
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory, Eberhard-Karls-Universität Tübingen
Number of pages: 14
Pages: 112-125
Publication date: 2017
Peer-reviewed: Yes

Publication information
Journal: NeuroImage
Volume: 158
ISSN (Print): 1053-8119
Ratings:
- BFI (2017): BFI-level 2
- Scopus rating (2017): CiteScore 6.15 SJR 3.679 SNIP 1.822
- Web of Science (2017): Impact factor 5.426
Neodymium-140 DOTA-LM3: Evaluation of an In Vivo Generator for PET with a Non-Internalizing Vector

140Nd (t1/2 = 3.4 days), owing to its short-lived positron emitting daughter 140Pr (t1/2 = 3.4 min), has promise as an in vivo generator for positron emission tomography (PET). However, the electron capture decay of 140Nd is chemically disruptive to macrocycle-based radiolabeling, meaning that an in vivo redistribution of the daughter 140Pr is expected before positron emission. The purpose of this study was to determine how the delayed positron from the de-labeled 140Pr affects preclinical imaging with 140Nd. To explore the effect, 140Nd was produced at CERN-ISOLDE, reacted with the somatostatin analogue, DOTA-LM3 (1,4,7,10-tetraazacyclododecane, 1,4,7-triacetic acid, 10-acetamide N-p-Cl-Phecyclo(D-Cys-Tyr-d-4-amino-Phe(carbamoyl)-Lys-Thr-Cys)2-Tyr-NH2) and injected into H727 xenograft bearing mice. Comparative pre- and post-mortem PET imaging at 16 h postinjection was used to quantify the in vivo redistribution of 140Pr following 140Nd decay. The somatostatin receptor-positive pancreas exhibited the highest tissue accumulation of 140Nd-DOTA-LM3 (13% ID/g at 16 h) coupled with the largest observed redistribution rate, where 56 ± 7% (n = 4, mean ± SD) of the in situ produced 140Pr washed out of the pancreas before decay. Contrastingly, the liver, spleen, and lungs acted as strong sink organs for free 140Pr³⁺. Based upon these results, we conclude that 140Nd imaging with a non-internalizing vector convolutes the biodistribution of the tracer with the accumulation pattern of free 140Pr. This redistribution phenomenon may show promise as a probe of the cellular interaction with the vector, such as in determining tissue dependent internalization behavior.

Optimized procedures for manganese-52: Production, separation and radiolabeling

Pressed chromium-powder cyclotron targets were irradiated with 16MeV protons, producing 52Mn with average yields of 6.2±0.8 MBq/µAh. Separation by solid-phase anion exchange from ethanol-HCl mixtures recovered 94.3±1.7% of 52Mn and reduced the chromium content by a factor of 2.2±0.4×10⁵. An additional AG 1-X8 column was used to remove copper, iron, cobalt and zinc impurities from the prepared 52Mn in 8M HCl. The macrocyclic chelator DOTA was rapidly radiolabeled with 52Mn in aq. ammonium acetate (pH 7.5R.T.) with a radiochemical yield >99% within 1min and was stable for >2 days in bovine serum. The improved separation and purification methodology facilitates the use of 52Mn in basic science and preclinical investigations.
Production and utilization of unconventional radiometals for advanced diagnostics and therapy

The continued development in biochemistry delivers vectors capable of specifically identifying foreign entities like malignancies and infections. Many of these vectors have long circulation time in vivo, resulting in optimal biodistribution for imaging several days post injection. The diagnostic potential of these can only be fully utilized if non-standard radionuclides with half-lives extending beyond those of the standard catalogue (11C, 18F, and 64Cu) are available. As for therapy, the increased specificity of new vectors strengthens the argument for using targeted radionuclide therapy, as they allow delivery of therapeutic doses to target tissues with minimal unspecific uptake and dose in healthy non-target tissues. This allows for the use of a wider range of radionuclides, like α-emitters, for which high specificity is needed due to their high toxicity. The development of highly specific, internalizing vectors opens for use of Auger emitters. The therapeutic effect of these radionuclides most likely relies on internalization and translocation to the cell nucleus, because of their extremely localized, short-range dose deposition. Although the selection such vectors is still limited, the development of robust production methods for Auger emitters is crucial for investigating the basic principles of Auger therapy. The focus of this thesis has been expanding the number of isotopes and techniques available in the nuclear medicine toolbox.

