Third Theranostics World Congress on Gallium-68 and PRRT: Abstracts

The Society of Nuclear Medicine and Molecular Imaging and Johns Hopkins University convened to cosponsor the Third Theranostics World Congress on Gallium-68 and PRRT, a conference held March 12–14, 2015, on the Johns Hopkins Medical Campus in Baltimore. This Congress provided updates on recent developments in the exciting field of theranostics—a term that epitomizes the inseparability of diagnosis and therapy, the pillars of medicine, and takes into account personalized management of the disease for a specific patient.

Innovative applications for and results of new research on ^{68}Ga-labeled PET radiopharmaceuticals, including PSMA- and CXCR4-targeted imaging, were presented. Radionuclide therapy applying the same peptides labeled with β emitters such as ^{177}Lu or ^{90}Y for peptide radioligand therapy of prostate cancer, small cell lung cancer, lymphoma, and other malignancies, along with a discussion of novel peptides (e.g., somatostatin antagonists for imaging and therapy of neuroendocrine tumors), rounded out the program. The increase in enthusiasm for ^{68}Ga use over the last few years can be ascribed to several factors, some of which promise an increasing role for ^{68}Ga as a theranostic tool in the selection of patients for peptide receptor radiotherapy (PRRT). Although widely used in Europe for more than a decade, ^{68}Ga and ^{177}Lu, as well as ^{90}Y-labeled somatostatin receptor ligands, have been used in the United States only in trials under Investigational New Drug applications (e.g.,^{68}Ga DOTATOC, DOTATATE, or DOTANOC) or in clinical trials (^{177}Lu DOTATATE). Efforts to obtain approval of these ligands in the United States have increased significantly over the past 2 years, and the potential of soon having an approved agent available in the United States is promising.

The program was uniquely developed to dedicate specific days to presenting work on related topics. Thursday was devoted to radiochemistry, peptide labeling, and updates on ^{68}Ga generators, modules, and postprocessing. Friday covered both preclinical and clinical topics, and Saturday provided information for clinicians and patients, with a session dedicated to the current approval status of ^{68}Ga-labeled agents in the United States. The congress included 2 plenary presentations. The Thursday plenary speaker was Prof. Dr. Jean Claude Reubi from the University of Bern, Switzerland, author of more than 500 scientific articles, inventor of a dozen of patents and patent applications, and recognized internationally for his research on peptide receptors. He presented "Peptide Membrane Receptors as Targets in Cancer." On Friday, Dr. Ralph Hruban, Professor of Pathology and Oncology at the Johns Hopkins University School of Medicine, presented "Genetic Alterations in NETs." Dr. Hruban has written more than 600 scientific papers and 5 books and has received numerous awards.

The international audience comprised physicians, chemists, physicists, technologists, and all scientists and clinicians interested in translational research and current state-of-the-art molecular imaging using ^{68}Ga-labeled radiopharmaceuticals and new peptides for radionuclide therapy. Attendees with limited knowledge on this class of agents found the conference to be particularly useful. Presentations on clinical applications and patient advocacy were new to this congress, providing a unique perspective for attendees.

This conference also offered opportunities for participation from junior scientists, with presentations being selected from the most highly rated abstracts submitted. In addition to the invited lectures and oral abstract presentations, the meeting included poster presentations. The first day's posters were primarily on radiochemistry, whereas those on the second day were on preclinical and clinical research. The abstracts in this supplement are listed alphabetically by the last name of the first author; however, the presenting author at the conference was not always the first author on the abstract. Six abstracts were selected to receive recognition-in-excellence awards: first, second, and third place for oral presentations as well as for poster presentations. The winners were announced at the closing ceremony and were presented with a certificate.

We hope these abstracts provide you with valuable insight into the work being done in this exciting field.

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Y90 PET-CT imaging in patients undergoing therapy with ^{90}Y-DOTATATE: comparison with ^{68}Ga-DOTATATE images. L. Aloj[1], L. D'Ambrosio[1], M. Aurilio[1], P. Chiaramida[2], A. Morisco[1], M. Malinconico[1], S. Lastoria[1]; [1]Istituto Nazionale Tumori, Napoli, Italy, [2]GE Healthcare, Rome, Italy

Objectives: ^{90}Y-DOTATATE is utilized for radionuclide therapy of somatostatin receptor–positive neuroendocrine tumors. Direct imaging of the distribution of this radiopharmaceutical has important clinical implications for estimating tumor and normal organ doses. The low-abundance positron emission of ^{90}Y (0.0032% of decays) can be utilized for PET imaging. We are evaluating the use of ^{90}Y PET to image and quantitate ^{90}Y-DOTATATE distribution in patients undergoing treatment. **Methods:** A GE D600 PET-CT system was used. Well counter correction and recovery coefficient measurements were performed. Patients undergoing peptide receptor radionuclide therapy (PRRT) underwent PET-CT imaging with ^{68}Ga-DOTATATE prior to treatment and underwent ^{90}Y PET studies 4–24 h following administration of ^{90}Y-DOTATATE. Images of selected areas were acquired for at least 15 min per bed position (iterative reconstruction; ML-OS-EM; Vue point HD; 2 iterations; 8 subsets; postfilter, 8 mm). **Results:** Eighteen patients with well-differentiated neuroendocrine tumors were studied. Most patients had pancreatic primary tumors (11/18; 61%), and liver metastases were present in 14/18 patients (78%). Administered activities ranged from 34 to 124 mCi. At least one known lesion was visible in the ^{90}Y PET images in 17/18 patients (94%). Sensitivity was highest for detection of disease in the pancreas (11/11 lesions detected). Liver areas of increased uptake were visible in all 14 patients who had known liver lesions, although most lesions under 2 cm in diameter were not detectable. ^{68}Ga PET–positive lymph node lesions were detectable in 3/6 patients, and bone lesions were detectable in 1/2 patients. **Conclusion:** The use of PET to image ^{90}Y-DOTATATE distribution is feasible and may have significant advantages compared with gamma-camera imaging. Although sensitivity and spatial resolution are rather poor, quantitation of uptake in larger lesions may provide the ability to perform dosimetry in patients undergoing ^{90}Y PRRT.

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Dramatic response with peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE and capecitabine in the treatment of metastatic thymic carcinoma. T. Armaghany[1], G. Vahdati[2], S. Broline[2], R. Goshen[3], M. Rogosnitzky[4], E. Delpassand[2]; [1]Westchase Oncology Center, Houston, TX, [2]Excel Diagnostics and Nuclear Oncology Center, Houston, TX, [3]Eliaso Consulting Ltd., Caesarea, Israel, [4]Adjuvant Medical Solutions, Telz Stone, Israel