The work performed using diagnostic isotopes includes:

52Mn: A production and separation method for high specific activity 52Mn was developed. Labeling conditions and serum stability for 52Mn-DOTA were investigated, and 52Mn was labeled to intact antibodies showing in vivo stability in mice. 89Zr: Very high specific activity 89Zr was produced. A labeling method for sensitive metalloproteins was developed. Further, the potential pitfalls in quality control of 89Zr labeled proteins were documented. 45Ti: A production and separation method for 45Ti was developed and optimized. This work includes one of the first ever in vivo studies of a 45Ti-compound.

The work performed using therapeutic isotopes includes:

177Lu: The sensitive metalloprotein FVIIai was conjugated with the chelator cDTPA and labeled with 177Lu for a therapeutic study. This included optimization of labeling conditions and development of quality control.

135La: Pressed Ba-targets were produced and production and separation methods for high specific activity 135La were developed. Labeling conditions were tested and cellular and human dosimetry of 135La was calculated.

165Er: A production method for 165Er was developed, based on electron-capture-mediated release of 165Er from DOTA. Finally, a method was developed using 144Nd for assaying cellular internalization of a compound in vivo. General dosimetry calculations and considerations are further presented to aid selection of the radionuclide when designing a radiopharmaceutical.

The combined work serves to aid further development in both pharmaceutical research, and diagnostic as well as therapeutic applications of radionuclides.
Radionuclide therapy with tissue factor targeting Lu-177-FVIIai inhibits growth in an experimental mouse model of human pancreatic cancer

Objectives: Tissue factor (TF) is related to aggressiveness and invasiveness of cancer and there is a correlation between tumor TF expression, metastatic potential, and patient outcome. The aim of the study was to test the therapeutic potential and toxicity of a novel compound for localized TF targeted radionuclide therapy. The radionuclide therapy was based on Factor VII (FVII), the natural ligand to TF. In the current study, we investigated the biodistribution, therapeutic potential and toxicity of 177Lu labeled active site inhibited FVIIa (177Lu-FVIIai) in an experimental mouse model of pancreatic cancer.

Methods: p-SCN-Bn-CHX-A''-DTPA was conjugated to FVIIai followed by radiolabeling with 177Lu (177Lu-CHX-A''-DTPA-FVIIai). A pancreas xenograft mouse model (8xPC3) was used to assess the therapeutic potential of 177Lu-FVIIai. NMRI nude mice with subcutaneous 8xPC3 tumors were used. The mice were randomized into groups receiving 177Lu-FVIIai, FVIIai, or vehicle when the tumor volumes were about 50 mm3. 177Lu-FVIIai was administered in doses of 15 MBq, 7.5 MBq or 2 x 7.5 MBq (n=8 mice/group). Tumor growth was monitored three times weekly. Biodistribution of 177Lu-FVIIai was studied ex vivo in several organs at 1, 4, 24, 72 and 168 hours after injection. The in vivo biodistribution of 177Lu-FVIIai was evaluated by SPECT/CT imaging. Furthermore, competition and dose escalation experiments (1-30 MBq) were performed. In a parallel set of NMRI mice, toxic effects of 177Lu-FVIIai were evaluated by hematology, histology and 99mTc-DMSA scintigraphy.