Background: Thymic carcinoma is a highly aggressive malignancy and carries a poor prognosis when metastatic. Chemotherapy combinations using agents such as cisplatin, cyclophosphomide, vincristine, and adriamycin (CVAP) are considered in the treatment. Some thymic carcinomas express somatostatin receptors that are evident by OctreoScan or Ga68-DOTATATE PET/CT. Peptide receptor radionuclide therapy (PRRT) is currently utilized in clinical trials in the treatment of neuroendocrine tumors due to somatostatin receptor expression. Capecitabine has shown a tumor response for thymic carcinomas, and it has also been used as a radiosensitizer during PRRT treatments for neuroendocrine tumors. **Case report:** A nonsmoking 70-year-old Caucasian man with a remote history of asthma presented with intractable cough and severe fatigue in August 2013. His symptoms were attributed to asthma, and steroids were prescribed. A workup showed a mediastinal mass and lung and liver lesions. CT scans showed an anterior chest mass that measured 48 × 20 mm, and the largest liver lesion was measured at 30 × 18 mm in diameter. An ^{18}F-FDG PET/CT scan confirmed the same and showed high aggressiveness (SUV, >7.0). CEA was reported to be normal; CA19-9 was moderately elevated, at 61; and LDH was slightly elevated, at 266 (normal, 243). In November, a CT-guided biopsy of the left lower lung lesion revealed moderately differentiated squamous cell carcinoma of the thymus. Immunohistochemistry results showed P16, napsin A, HPV, TTF1, and PAx8 negativity and CK7 CD5, CD 5/6, CD11 P63, and C-KIT positivity. FISH analysis of ALK/EML4 gene rearrangement was negative, and an EGFR mutation was not detected. Chemotherapy with a combination of cisplatin, cytoxan, vincristine, and adriamycin was administered from November 2013 to February 2014. He initially showed a mixed response, but subsequent restaging images in May 2013 showed progression of disease. A ^{111}In-pentetreotide scan (OctreoScan) performed in May 2014 showed intense activity in the same lesions, correlating well with the lesions on the PET/CT scan. He was enrolled in a clinical trial of peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE at our center. Baseline CT scans showed a 6-cm conglomerate mass in the anterior mediastinum and multiple pulmonary nodules, with the largest in the left lower lobe measuring 4.8 cm. His liver MRI showed multifocal bilobar hepatic 2 metastasis with complete replacement of the entire left hepatic and caudate lobes. The sum of the longest diameters of target lesions in the liver was measured at 21 cm. A baseline Ga68-DOTATATE PET/CT scan showed increased tracer uptake in the enlarged thymus, with an SUV of 8.1, consistent with a primary thymus neoplasm. The largest mass in the right lobe of the liver measured 6 × 8 cm and had an SUV of 15. The largest mass in the lung was in the posterior aspect of the left lower lobe, measured 4 × 3.9 cm, and had an SUV of 7.10. These correlated very well with the ^{18}F-FDG PET/CT scan confirming high aggressiveness. His baseline lab results were significant for a WBC count of $14.4 \times 10^3/\mu L$, with a left shift; normal AST and ALT; elevated alkaline phosphatase (ALKP), at 307 IU/L (normal, 150); CA-125 of 78 u/mL (normal, <35); CA 19-9 of 1,213 u/mL (normal, <35); and high ESR, at 66 mm/h. A ^{177}Lu-DOTATATE PRRT and capecitabine combination was initiated in June 2014. Additionally, he was taking several medications and supplements that are known to have in vivo and/or in vitro anticancer properties or are hepatoprotective during chemotherapy. These consisted of injectable low-dose enoxaparin, alpha-lipoic acid, mebendazole, milk thistle, opioid growth factor (OGF; met-enkephalin), and noscapine. PRRT treatment consisted of 4 cycles of 200 mCi ^{177}Lu-DOTATATE administered 6–9 weeks apart, and capecitabine was given at 1,500 mg/m^2 orally in a divided dosage for 2 weeks during a 3-week cycle. Capecitabine was continued during and in between PRRT cycles. After the first cycle of PRRT + capecitabine treatment, his repeat images with MRI and Ga68-DOTATATE PET/CT scans showed a dramatic response and near to complete resolution of liver and lung lesions. His cough completely subsided, and his energy level had improved to the stage that he went back to work. Capecitabine was tapered to his tolerance due to grade II hand–foot syndrome. Ga68-DOTATATE PET/CT was repeated before the initiation of cycle 3 in September 2014. Complete resolution of the abnormal uptake throughout the liver was seen, and the SUV of the left lower pulmonary lobe had dramatically decreased, from 7.1 to 1.3. Abdominal MRI also showed total resolution of the conglomerate mass in the liver, with a residual lesion measuring 15 mm in the right lobe. An ^{18}F-FDG PET/CT scan done before his fourth treatment showed a complete response in the liver and lung. Tumor markers such as CA19-9, ESR, and liver function tests were completely normalized. **Conclusion:** Metastatic thymic carcinoma with squamous cell differentiation is a rare but highly aggressive malignancy. Chemotherapy options are limited, and the response is modest and short. This cancer is known to express somatostatin receptors; hence, Sandostatin injection is considered for the treatment of this condition. The combination of capecitabine and ^{177}Lu-DOTATATE PRRT showed a dramatic response in our case. To our knowledge, this is the first case reported of a patient treated with this combination and showing a complete response on imaging and laboratory evaluation. PRRT with or without capecitabine should be further investigated for the treatment of this malignancy. Exploring the role of the additional alternative medications and supplements mentioned above also deserves further research.

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(^{68}Ga)gallium-PSMA PET/CT in the evaluation of prostate cancer patients. C. Bal, S. Ballal, M. Tripati, P. Chakraborty, P. Thakral, G. Arora; Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India

Objectives: Prostate-specific membrane antigen (PSMA) is upregulated in prostate cancer and its metastasis. PSMA has been targeted for prostate cancer imaging and therapy. ^{111}In-capromab pendetide, a commercially available monoclonal antibody, has been used to target PSMA for prostate cancer imaging. However, it binds to the intracellular domain of PSMA, where internal binding occurs mainly in the dead cells. A newer urea-based agent, the gallium(III) chelator *N,N′*-bis[2-hydroxy-5-(carboxyethyl)benzyl]

ethylenediamine-*N,N′*-diacetic acid (HBED-CC) (^{68}Ga-PSMA HBED-CC), has been designed to target the extracellular domain of PSMA. The urea motif (Glu-NH-CO-NH-Lys) is of low molecular weight and binds to the active binding site of PSMA. This compound exhibits a high target-to-background ratio and a high specific internalization property. In this ongoing study, as a primary objective, we present the utility of ^{68}Ga-PSMA HBED-CC for assessing the primary tumor, lymph nodal involvement, and distant metastasis. As a secondary objective, we compared ^{68}Ga-PSMA HBED-CC with ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scan findings in the detection of skeletal metastasis. **Methods:** A total of 55 patients with high Gleason scores and/or rising PSA levels underwent ^{68}Ga-PSMA PET/CT either for the purpose of preoperative staging or to look for recurrence of the disease postoperatively. At 30 minutes after injection of 2.5 mCi tracer, scans were acquired in an mCT scanner (Siemens, Germany). The scan interpretations were done by two experienced nuclear medicine physicians; both were blinded to the clinical and radiological data of the patients. All lesions with focal increased uptake higher than the background were considered as pathological. For patients with skeletal metastasis, ^{68}Ga-PSMA scans were compared with conventional ^{99m}Tc-MDP bone scans to look for concordance by the McNemar test. A P value < 0.05 was considered significant. **Research:** A total of 55 patients (ages ranging from 38 to 83 years; mean ± SD, 65 ± 9 years) were recruited, 31 for initial staging and 24 for suspected recurrence. The mean serum PSA level was 153.91 ng/mL (range, 0.26–2,166.45 ng/mL), and the mean Gleason score was 7.1 ± 1.1. In the ^{68}Ga-PSMA images, local residual/recurrent disease uptake and lymph node, bone, and other soft-tissue metastases were detected in 28 (50.9%), 20 (36.36%), 22 (40%), and 11 (20%), respectively. The qualitative comparison of skeletal metastasis between ^{68}Ga-PSMA and ^{99m}Tc-MDP scans revealed that both scans were positive for 22 patients and that both scans were negative for 18 patients, leading to 40 (73%) concordant and 15 (27%) discordant results. On analysis of discordant results, ^{68}Ga-PSMA scans identified additional lesions in 9 patients that were missed by ^{99m}Tc-MDP scans; similarly, ^{99m}Tc-MDP scans identified additional lesions in 6 patients that were missed by ^{68}Ga-PSMA scans. However, there was no statistically significant difference (P = 0.6072) between the two modalities as far as skeletal lesion detection is concerned. **Conclusion:** ^{68}Ga-PSMA PET/CT appears to be a "one-stop-shop" imaging method in prostate cancer evaluation, with high detection rates for primary/recurrent tumors and lymph node, bone, and soft-tissue metastases. Our results encourage the theranostic approach for PSMA-targeted imaging and therapy in prostate cancer.

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Kinetics and mechanisms of Ga(DOTA) formation in ethanol-water mixture. Z. Baranyai, I. Tóth, G. Szabó, A. Vágner, E. Brücher; Department of Inorganic and Analytical Chemistry, University of Debrecen, Debrecen, Hungary

Objectives: Radioisotopes of Ga are gaining interest in nuclear medicine (*1*). Ga(III) complexes used in PET rely on well-known macrocyclic (MC) NOTA and DOTA bioconjugates (*2,3*). The formation rate for MC complexes is low, and a special procedure (i.e., high temperature) is required. Due to the short half-life of ^{68}Ga, there is a need to accelerate the reaction without denaturation of the biofragment. Recent studies proposed solvent mixtures (*4*). Our aim is to explore the kinetics and suggest a mechanism for these experimental findings. **Methods:** The protonation constants of H_4DOTA were determined by pH potentiometry in a 0–70 V/V% ethanol–water mixture. The formation reaction was followed in 0–40 V/V% mixtures by monitoring the release of H^+ from DOTA with VIS spectrophotometry (indicator method). The reaction was also followed by ^{1}H and ^{71}Ga NMR spectroscopy. **Results:** The $\log K^H_1$ and $\log K^H_2$ values of DOTA (attributed to the ring nitrogens) decrease with increasing EtOH concentration. The formation of Ga(DOTA) happens via the formation of unusually stable diprotonated *Ga(H_2DOTA). The loss of the first proton might be fast, and the rate-determining step is the (water-assisted) deprotonation of *Ga(HDOTA), followed by its rearrangement to the final Ga(DOTA) complex. EtOH does not play a direct role in the formation reaction. **Conclusion:** EtOH has an effect on the basicity of the ring nitrogens of DOTA. The formation reaction goes through long-lived intermediates (similar to lanthanide MC systems). The decreased basicity in water–EtOH helps the formation of the reactive monoprotonated intermediate, i.e., speeds up the formation reaction. These results are useful to optimize the labeling procedure for DOTA conjugates with Ga^{3+} isotopes at ambient temperature. **References:** 1. Wadas TJ, Wong EH, Weisman GR, Anderson CJ. *Chem Rev.* 2010;110:2858–2902. 2. Fani M, André JP, Maecke HR. *Contrast Media Mol Imaging*. 2008;3:67–77. 3. Tanaka K, Fukase K. *Org Biomol Chem.* 2008;6:815–828. 4. Rösch F, Malo-Cruz M. Efficient radiometal-labelling of drug delivery systems utilizing water/ethanol mixtures. COST Action TD1004 Annual Meeting, Athens, Greece; 2013.

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Theranostics of prostate cancer using Lu-177-labeled PSMA small molecule for peptide radioligand therapy (PRLT). R.P. Baum[1], H.R. Kulkarni[1], H.-J. Wester[2]; [1]THERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging (PET/CT), Zentralklinik Bad Berka, Bad Berka, Germany, [2]Pharmaceutical Radiochemistry, Technical University Munich, Munich, Germany

The significant overexpression of the prostate-specific membrane antigen (PSMA) on tumor cells makes this enzyme an ideal target for the diagnosis as well as therapy (theranostics) of prostate cancer. Ga-68–PSMA is a sensitive and specific tracer for the detection of primary prostate cancer, recurrent tumors, and metastases. We have performed over 350 Ga-68–PSMA PET/CT studies to date, also applying the new Ga-68-labeled peptide DOTAGA PSMA I&T. On the basis of our experience, the potential indications for PET/CT in prostate cancer are elevated PSA without tumor detection by conventional imaging or patients with negative biopsies and high serum PSA (for well-differentiated tumors, bombesin antagonists also may be useful); initial staging in patients with intermediate or high risk (detection of lymph node and distant metastases), especially in cases of strongly elevated PSA levels (suspicious distant metastases); detection of recurrence after initial therapy (which is a proven indication for choline PET/CT if PSA levels are above 1.5 ng/mL) (in our experience, Ga-68–PSMA is far superior to choline due to the detection of recurrence at very low PSA levels [<0.5 ng/mL], especially in undifferentiated tumors with a high Gleason grade); therapy monitoring (depending on the clinical question that needs to be answered); molecular radiation therapy planning (MRTP), e.g., for dose painting/sculpting; and theranostics before planned PRLT for selection of the most appropriate radiopharmaceutical for therapy as well as for follow-up and assessment of the therapy response after radionuclide therapy (this indication holds great future potential). On the basis of the principles of targeted radionuclide therapy, Lu-177-labeled ligands binding specifically to PSMA were developed using the suitable chelator DOTAGA. Peptide radioligand therapy with Lu-177 DOTAGA PSMA ligands "PSMA TUM-1" (Technical University of Munich molecule 1) and "PSMA I&T" (imaging and therapy) was performed in 53 patients with progressive, metastasized, castrate-resistant prostate cancer. Ga-68–PSMA PET/CT was used for patient selection and follow-up. Thirty-four patients received multiple cycles (range, 2–5; in total, 106 administrations). The mean injected activity of Lu-177 PSMA per cycle was 5.7 ± 0.8 GBq (median, 5.8 GBq). The posttherapy response could not be assessed until now in 27 patients. Patient-specific dosimetry was carried out according to the MIRD scheme. The metastases exhibited intense PSMA expression, as demonstrated by baseline Ga-68–PET/CT, and high Lu-177 PSMA uptake on posttherapy planar scans and on SPECT/CT images. A molecular treatment response (partial remission) was observed in 11 patients, and a morphological response (according to RECIST) was seen in 6 patients. Stable disease was noted in 5 and 13 patients, according to molecular and morphological response criteria, respectively, whereas disease progressed in 8 patients. All symptomatic patients reported significant improvement in pain and quality of life after therapy. The treatment was very well tolerated by all patients; absolutely no acute (vomiting, emesis) or long-term side effects were reported (especially, there was no evidence of any salivary or lacrimal gland toxicity). There were no significant alterations in any of the laboratory parameters (blood, renal, and hepatic panel and chemistry); especially, no hematotoxicity was observed (despite extensive bone metastases in many of the patients), and no change in renal function was observed (as determined by creatinine, GFR clearance, and Tc-99m MAG3/TER scintigraphy). Organ and tumor doses were as follows: whole body, 0.02 ± 0.01 mGy/MBq; kidneys, 0.35 ± 0.14 mGy/MBq; and tumor lesions, 0.14–19.8 mGy/MBq. In bone metastases, the maximum dose reached by a single cycle was up to 300 Gy in some cases; complete remission of lymph node metastases

was observed in some patients. The median for progression-free survival (PFS) and overall survival (OS) has not yet been reached. In conclusion, Lu-177 DOTAGA PSMA small molecules exhibit very high tumor uptake, rapid blood clearance, and fast renal washout. PRLT using Lu-177 PSMA is effective in end-stage disease after failure of all conventional/approved therapies (killing the tumor and not just improving symptoms). There was excellent tolerability in all patients treated; i.e., no hematological, renal, or salivary gland toxicity was observed. Selection of suitable patients as well as follow-up after PRLT by Ga-68–PSMA PET/CT is feasible and successful (theranostics concept). Improving treatment potency and safety by means of hyperfractionation, increasing treatment activity, new methods for kidney protection (e.g., by using PMPA), application of radiosensitizers, different radionuclides, and combinations of various therapies must be considered in future.

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A new anionic purification method of ^{68}Ge/^{68}Ga generator eluate for automated production of ^{68}Ga-peptides. R. Ben Azzouna[1], F. Al-Shoukr[1], S. Leygnac[1], D. Guiloteau[2], D. Le Guludec[1]; [1]Bichat University Hospital, Paris, France, [2]Centre Hospitalier Régional et Universitaire de Tours, Tours, France

Objectives: The aims of our purification approach are to convert $^{68}Ga^{3+}$ to anionic forms by use of NaCl as an alternative Cl^- source to highly concentrated HCl, which is very corrosive, and to combine the three standard steps (elution, anionizing, and loading) in a single step. The developed method, tested with an old generator, enables rapid and high-efficiency labelling of DOTA-conjugated peptides at a high radiochemical purity. **Methods:** The generator was eluted directly into an in-house–made NaCl cartridge connected in series with a piperazine ion resin. After the "elution–anionizing–loading" step, the anionic exchanger was washed with 5 M NaCl, and ^{68}Ga was then eluted in the reactor with 1 mL of water. DOTANOC was used as a test tracer; the eluate was added to a DOTANOC solution buffered with sodium acetate buffer. The mixture was heated for 5 min at 95°C and then diluted with 1 mL of saline. No further purification is required. **Results:** With a retention of 99%, the new method shows that elution of the generator through the in-house–made NaCl cartridge quantitatively converts $^{68}Ga^{3+}$ into the anionic form. The recovery yield of better than 90% shows that the tested weak anion exchanger is a promising resin for automated concentration and purification of a ^{68}Ga eluate. Radionuclidic purities are 10 times better than the maximum tolerated Eur. Phar. limit. The removal of Ti impurities is quantitative. The total duration of the automated synthesis was 13 min, which is suitable for the routine production of ^{68}Ga-DOTANOC for clinical use. The radiochemical purity exceeds 99% (n = 5). The radiochemical yield is greater than 80%. The final product is isoosmolar. The final pH is suitable for IV injection. **Conclusion:** We have developed a rapid and effective ^{68}Ga eluate anionic purification method that avoids the use of corrosive HCl; that provides high ^{68}Ga recovery, removal of ^{68}Ge, and removal of Ti impurities; and that offers the possibility of using the generator until 20 months after the calibration date.