Results: FVIIai was successfully radiolabeled with 177Lu with a specific activity of 10-25 GBq/µmol after EDTA scavenging and PD-10 purification. Treatment with FVIIai did not change tumor growth compared to the vehicle groups. The mice that received 15 MBq 177Lu-FVIIai had a significantly reduced tumor growth from day 0 to day 19 compared with mice from the control groups (425.5±44.8% versus 614.2±49.1%; p=0.02). The groups receiving 7.5 MBq or 2 x 7.5 MBq 177Lu-FVIIai had no significant different tumor growth compared with controls on day 19. Tumor uptake of 177Lu-FVIIai measured ex vivo was 1.16±0.04, 1.97±0.18, 1.95±0.07, 1.01±0.06, 0.31±0.02 percent injected dose per gram (%ID/g) at 1, 4, 24, 72 and 168 hours post-injection, respectively. Injection with unlabeled FVIIai 10 minutes before 177Lu-FVIIai injection significantly reduced tumor uptake of 177Lu-FVIIai (from 2.5±0.16 %ID/g to 1.7±0.05 %ID/g; p<0.05). Escalating the dose of 177Lu-ASIS from 1-30 MBq did not change tumor uptake (%ID/g). A transient decrease in leucocyte counts was observed for the mice receiving 15 and 7.5 MBq 177Lu-FVIIai. Ten weeks after injection of 177Lu-FVIIai kidney uptake of 99mTc-DMSA was significantly decreased in all the treatment groups compared to the vehicle group when measured by SPECT imaging. Conclusion: FVIIai was successfully radiolabeled with 177Lu. 177Lu-FVIIai showed anti-tumor activity in a mouse model of human pancreatic cancer. Treatment with 177Lu-ASIS induced a transient decrease in leucocyte counts and a decreased kidney function ten weeks after injection.

General information
Publication status: Published
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory, Department of Photonics Engineering, Administration, University of Copenhagen
Publication date: 2017
Peer-reviewed: Yes

Publication information
Journal: Journal of Nuclear Medicine
Volume: 58
Issue number: suppl. 1
Article number: 463
ISSN (Print): 0161-5505
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 5.12 SJR 2.307 SNIP 1.737
Web of Science (2017): Impact factor 7.439
Web of Science (2017): Indexed yes
Original language: English
Source: FindIt
Source ID: 2372651058
Research output: Contribution to journal – Journal article – Annual report year: 2017 – Research – peer-review
Tissue factor targeted radionuclide therapy with $^{177}$Lu-FVIIai inhibits tumor growth of human pancreatic cancer xenografts

**General information**
Publication status: Published
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory, Minerva Imaging ApS, University of Copenhagen
Publication date: 2017
Peer-reviewed: Yes

**Publication information**
Journal: Cancer Research
Volume: 77
Issue number: 13 Supplement
Article number: 5203
ISSN (Print): 0008-5472
Ratings:
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 7.35 SJR 4.26 SNIP 1.708
Web of Science (2017): Indexed yes
Original language: English
DOI:
10.1158/1538-7445.AM2017-5203
Source: PublicationPreSubmission
Source ID: 141962850
Research output: Contribution to journal | Conference abstract in journal – Annual report year: 2017 | Research | peer-review

Towards Translational ImmunoPET/MR Imaging of Invasive Pulmonary Aspergillosis: The Humanised Monoclonal Antibody JF5 Detects Aspergillus Lung Infections In Vivo

Invasive pulmonary aspergillosis (IPA) is a life-threatening lung disease of hematological malignancy or bone marrow transplant patients caused by the ubiquitous environmental fungus Aspergillus fumigatus. Current diagnostic tests for the disease lack sensitivity as well as specificity, and culture of the fungus from invasive lung biopsy, considered the gold standard for IPA detection, is slow and often not possible in critically ill patients. In a previous study, we reported the development of a novel non-invasive procedure for IPA diagnosis based on antibody-guided positron emission tomography and magnetic resonance imaging (immunoPET/MRI) using a $[^{64}\text{Cu}]$ DOTA-labeled mouse monoclonal antibody (mAb), mJF5, specific to Aspergillus. To enable translation of the tracer to the clinical setting, we report here the development of a humanised version of the antibody (hJF5), and pre-clinical imaging of lung infection using a $[^{64}\text{Cu}]$ NODAGA-hJF5 tracer. The humanised antibody tracer shows a significant increase in in vivo biodistribution in A. fumigatus infected lungs compared to its radiolabeled murine counterpart $[^{64}\text{Cu}]$ NODAGA-mJF5. Using reverse genetics of the pathogen, we show that the antibody binds to the antigenic determinant beta 1,5-galactofuranose (Galf) present in a diagnostic mannoprotein antigen released by the pathogen during invasive growth in the lung. The absence of the epitope Galf in mammalian carbohydrates, coupled with the enhanced imaging capabilities of the hJF5 antibody, means that the $[^{64}\text{Cu}]$ NODAGA-hJF5 tracer developed here represents an ideal candidate for the diagnosis of IPA and translation to the clinical setting.