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Optimizing and assessing staff exposure during ^{177}Lu-DOTATATE PRRT. M. Ben Reguiga; APHP–Beaujon Hospital, Clichy, France

Objectives: ^{177}Lu-DOTATATE PRRT is an emerging strategy for metastatic neuroendocrine tumor treatment. Lu-177 emits β particles (Eβmax, 490 keV) and γ rays (113 keV and 210 keV). Regarding this multiple emission, the aims of this study were to assess the shielding to be used during ^{177}Lu-DOTATATE PRRT and then to evaluate the staff exposure in these conditions. **Methods:** For the shielding assessment, tungsten pots (5 mm) and syringe shields (3 mm), PMMA pots (10 mm) and syringe shields (5 mm), and leaded mobile screens (2 mm Pb) and lead aprons (0.5 mm Pb) were used with 1 GBq of Lu-177. Dose rates were measured (n = 3–5) with a Fieldspect dosimeter. Attenuation ratios were then calculated for each screen type. With regard to occupational exposure, personal exposure was evaluated (7.4 GBq/cycle; n = 6–10) using an Mk2 APD for the whole-body effective dose [Hp(10)] and an UNFORS NED extremity dosimeter for fingertip dosimetry [Hp(0.07)]. **Research:** Tungsten screens were significantly more effective than those of PMMA; the dose rate in contact with tungsten pots was 0.11 ± 0.03 mSv/h·GBq vs. 2.7 ± 0.3 mSv/h·GBq with PMMA. When placed 30 cm–50 cm from unprotected Lu-177 sources, lead aprons allowed 45%–51% attenuation, whereas mobile screens allowed 93%–97% at the same distances. Tungsten screens definitely were preferred over PMMA screens. In these conditions, for each treatment, radiopharmacy staff (for handling, sampling, measuring, packaging, and draining infusion lines) received 902.5 ± 293.0 μSv [Hp(0.07)] and 5.5 ± 1.7 μSv [Hp(10)]. NM technicians (for connecting tubing, patient monitoring for 4 hours, and imaging) received 204.3 ± 96.1 μSv [Hp(0.07)] and 7.9 ± 1.8 μSv [Hp(10)]. Nurse aids received 2.6 ± 1.8 μSv [Hp(10)] and <10 μSv [Hp(0.07)], and hospitalization nurses received 2.1 ± 0.5 μSv [Hp(10)]. **Conclusion:** Tungsten and lead screens are preferred over PMMA during Lu-177 handling and patient monitoring. In these conditions, ^{177}Lu-DOTATATE PRRT generates limited staff exposure, not exceeding regulatory limits.

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Optimized conditions for radiolabeling DOTATATE for personalized medicine with PRRT. W.A.P. Breeman, E. de Blois; Department of Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

Objectives: Peptide receptor radionuclide therapy (PRRT) of receptor-mediated processes in nuclear medicine is performed with DOTA-peptides and radiolabeling with ^{177}Lu at high specific activities (SA, expressed in MBq per mass of DOTA-peptide). Among other factors, the success of PRRT depends on the availability of the radiopharmaceutical at adequately high SA, so that the required therapeutic efficacy can be achieved before saturation of the limited number of receptors available on the target lesions. This, in turn, directly depends on the SA of ^{177}Lu (here expressed in activity per mass of Lu) and the SA of the radiopharmaceutical (expressed in MBq per mass of DOTA-peptide). Moreover, from a dosimetric and pharmacodynamics point of view, for pretherapeutic measurements and PRRT, the same amount of the same substance is recommended (Kletting et al*., Med Phys.* 2012). Balancing benefits (clinical response to PRRT) versus risks (normal organ radiotoxicity) is a significant challenge, and careful assessment of biodistribution, dosimetry, and toxicity is thus essential, preferably on a personalized basis (Hofman and Hicks, *Eur J Nucl Med Mol Imaging.* 2014). The ^{177}Lu described here is reactor-produced via the (n,γ) reaction from enriched ^{176}Lu. In high-flux reactors, the target "burn up" after days of irradiation is considerable due to the high thermal neutron capture cross-section of ^{176}Lu. Hence, the assumption (also by the vendors of ^{177}Lu) that the number of target atoms ($^{175+176}$Lu) remains constant during the period of irradiation is not valid. As a consequence, the SA of ^{177}Lu will be higher, but unknown is how much higher. To label the radiopharmaceutical at a high SA, it is essential to know the concentration of the reaction ingredients for the production of the radiopharmaceutical. Therefore, DOTA-peptide and all other ingredients, such as quenchers and buffers, should be pure. The purity of ^{177}Lu and its SA (expressed in activity per mass of metal) should be high and also known. In addition, the concentration of metal ions, such as Fe-, Zn-, and Cu-ions, should be low, because these metal ions will also incorporate in the DOTA moiety and form stable complexes as well. Here we present an overview of investigations with ^{177}Lu-labeled DOTA-peptides, addressing analytical and radiochemical parameters. This will open the possibility for personalized PRRT to increase the dose in GBq at a constant amount of DOTATATE. **Methods:** Several methods were developed: first, to quantify the content and purity of DOTA-peptides and based on metal titration (with a known amount of metal ions) of the DOTA-peptide (an unknown amount of DOTA-peptide) and a base-to-base chromatographic separation of DOTA-peptide and metal-DOTA-peptide by UPLC or HPLC. Eventually, these peaks are quantified by UV detection. Quantification of these peaks reveals an accurate and sensitive method for quantifying the purity and content of DOTA-peptides. Moreover, this technique enables monitoring of the process of radiolabeling and cointroduction of impurities, including metal ions (Breeman et al., *J Radioanal Nucl Chem.* 2014). In addition, a second method, based on a similar titration technique, was developed to determine the SA of ^{177}Lu when the amount of DOTA-peptide is known and the amount of Lu ($^{175+176+177}$Lu) is unknown. After a base-to-base chromatographic separation of the peaks of DOTA-peptide and metal-DOTA-peptide and quantification by UV detection, the unknown concentration of the counterpart can be calculated (Breeman et al., *Curr Radiopharm.*, in press). These 2 methods were used to monitor the radiolabeling of DOTA-peptides, such as DOTATATE (DOTA^0,Tyr^3-octreotate), DOTATOC

(DOTA^0,Tyr^3-octreotide), and DOTA-bombesins. **Research:** The peptide content of DOTA-peptides was always below 100% (of the value as stated by vendors; range, 80%–99%), and the rest was water and salts. Moreover, up to 20% of the DOTA-peptides were already metal-labeled. Different metal-labeled DOTA-peptides were also identified as contaminants already complexed in the DOTA-peptides. Although metal-labeled DOTA-peptides have intact receptor-binding characteristics, the available DOTA moiety for labeling with ^{177}Lu will accordingly be reduced. As a result of these studies, we were able to monitor the process of radiolabeling, including the cointroduction of impurities, and to trace (and eliminate) the sources of these impurities. We found that the SA of ^{177}Lu was 30% higher (range, 10%–70%) than that stated by the vendors of ^{177}Lu. Eventually, DOTA-peptides were labeled at a molar ratio versus Lu of 1.05, with >99% incorporation of Lu in the DOTA-moiety. A typical formulation for PRRT with ^{177}Lu-DOTATATE includes 7.4 GBq ^{177}Lu-DOTATATE and 0.14 μmol (0.2 mg) DOTATATE per treatment (Breeman et al., *Curr Radiopharm.*, in press). At an SA of ^{177}Lu of 740 GBq per mg Lu, 7.4 GBq equals 10 μg Lu and 57 nmol Lu. With this formulation, we found, after labeling, 59% in the form of DOTATATE and 41% as Lu-DOTATATE (including 7% ^{177}Lu-DOTATATE). We also investigated whether DOTATATE (0.14 μmol; 0.2 mg) could adequately be labeled with ^{177}Lu at an SA of 370 GBq per mg Lu. Under these conditions, 7.4 GBq ^{177}Lu equals 20 μg Lu and 114 nmol Lu. We found, after labeling 0.14 μmol DOTATATE, 81% as Lu-DOTATATE (including 7% ^{177}Lu-DOTATATE) and 19% as DOTATATE. In addition, at a dose of 11.1 GBq ^{177}Lu, an SA of ^{177}Lu of 740 GBq per mg Lu, and 0.14 μmol DOTATATE, we found, after labeling, 61% as Lu-DOTATATE (including 11% ^{177}Lu-DOTATATE) and 39% as DOTATATE. The summarized data presented here on increased knowledge of the components and the reaction kinetics during labeling of ^{177}Lu-DOTATATE clearly show that the dose can be increased from 7.4 GBq to 11.1 GBq ^{177}Lu at a preferred constant dose of 0.14 μmol DOTATATE. **Conclusions:** After combining the newly developed methods of determining the peptide content and purity of DOTA-peptides, monitoring the process of radiolabeling, and measuring the SA of ^{177}Lu, we are now able to improve the SA of ^{177}Lu-labeled DOTA-peptides for PRRT. Thus, we have an extra tool for personalized medicine with PRRT and ^{177}Lu-DOTATATE.

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Requirements on specific activity (SA) of ^{177}Lu to radiolabel DOTATATE for PRRT: studies on labeling 0.2 mg DOTATATE with 7.4 GBq ^{177}Lu at several SA of ^{177}Lu. W.A.P. Breeman, E. de Blois; Department of Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

Objectives: Peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumors via somatostatin receptor–mediated processes in nuclear medicine is performed with ^{177}Lu-DOTATATE (DOTA^0,Tyr^3-octreotate) at high specific activities (SA, expressed in MBq per mass of DOTATATE). Among other factors, the success of PRRT depends on the availability of ^{177}Lu-DOTATATE at adequately high SA, so that the required therapeutic efficacy can be achieved before saturation of the limited number of receptors available on the target lesions. This, in turn, directly depends on the SA of ^{177}Lu (here expressed in activity per mass of Lu). The ^{177}Lu described here is reactor-produced via the (n,γ) reaction from enriched ^{176}Lu. In high-flux reactors, the target "burn up" after days of irradiation is considerable due to the high thermal neutron capture cross-section of ^{176}Lu. Hence, the assumption (also by the vendors of ^{177}Lu) that the number of target atoms ($^{175+176}$Lu) remains constant during the period of irradiation is not valid. As a consequence, the SA of ^{177}Lu will be higher, but unknown is how much higher. From a dosimetric point of view, for pretherapeutic measurements and PRRT, the same amount of the same substance is recommended (Kletting et al*., Med Phys.* 2012). A typical formulation of ^{177}Lu-DOTATATE for PRRT contains 0.2 mg DOTATATE and is labeled with 7.4 GBq ^{177}Lu per treatment. The highest achievable SA of ^{177}Lu-DOTATATE can be radiolabeled, in theory, at a level of 0.72 GBq ^{177}Lu per nmol DOTATATE. However, several factors influence the SA of DOTATATE, such as ^{177}Lu produced via the (n,γ) reaction from enriched ^{176}Lu. The presence of ^{175}Lu and ^{176}Lu reduces the maximally achievable SA, in practice, to 0.12 GBq ^{177}Lu per nmol DOTATATE. Here we present an overview of investigations with ^{177}Lu-DOTATATE, addressing the requirements for the SA of ^{177}Lu for radiolabeling at a constant amount of 0.2 mg DOTATATE labeled with 7.4 GBq ^{177}Lu at various SA of ^{177}Lu. **Methods:** To label DOTATATE at high SA, it is essential to know the concentrations of all reaction ingredients for the production of ^{177}Lu-DOTATATE. Therefore, several methods were developed: first, a method to quantify the content and purity of DOTA-peptides (Breeman et al., *J Radioanal Nucl Chem.* 2014), and second, a method to determine the SA of ^{177}Lu (Breeman et al., *Curr Radiopharm.*, in press). These 2 methods were used to monitor radiolabeling. In addition, the SA of ^{177}Lu, expressed as a function of time, are frequently calculated without the correction of decay of ^{177}Lu; thus, the SA of ^{177}Lu are underestimated. Here we present a comparison between a method with and a method without this correction and the effect on the SA of ^{177}Lu-DOTATATE. **Research:** After combining the newly developed methods of determining the peptide content and purity of DOTATATE and measuring the SA of ^{177}Lu, we were able to monitor the process of radiolabeling (e.g., introduction of metals in the reaction vial). The peptide purity and content were lower and the SA of ^{177}Lu was always higher (range, 10%–70% higher) than that stated by the vendors. As a result of these studies, we were able to monitor the process of radiolabeling, including the cointroduction of impurities, and to trace (and eliminate) the sources of these impurities. **Conclusions:** The summarized data presented here on increased knowledge of the components and the reaction kinetics during labeling of ^{177}Lu-DOTATATE clearly show that the preferred constant dose of 0.14 μmol DOTATATE and 7.4 GBq ^{177}Lu can be labeled even with an SA of ^{177}Lu of 350 GBq per mg Lu.

*Third-place poster winner.

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An enantioselective synthetic route of 1-(1-carboxy-3-carbo-tert-butoxypropyl)-4,7-(carbo-tert-butoxymethyl)-1,4,7-triazacyclononane [NODA-GA(tBu)3]. F. Broschetti[1], H.R. Mäcke[2], H. Bouterfa[3], J. Kaufmann[3]; [1]CheMatech, Dijon, France, [2]University Hospital Freiburg, Freiburg, Germany, [3]OctreoPharm Sciences GmbH, Berlin, Germany

Objectives: The macrocycle NODA-GA proved to be an important chelator for radiometals coupled to a corresponding bioactive vector, like peptides or antibodies, for PET imaging with ^{68}Ga radiolabeling already proceeding at room temperature and the generation of stable ^{64}Cu complexes. Up to now, the prochelator NODA-GA(tBu)$_3$ was only available as a mixture of the *R* and *S* enantiomers. To overcome regulatory issues concerning bioactivity and toxicological profiles of the corresponding conjugates as well as to simplify purification of the resulting products, we aimed to develop an enantioslective synthesis route yielding either (*R*)- or (*S*)-NODA-GA(tBu)$_3$ in order to couple the precursor with a somatostatin antagonist to yield a single diastereomer at a high chemical purity. **Methods:** Commercially available enantiopure (*S*)- or (*R*)-5-oxotetrahydrofuran-2-carboxylic acid was converted to the corresponding activated acid chloride followed by t-Boc protection. The lactone was hydrolyzed, and the resulting carboxylate was converted into benzyl ester, yielding the orthogonally protected glutaric acid diester arm. The activated triflate ester was generated under mild conditions, followed by the alkylation of NO_2AtBu to give (*R*)- or (*S*)-NODA-GA(tBu)$_3$ after debenzylation. The enantiomeric purity of the product was determined by chiral reversed-phase HPLC, and each fraction was analyzed by mass spectrometry. The prochelator (*R*)-NODA-GA(tBu)$_3$ was N terminally conjugated by solid-phase synthesis to the somatostatin antagonist JR11 to yield the tracer compound OPS202 (NODAGA-JR11), and the results were compared with those of the conventional synthetic route. **Research:** The literature described a synthetic route for NODA-GA(tBu)$_3$ via the 5-benzyl 1-*tert*-butyl 2-bromopentanedioate, leading to an enantiomeric purity ranging from 65%–95% (n = 3). The key step, mild triflation of the hydroxyl function, generates an ideal leaving group, avoiding racemization of the asymmetric center. The enantioselectivity of the reaction between the enantiopure triflate glutamic arm and NO_2AtBu under controlled conditions was determined to be ee = 98.2%–99% (n = 3) for the (*S*)- as well as for the (*R*)-enantiomer, with an overall yield of 70% and batch sizes ranging from 1 g to 40 g. The identity of the enantiomers was confirmed by mass spectrometry. Depending on the batch of NODA-GA(tBu)$_3$ employed for conversion with the antagonistic JR11 moiety, the diastereomeric purity of the corresponding conjugated peptide OPS202 correlates directly with the enantiomeric purity of NODA-GA(tBu)$_3$ batches, ranging from de = 54%–66% for racemic and de ≥ 95 purity for enantiopure starting material. **Conclusions:** A multigram asymmetric synthesis of the NODA-GA(tBu)$_3$ prochelator was developed. The stereochemistry of the precursor originated from enantiopure lactone acid and stereochemical.

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Study of ^{68}Ga-labeled RGD-peptides. V.B. Bubenschikov, A.Y. Maruk, A.A. Larenkov, O.E. Klementyeva, G.E. Kodina; Burnasyan Federal Medical Biophysical Center, Moscow, Russia

Objectives: RGD-peptides are known as promising agents for the visualization and therapy of angiogenesis. In this work, ^{68}Ga-RGD-conjugates were studied. The aim of the study was to determine the influence of different chelators, the quantity of c(RGDfK) fragments in the peptide, and the conditions of the labeling reaction on the radiochemical properties of ^{68}Ga and the in vitro behavior of labeled peptides. **Methods:** ^{68}Ge/^{68}Ga generators were obtained from Cyclotron Co. Ltd. (Obninsk, Russia). RGD-peptides were purchased from ABX (Radeberg, Germany). DTPA-, DOTA-, and NODAGA-peptides containing mono- and dimeric c(RGDfK) were investigated. Various parameters, such as pH, ligand concentration, incubation time, and temperature, were varied. The biological behavior of the radiotracers was preliminarily estimated by an in vitro experiment using an ovarian carcinoma cell culture (SKOV 3 line, expressing $\alpha_v\beta_3$ integrin); a 0.2 M sodium acetate solution was used to adjust the pH level. **Results:** Optimal conditions for labeling every single peptide were found. Labeled compounds were stable in the reaction mixture as well as in the blood serum for at least 4 h. Also of note is that RGD-peptides conjugated with DTPA using a benzyl fragment were not stable at high temperatures (such as 95°C). A level of cell binding of ^{68}Ga-labeled peptides with SKOV 3 of 12% of the applied dose per 10^6 cells was reached. The comparative results for the different conjugates will be presented. **Conclusion:** As a result of this study, we can conclude that both different chelating agents and the quantity of c(RGDfK) fragments affect not only the process of the labeling reaction but also the binding properties of the labeled compounds. According to our data, NODAGA is a more suitable chelating agent for Ga^{3+} labeling than DTPA and DOTA.