**General information**
Publication status: Published
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory, University of Exeter, University of Tubingen, Paul Scherrer Institute, University of Duisburg-Essen, CheMatech, Universite de Bourgogne
Number of pages: 17
Pages: 3398-3414
Publication date: 2017
Peer-reviewed: Yes

**Publication information**
Journal: Theranostics
Volume: 7
In Vivo Radionuclide Generators for Diagnostics and Therapy

In vivo radionuclide generators make complex combinations of physical and chemical properties available for medical diagnostics and therapy. Perhaps the best-known in vivo generator is $^{212}$Pb/$^{212}$Bi, which takes advantage of the extended half-life of $^{212}$Pb to execute a targeted delivery of the therapeutic short-lived α-emitter $^{212}$Bi. Often, as in the case of $^{81}$Rb/$^{81}$Kr, chemical changes resulting from the transmutation of the parent are relied upon for diagnostic value. In other instances such as with extended alpha decay chains, chemical changes may lead to unwanted consequences. This article reviews some common and not-so-common in vivo generators with the purpose of understanding their value in medicine and medical research. This is currently relevant in light of a recent push for alpha emitters in targeted therapies, which often come with extended decay chains.
52Mn – a new PET tracer for imaging neural pathways

135La for Auger-based therapy: preparation, imaging and emissions
Bringing Radiotracing to Titanium-Based Antineoplastics: Solid Phase Radiosynthesis, PET and ex Vivo Evaluation of Antitumor Agent [45Ti](salan)Ti(dipic)

We present a novel solid-phase based 45Ti radiolabeling methodology and the implementation of 45Ti-PET in titanium-based antineoplastics using the showcase compound [45Ti](salan)Ti(dipic). This development is intended to allow elucidation of the biodistribution and pharmacokinetics of promising new Ti-based therapeutics.

Decay induced de-chelation of positron-emitting electron-capture daughters and its use in preclinical PET

Decay induced de-chelation of positron-emitting electron-capture daughters and its use in preclinical PET
Novel Preparation Methods of $^{52}\text{Mn}$ for ImmunoPET Imaging

$^{52}\text{Mn}$ ($t_{1/2} = 5.59$ d, $\beta^+ = 29.6\%$, $E_{\beta^{ave}} = 0.24$ MeV) shows promise in positron emission tomography (PET) and in dual-modality manganese-enhanced magnetic resonance imaging (MEMRI) applications including neural tractography, stem cell tracking, and biological toxicity studies. The extension to bioconjugate application requires high specific activity $^{52}\text{Mn}$ in a state suitable for macromolecule labeling. To that end a $^{52}\text{Mn}$ production, purification, and labeling system is presented, and its applicability in preclinical, macromolecule PET is shown using the conjugate $^{52}\text{Mn}$-DOTA-TRC105. $^{52}\text{Mn}$ is produced by 60 µA, 16 MeV proton irradiation of natural chromium metal pressed into a silver disc support. Radiochemical separation proceeds by strong anion exchange chromatography of the dissolved Cr target, employing a semi-organic mobile phase, 97:3 (v:v) ethanol: HCl (11M, aqueous). The method is $62 \pm 14\%$ efficient ($n=7$) in $^{52}\text{Mn}$ recovery, leading to a separation factor from Cr of $(1.6 \pm 1.0) \times 10^6$ ($n = 4$), and an average effective specific activity of 0.8 GBq/µmol ($n = 4$) in titration against DOTA. $^{52}\text{Mn}$-DOTA-TRC105 conjugation and labeling demonstrate the potential for chelation applications. In vivo images acquired using PET/CT in mice bearing 4T1 xenograft tumors are presented. Peak tumor uptake is $18.7 \pm 2.7$ %ID/g at 24 hours post injection and ex vivo $^{52}\text{Mn}$ biodistribution validates the in vivo PET data. Free $^{52}\text{MnCl}_2$ (as chloride or acetate) is used as a control in additional mice to evaluate the non-targeted biodistribution in the tumor model.
Optimized $^{52}\text{Mn}$ Production for Long-lived PET Applications