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^{68}Ga-labelled silica-coated iron-oxide nanorods: PET/MRI multimodal imaging and hyperthermia therapy. B. Burke[1], N. Baghdadi[1], G. Clemente[1], J. Seemann[1], S. Nigam[1], A. Kownacka[1], J. Domarkas[1], M. Lorch[1], R. Tripier[2], C. Cawthorne[1], S. Archibald[1]; [1]University of Hull, Hull, United Kingdom, [2]Université de Brest, Brest, France

Objectives: The combination of PET and MRI offers potential advantages as they complement each other (*1,2*). Iron oxide nanorods (NRs) provide high negative MRI contrast by enhancing the T2 relaxivity of surrounding water protons. Therefore, the aim of this work is to develop siloxane-coated iron oxide NRs for final-step radiolabelling with ^{68}Ga to form PET/MRI multimodal imaging agents with therapeutic applications in magnetic hyperthermia. **Methods:** Iron oxide NRs previously coated with a siloxane-derivatized macrocycle (DO3A) and siloxane-PEGylated arms in various ratios were radiolabelled with ^{68}Ga. Stability in PBS buffer and in human serum (37°C) was followed by radioTLC. In vivo imaging with microPET and a preclinical (11.7-T) MRI scanner was carried out. NR size (by nanosize tracking analysis), zeta potential, and NMR relaxivities (T1 and T2) were also measured to confirm the suitability of these nanoparticles for further therapeutic studies. **Results:** Radiolabelling conditions produced quantitatively ^{68}Ga-radiolabelled NRs stable in vitro and in vivo (*3*). The different coatings tested did not significantly affect the radiochemistry or stability. NR size and magnetic characteristics were shown to be compatible with a further preclinical application in imaging and therapy. In vivo images showed the expected liver uptake, which is in accordance with the future step of specific vectorization of the NRs. **Conclusions:** A range of NRs have been coated with various ratios of PEG and a macrocycle, successfully characterized, and radiolabelled with ^{68}Ga to form highly stable constructs with applications in bimodal imaging (e.g., tumor targeting) and magnetic hyperthermia therapy. **References:** 1. de Rosales RTM. *J Labelled Comp. Radiopharm.* 2014;57:298. 2. Thomas R, et al. *Int J Mol Sci*. 2013;14:15910. 3. Burke BP, et al. *Faraday Discuss.* doi: 10.1039/C4FD00137K.

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Initial clinical experience with nanoceria-polyacrylonitrile composite sorbent–based ^{68}Ge/^{68}Ga generator and freeze-dried DOTANOC kits developed by BARC. P. Chandra[1], V. Rangarajan[1], B. Shetye[1], N. Purandare[1], A. Agarwal[1], S. Sneha[1], A. Mukherjee[2], P. Usha[2], R. Chakravarty[2], A. Dash[2]; [1]Tata Memorial Hospital, Mumbai, India, [2]Bhabha Atomic Research Centre, Mumbai, India

Introduction: The widespread availability of PET/CT, along with the development of many radiolabeled DOTA-conjugated peptides for imaging and therapy of neuroendocrine tumors, has led to significant progress in the rapidly evolving field of theranostics. In a major step toward providing a cost-effective molecular imaging service to the increasing demands of many nuclear medicine centers in India, Bhabha Atomic Research Centre (BARC), Mumbai, developed a nanoceria-polyacrylonitrile (CeO_2-PAN) composite sorbent–based ^{68}Ge/^{68}Ga generator along with single-vial freeze-dried cold kits of DOTANOC for instantaneous labeling with ^{68}Ga from the generator without the need for automated systems. **Objective:** Our aim was to study the performance of the indigenous (CeO_2-PAN) sorbent–based ^{68}Ge/^{68}Ga generator and freeze-dried DOTANOC ready-to-use kits in various clinical indications. **Materials and Methods:** We retrospectively studied, from June–July 2013, 32 patients (age, 16–73; mean, 52) for whom ^{68}Ga-DOTANOC PET/CT was done as part of their treatment management. All ^{68}Ga-DOTANOC PET/CT studies were carried out in accordance with the European Association of Nuclear Medicine (EANM) procedural guidelines. In addition to the ^{68}Ga-DOTANOC scan, all patients underwent a ^{99m}Tc-HYNIC-TOC whole-body scan as part of the standard protocol followed in our hospital. The relative performances of both scans were studied. All ^{68}Ga-DOTANOC PET/CT studies were acquired with prior informed consent from patients. **Research/Results:** The generator was able to provide ^{68}Ga activity (in the form of $^{68}GaCl_3$) in consistent yields and acceptable radionuclidic purity ($<10^{-4}$% of ^{68}Ge breakthrough). Consistently high radiochemical yields (>95%) were obtained on radiolabeling the ready-to-use cold kits with 92.5–148 MBq ^{68}Ga.^{68}Ga-DOTANOC PET/CT was positive in 22/32 patients (for 12, initial characterization/staging/diagnosis; for 10, restaging). In 4 patients, PET/CT was successful in localizing the primary tumor (1 with tumor-induced osteomalacia; 3 with metastatic neuroendocrine tumor from an unknown primary tumor). PET/CT was negative in 10/32 patients (4 with medullary Ca thyroid; 1 with suspected insulinoma; 3 with metastatic NET with a high MiB index; 1 with ectopic Cushing syndrome; 1 with thymoma). ^{68}Ga-DOTANOC PET/CT performed better than ^{99m}Tc-HYNIC-TOC scintigraphy by identifying a greater number of lesions. **Conclusion:** The first clinical experience with an indigenous CeO_2-PAN sorbent–based ^{68}Ge/^{68}Ga generator and freeze-dried DOTANOC kits was found to be satisfactory in various clinical indications. Larger studies can be considered to promote its widespread use as a cost-effective molecular imaging modality for the assessment of neuroendocrine tumors.

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Validation of cleaning procedures for radiolabelling DOTATOC and NODAGA-RGD using a fixed-tubing module. M. Chomet[1], M. Bernad[2], A.S. Chipan[1], B. Geraudie[1], T. Henriet[2], V. Nataf[1]; [1]Radiopharmacy, Tenon Hospital, Paris, France, [2]Pharmaceutical Establishment, APHP, Paris, France

Objectives: The use of a fixed-tubing module for the preparation of different ^{68}Ga-radiolabelled drugs presents the risk of cross contamination. This issue can be solved by an appropriate cleaning procedure between radiolabelling events. In this study, we validated a cleaning sequence for two peptides, DOTATOC and NODAGA-RGD, allowing the possibility of radiolabelling both for routine production with the same fixed-tubing system. **Methods:** We used an EluSynth-^{68}Ga module and lyophilized peptides, all purchased from Iason (Austria). For each peptide, we simulated radiolabelling without ^{68}Ga, using 0.1 M HCl instead of $^{68}GaCl_3$. Then, we tested a cleaning procedure and finally performed a new simulated radiolabelling without a peptide (blank radiolabelling). The reaction mixture was analyzed by LC-MS/MS. A correct cleaning procedure was approved for a detected amount of peptide below 5% of the initial amount used. The cleaning procedures tested are described below (n = 5): process A is 1 cleaning with 96% ethanol followed by 2 cleanings with sterile water; process B is 1 cleaning with 0.1 M NaOH followed by process A; and process C is 1 cleaning with 0.1 M HCl followed by process A. **Results:** Process A was efficient for cleaning DOTATOC, with less than 0.5% of the peptide recovered in the reaction mixture of the blank radiolabelling. This procedure was not efficient for RGD, with more than 13% remaining in the

reaction mixture. Processes using 0.1 M NaOH or 0.1 M HCl provided results in accordance with the specifications (1.7% and 1.4% of RGD, respectively). **Conclusion:** In order to radiolabel DOTATOC and RGD with the same module with fixed tubing, we chose cleaning with 96% ethanol and water after each DOTATOC-^{68}Ga preparation. The procedure with 0.1 M HCl, 96% ethanol, and water is preferred after RGD labelling. This proved to be a good flexible solution that can be applied to other peptides as well and an alternative for those who do not possess the most recent modules with disposable cassettes.

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Design and synthesis of Ga-68–based ligand for ER+ tumor imaging. A. Datta, K. Chauhan, A.K. Mishra; Institute of Nuclear Medicine and Allied Sciences, DRDO, Delhi, India

Objectives: Breast cancer is the most commonly diagnosed malignancy and a foremost cause of mortality in women. Diagnosis predictions reveal that approximately 75% of tumors express estrogen receptors (ER). These receptors are also upregulated in osteoporosis and ovarian cancer and thereby represent promising targets for molecular imaging and therapy. Whole-body PET imaging with 16α-fluoro-17β-estradiol (^{18}F-FES) has been widely utilized for the prediction of ER expression and the treatment response in breast cancer patients. Although the agent has shown splendid results in clinical imaging, the availability and accessibility of the source are still issues. Also, the poor water solubility makes it difficult to dispense the agent for clinical practice on a routine basis. Alternatively, Ga-68–based tracers may overcome these difficulties by simple and efficient chelating chemistry. It is known that ER, after binding with estrogens, undergo dimerization, which is an important phenomenon for their transcriptional activity. Thus, the bivalent ligand approach may serve as an alternative strategy for the targeted imaging and therapy of ER-based cancer or metastases. The approach requires the use of an appropriate bifunctional chelating system that allows biovector conjugation along with the ability for fast complexation with Ga-68 due to its short half-life (68 min). In this respect, diethylenetriaminepentaacetic acid was the choice for a chelator. Here we report the design and synthesis of an estradiol-based derivative, Est2DTPA, using a bivalent ligand approach for PET and therapeutic applications. It is hypothesized that the dimeric estradiol moeity may lead to an enhancement in biological activity. The widely used concept of click chemistry was applied during synthesis. The biological activity of the final molecule for use in therapy has also been evaluated in ER-positive human breast cancer cell line MCF-7. **Method:** Synthesis was facile and performed using a bivalent approach, in which two molecules of the biovector, 17α-ethinylestradiol, were conjugated to DTPA via amide linkage in three simple steps. The complex formation equilibria of the ligand with Ga(III)chloride were evaluated through potentiometric studies, and the optimum pH for complexation was evaluated. Est2DTPA was complexed with Ga(III)chloride at pH 3.5 in water and purified using a preconditioned C-18 cartridge. The serum stability of the complex was studied in human serum. In vitro cellular uptake studies were performed to test the uptake of the tracer in MCF-7 cells with time. Cytotoxicity studies in the normal HEK-293 cell line were carried out and compared with the standard anticancer agent tamoxifen. Further, apoptosis studies are in progress for the evaluation of its therapeutic efficiency. **Research:** Synthesis of the intermediates and the final compound was achieved at >95% purity. All compounds were well characterized by NMR, IR, and mass spectrometry. The optimum pH for metal complexation was 3.5, which is similar to those for the other reported Ga complexes. Serum stability indicated that the Ga complex remained stable for up to 6 h. Cellular uptake studies showed 7.6% uptake at 2 h, and blocking studies with β-estradiol revealed the decrease in cell uptake by ~40% displaying the ER-mediated binding mode. In the cytotoxicity studies, the developed ligand (IC_{50}, 74.1 μM) was found to be less toxic than the standard agent, tamoxifen (IC_{50}, 23.6 μM), suggesting that Est2DTPA is significantly safe for further in vitro and in vivo studies. This property is crucial for the application of any drug in medical imaging or therapy. Further, the bioactivity of the ligand has to be evaluated in cancer cell lines to test its therapeutic potential. **Conclusion:** Est2DTPA can be labeled with Ga-metal with high efficiency and stability. Preliminary studies suggest that the tracer can be utilized in PET imaging. Biological activity studies of Est2DTPA in a normal cell line suggest that the ligand is significantly safe. Studies of bioactivity against cancerous cell lines, scintigraphy studies, and studies of biodistribution characteristics in tumor-bearing mice are in progress.

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Side-by-side comparison of the performance of ^{68}Ga-DOTATATE PET/CT and ^{111}In-DTPA-octreotide SPECT in patients with somatostatin-expressing neuroendocrine tumors. E. Delpassand[1], S. Broline[1], R. Amerinia[1], S. Thamake[2], D. Ranganathan[3], N. Wagh[3], I. Tworowska[2]; [1]Excel Diagnostics & Nuclear Oncology Center, Houston, TX, [2]RadioMedix Inc., Houston, TX, [3]Radio-Isotope Therapy of America (RITA) Foundation, Houston, TX

Objectives: ^{111}In-DTPA-octreotide (OctreoScan) is currently the standard of care and the only FDA-approved diagnostic test for somatostatin receptor (SSR)–expressing neuroendocrine tumors (NETs). OctreoScan has a high affinity for SSR2 but has lower image resolution than PET, resulting in a high failure rate (20%–50%) of NET detection. In comparison, ^{68}Ga-DOTATATE has a higher affinity for SSR2, and PET/CT has 2- to 3-fold-higher spatial resolution than gamma-camera imaging. The purpose of this study was to compare the performance of ^{68}Ga-DOTATATE PET/CT (^{68}Ga PET/CT) with OctreoScan in NET patients. **Methods:** Seventy-nine patients underwent whole-body and OctreoScan SPECT and ^{68}Ga PET/CT. ^{68}Ga PET/CT was performed ≤42 days after OctreoScan (mean, 4.1 days). Areas of abnormal uptake were compared with the standard of truth (SOT), including histology, CT, MRI, bone scan, and NaF and FDG PET/CT, and follow-up to confirm the presence of lesions. OctreoScan was read by a nuclear medicine (NM) physician blinded to the ^{68}Ga PET/CT results, and the ^{68}Ga PET/CT scan was read by another NM, who was blinded to the OctreoScan results. A consensus read was then performed. Lesions quantified were in organs, lymph nodes, and bones. **Results:** Paired *t* test analysis was performed. ^{68}Ga PET/CT showed significantly higher detection rates than OctreoScan for organs (*P* value of < 0.0001); lymph nodes (*P* value of < 0.0001); bones (*P* value of < 0.0001); and combined organ, lymph node, and bone lesions (*P* value of < 0.0001). A McNemar test performed to compare diagnostic efficacy showed that ^{68}Ga PET/CT had significantly (*P* value = 0.023) higher performance in the detection of SSR-expressing NET than OctreoScan. **Conclusions:** ^{68}Ga PET/CT is more accurate for staging and superior to OctreoScan SPECT in the detection of overall numbers of lesions in the body as well as organs, lymph nodes, and bones. ^{68}Ga PET/CT also allows for the calculation of the SUV, involves less whole-body radiation, and is performed in less time than OctreoScan. **Acknowledgment:** This research was supported by the RITA Foundation, Houston, Texas.

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^{177}Lutetium-DOTA-octreotate therapy in progressive somatostatin receptor–expressing neuroendocrine neoplasms. E. Delpassand[1], H. Mohammadali[1], S. Thamake[2], S. Broline[1], D. Ranganathan[3], N. Wagh[3], I. Tworowska[2], A. Delpassand[2], J. Puentes[2]; [1]Excel Diagnostics & Nuclear Oncology Center, Houston, TX, [2]RadioMedix Inc., Houston, TX, [3]Radio-Isotope Therapy of America (RITA) Foundation, Houston, TX

Objective: The study aim was to evaluate PRRT with radiolabeled somatostatin analogs in patients with metastatic neuroendocrine tumors (NETs). **Methods:** One hundred patients (57 M, 45 F; age range, 11–87; median, 59.5) with G1, G2 disseminated, and progressive NETs after first-line therapies were enrolled in a nonrandomized, phase 2 clinical trial. Repeated cycles of 200 mCi (7.4% ± 10% GBq) were administered up to the cumulative dose of 800 mCi (29.6% ± 10% GBq). All patients were further categorized as receiving one cycle (n = 30), two cycles (n = 20), three cycles (n = 15), and four cycles (n = 35) of therapy. **Results:** Patients were evaluated by RECIST criteria 3 months after the last treatment. Among 58 evaluable patients, a radiological response (complete response + partial response + minimal response) was observed in 12 patients (20.6%). Stable disease (SD) was seen in 37 patients (63.7%), and progressive disease (PD) occurred in 9 patients (16.7%). The progression-free survival (PFS) and time to progression (TTP) were calculated in 27 evaluable patients who had at least 2 cycles of Lu-177 therapy and demonstrated progression. The mean TTP was 10.26 months (1.3–26.06). Data revealed that PFS (2.06–29.2 months; mean, 13.02) was longer in patients with less liver involvement, more therapy cycles, and negative FDG PET scan results. There was a significant improvement of overall quality of life in evaluable patients with a median survival of 26.6 months. Sixty-five patients (65%) had moderate to severe nausea/vomiting during amino acid infusion. Fourteen patients had grade 2 or 3 hematological toxicity. Grade 3 hepatic toxicity was

observed in 3 patients. Acute and grade 4 toxicities were not noted in any patients. **Conclusion:** Treatment with multiple cycles of ^{177}Lu-DOTATATE PRRT is safe and well tolerated. The treatment results in tumor remission or stabilization of the disease in the majority of patients with prior progressive disseminated NETs and improves the quality of life. Systemic toxicities are limited and reversible.