General information
Publication status: Published
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory, Department of Electrical Engineering, University of Wisconsin-Madison
Number of pages: 1
Publication date: 2015

Host publication information
Title of host publication: Proceedings - World Molecular Imaging Congress 2015
Electronic versions:

Abstract
Research output: Chapter in Book/Report/Conference proceeding – Conference abstract in proceedings – Annual report year: 2015 › Research › peer-review

Hydrolytically stable titanium-45

Introduction
Titanium-45, a candidate PET isotope, is under-employed largely because of the challenging aqueous chemistry of Ti(IV). The propensity for hydrolysis of Ti(IV) compounds makes radio-labeling difficult and excludes $^{45}\text{Ti}$ from use in bioconjugate chemistry. This is unfortunate because the physical characteristics are extremely desirable: $^{45}\text{Ti}$ has a 3 hour half-life, a positron branching ratio of 85 %, a low $E_{\beta}^\text{max}$ of 1.04 MeV, and negligible secondary gamma emission. In terms of isotope production, $^{45}\text{Ti}$ is transmuted from naturally mono-isotopic $^{45}\text{Sc}$ by low energy proton irradiation. The high cross-section and production rates on an unenriched metal foil target contribute to make $^{45}\text{Ti}$ an ideal PET radionuclide.

In order to bring $^{45}\text{Ti}$ to even a preclinical platform, the hydrolytic instability of aqueous Ti(IV) needs to be addressed. Recently, the groups of Edit Tshuva (Hebrew University of Jerusalem) and Thomas Huhn (University of Konstanz) have synthesized several stable Ti(IV) compounds based upon the salan ligand $^{[1,2]}$. Additionally, these compounds have shown heightened cytotoxicity against HT-29 (human colorectal cancer) cells, amongst others, as compared to traditional metal-based chemotherapeutics such as cisplatin.
The aim of our work has been to produce the radioactive analogue of one of these Ti(IV)-salan compounds, Ti-salan-dipic [2], which has hydro-lytic stability on the order of weeks. Not only will this allow us to shed some light on the still un-known mechanism of antiproliferative action of titanium-based chemotherapeutics, but it will also make progress toward bioconjugate 45Ti PET tracers.

In the current abstract, we present some of the methods we are using to separate 45Ti from irradiated Sc, and subsequent labeling conditions.

Material and Methods
45Ti was produced by proton irradiation of 250μm scandium foils at currents ranging from 10-20μA on a GE PETTrace. In order to increase production rate in the thin foil, an 800μm aluminum degrader was used to take the proton energy down from the nominal 16 MeV. The scandium was cooled by contact to a water-cooled silver plate.

The activated foil was dissolved in 4M HCl, dried under argon at 120 oC, and taken back up in 12M HCl. Here, four (i-iv below) different approaches to removing the Ti from the Sc and labeling were taken with varying success.
Briefly: i. 45Ti was separated on hydroxamate resin, as presented by K. Gagnon [3], only at 12M acid concentration followed by on-column radiolabeling. ii. 45Ti was extracted into 1-octanol [4], stripped with 12M HCl, and used directly for labeling from the organic phase. iii. 45Ti was trapped on a C-18 cartridge that had been pre-loaded with 1-octanol, similar to ion-pairing, and eluted with isopropanol. iv. 45Ti was extracted onto a polystyrene based 1,3 diol resin (RAPP polymers) and labeling commenced on the column.

Radiolabeling was slightly different in each condition, but in general the salan and dipic ligands were added to the 45Ti in pyridine and reacted at elevated temperature (60–100 oC) for several (10–30) minutes. Reaction progression and radiochemical purity were assessed with silica TLC in chloroform : ethyl acetate (1 : 1).

Results and Conclusion
The trap, release, and yields for the four methods listed above are shown in TABLE 1. The best result was with the 1,3 diol resin which had the added advantage of reacting on-column.

Further optimization is underway including a test of a solid supported 1,2 diol, and preclinical imaging with HT-29 xenografts.
We conclude that hydrolytically stable 45Ti com-pounds can be synthesized in high yield, and hope that this advances the radiochemistry and use of 45Ti toward more widespread applications.

General information
Publication status: Published
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory, Department of Electrical Engineering
Contributors: Severin, G., Fonslet, J., Zhuravlev, F.
Number of pages: 4
Publication date: 2014

Host publication Information
Title of host publication: Proceedings of the 15th International Workshop on Targetry and Target Chemistry
Place of publication: Prague, Czech Republic
Electronic versions:
60_SeverinWTTC15_FINALdraft_corrected_kw.pdf
URLs:
Source: PublicationPreSubmission
Source ID: 112537201
Research output: Chapter in Book/Report/Conference proceeding > Article in proceedings – Annual report year: 2015 > Research > peer-review

Preparation of [45Ti] Ti-salan-dipic
We report the carrier-free radiochemical synthesis of a neutral, bio-active, titanium-45 complex, [45Ti]Ti-salan-dipic. In 2012, the Huhn group at Universität Konstanz reported the non-radioactive compound, Ti-salan-dipic, and demonstrated therapeutic efficacy in a xenograft cervical cancer mouse model as well as enhanced in-vitro cytotoxicity over several other titanium-based chemotherapeutics [1]. The mechanism of action for this class of therapeutics is under investigation and the determination of which will be aided by radiotracing and PET with 45Ti.
45Ti was prepared by proton irradiation of natSc foil followed by extraction onto a polystyrene-based diol-resin (RAPP polymers) after dissolution of the foil in 37% HCl. Synthesis proceeded on the column after quenching the residual acidity with pyridine. The ligands, salan and dipic, were added sequentially in pyridine, with the release of the final compound upon ligand exchange to dipic. [45Ti]Ti-salan-dipic was characterized by radio-TLC on silica in 1:1 ethylacetate:chloroform in comparison to the cold compound.
This is a hydrolytically stable, cytotoxic, 45Ti compound. The solid-phase synthesis is robust, and provides opportunity for producing other 45Ti tracers. PET and radiotracer studies with [45Ti]Ti-salan-dipic and other Ti-based cytotoxic compounds will aid in mechanism determination, drug design, and eventually more effective treatment of cancer.

General information
Publication status: Published
Organisations: Center for Nuclear Technologies, The Hevesy Laboratory
Number of pages: 1
Pages: 632-632
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: Nuclear Medicine and Biology
Volume: 41
Issue number: 7
ISSN (Print): 0969-8051
Ratings:
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 2.53 SJR 0.946 SNIP 0.946
Web of Science (2014): Impact factor 2.412
Web of Science (2014): Indexed yes
Original language: English
Keywords: RADIOLOGY,
DOIs:
10.1016/j.nucmedbio.2014.05.107
Source: Findit
Source ID: 269269556
Research output: Contribution to journal › Conference abstract in journal – Annual report year: 2014 › Research › peer-review

Projects:

Production of biologically relevant radionuclides to be used as diagnostics and therapeutics
Fonslet, J., PhD Student, Department of Physics
Jensen, M., Main Supervisor
Severin, G., Supervisor
Lindvold, L. R., Examiner
Engle, J. W., Examiner
Hemmingsen, L. B. S., Examiner
EU-finansieret
01/03/2014 → 25/09/2017
Award relations: Production of biologically relevant radionuclides to be used as diagnostics and therapeutics
Project: PhD