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Initial experience with lyophilized kits for production of [Ga-68] DOTATOC. D. Dick, C. North; University of Iowa, Iowa City, IA

Objectives: Imaging of neuroendocrine tumors (NET) with somatostatin receptor analogs is a burgeoning part of nuclear medicine. The University of Iowa has a multiple-year history of manufacturing Ga-68-DOTATOC using an automated synthesis module. Recently, inviCRO made lyophilized DOTATOC kits available. This work evaluates the potential of these DOTATOC kits for the production of [Ga-68]DOTATOC. **Methods:** Ga-68 was obtained from an Eckert & Ziegler (E&Z) generator. The generator eluate was added to the lyophilized DOTATOC vial, and labeling reactions occurred in a boiling water bath on a hot plate. After ten minutes, the vial was removed from the water bath and allowed to cool to room temperature. Once cooled, two different methods were employed for the preparation of the final product solution. Method 1 involves passing the reaction mixture through treated tC18 SepPak, eluting with 1 mL of a 47.5% ethanol solution, diluting with 8 mL of saline for injection (USP), and passing through a final sterilizing filter. Method 2 involves adding 0.5 mL of sodium acetate for injection (USP) and 3 mL of saline for injection (USP) to the reaction mixture and passing the entire solution through a final sterilizing filter. Quality control consisted of pH analysis, a filter integrity test, iTLC for radiochemical identity/purity, sterility, and gamma spectroscopy on decayed samples to check for Ge-68 breakthrough. **Research:** The entire volume of eluate from the E&Z generator could not be added to the lyophilized DOTATOC kit because there was not enough sodium acetate buffering capacity in the kit to keep the pH in a range amenable for labeling. Good labeling was observed when half (3 mL) of the generator eluate was used. Both employed methods provided [Ga-68]DOTATOC that passed QC criteria. **Conclusion:** We have been able to produce [Ga-68]DOTATOC with lyophilized kits that meet QC criteria for imaging. Producing [Ga-68] DOTATOC with these kits via compounding under the practice of pharmacy would lower the barrier for starting a NET imaging program, provided that regulatory issues are resolved.

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First clinical experience with Ga-68 compounds at the Western Cape Academic PET/CT Centre. A. Doruyter, A. Ellmann, S. Rubow; Stellenbosch University and Tygerberg Hospital, Tygerberg, South Africa

Objectives: The study aims were to present our initial clinical experience with Ga-68-DOTANOC PET/CT and to discuss differences in biodistribution compared with previous agents, including a potential pitfall in interpretation. **Methods:** In September 2013, the Western Cape Academic PET/CT Centre began using ^{68}Ga compounds. Referral, imaging, laboratory, and clinical data were collated for patients referred for Ga-68-DOTA PET/CT during the first year. The biodistribution of Ga-68-DOTANOC was compared with experience with the traditional somatostatin receptor imaging (SRI) agents In-111-DTPA-octreotide and Tc-99m-HYNIC-octreotide. Clinical follow-up allowed us to identify any interpretative pitfalls in initial reporting. **Results:** There was enthusiastic uptake of the new imaging modality by referring clinicians, including from the private sector (57% of referrals). Scans for 28 patients were reviewed. Several differences between the normal biodistribution of Ga-68-DOTANOC and that of traditional single-photon emission agents were identified. In 22 studies for which correlative information was available, there were 17 true-positives (77.5%), 1 true-negative (4.5%), 2 false-positives (9%), and 2 false-negatives (9%). Clinical follow-up and subsequent literature review identified an important pitfall in interpretation, namely, physiological uptake in that uncinate process of the pancreas that accounted for the two false-positive results. **Conclusion:** Ga-68-DOTANOC PET/CT offers several advantages over traditional SRI methods, including improved sensitivity and shorter total scan duration. Although both methods image predominantly SSTR-2, several notable differences exist in biodistribution. It is important that nuclear physicians be mindful of the differences in biodistribution, as well as potential pitfalls in the interpretation of these studies. Ga-68-DOTANOC PET offers significant benefit in terms of directing clinical intervention and subsequent follow-up.

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Radiopharmaceutical implications toward peptide radiolabeling considering longitudinal performance aspects of SnO2-based ^{68}Ge/^{68}Ga generators. T. Ebenhan[1,2], L. Sepini[3], D. Kotze[3], B.B. Mokaleng[1], I. Schoeman[4], M. Vorster[1], M.M. Sathekge[1], J.R. Zeevaart[4]; [1]University of Pretoria & Steve Biko Academic Hospital, Pretoria, South Africa, [2]Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu–Natal, Durban, South Africa, [3]Radiochemistry and Radioanalysis, The South African Nuclear Energy Corporation, North West Province, South Africa, [4]Preclinical Drug Development Platform, Department of Science and Technology, North West University, North West Province, South Africa

There is mounting interest in using radioisotopes such as gallium-68 (^{68}Ga) for peptide labeling; i.e., ^{68}Ga could be a vital alternative to ^{18}F, offering shorter imaging times, no special patient preparation, and on-demand and year-round tracer availability. The Food and Drug Administration recently assigned orphan-drug status to GMP kit–produced ^{68}Ga-1,4,7,10-tetraazacyclododecane-*N′*,*N″*,*N‴*,*N⁗*-tetraacetic acid-octreotate (^{68}Ga-DOTATATE) as a diagnostic agent for neuroendocrine tumors, exemplifying the trust in the manufacture of generator-based radiopharmaceuticals. The more cost-efficient, decentralized approach of diagnostic imaging, especially in areas without access to a nearby cyclotron, will have an enormous impact on personalized patient care. Because very few studies have considered the longitudinal verification of ^{68}Ga being eluted from SnO_2-based ^{68}Ge/^{68}Ga generators, we have used a retrospective analysis to supervise the impact of altering ^{68}Ga-eluate quality on the production of different peptide-based radiopharmaceuticals with prolonged generator operation. The primary aim is to determine the most economical approach to correlate cost-efficient production with potential influencing aspects in ^{68}Ga-eluate quality. As a secondary goal, we envisage implementing a fully applicable procedure for ^{68}Ga radiolabeling of various peptide derivatives in a South African hospital environment.

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Novel radiopharmaceutical and preclinical aspects of ^{68}Ga-UBI: a selective PET tracer for imaging of infection. T. Ebenhan[1,2], J.D. Venter[3], G.EM. Maguire[4], H.G. Kruger[2], T. Mkhize[5], J. Wagener[6], J.R. Zeevaart[7], M.M. Sathekge[1]; [1]University of Pretoria & Steve Biko Academic Hospital, Pretoria, South Africa, [2]Catalysis and Peptide Research Unit, School of Health Sciences, University of KwaZulu–Natal, Durban, South Africa, [3]Medical Research Council, Pretoria, South Africa, [4]Catalysis and Peptide Research Unit, School of Chemistry and Physics, University of KwaZulu–Natal, Durban, South Africa, [5]Center for Applied Radiation Science and Technology, North West Province, South Africa, [6]The South African Nuclear Energy Corporation, North West Province, South Africa, [7]Preclinical Drug Development Platform, Department of Science and Technology, North West University, North West Province, South Africa

Objectives: Noninvasive diagnosis of osteomyelitis, endocarditis, and diabetic foot; monitoring of prosthetic vascular graft infections; or simply verifying fever of unknown origin represents a clinical challenge. Initiatives have been made to develop novel positron emission tomography (PET) agents for visualization and therapy monitoring of bacterial infections. Fragments of cationic antimicrobial peptides (CAMP) sensitively target negatively charged structures of the bacterial cell envelope, causing membrane alterations. Initially, a preclinical pilot study presenting a NOTA (1,4,7-triazacyclononane-triacetic acid)-conjugated fragment of ubiquicidin (UBI) complexed with gallium-68 as an infection-selective imaging agent (^{68}Ga-UBI) in rabbits was conducted. To date, CAMP derivatives have been almost unexploited for noninvasive molecular localization of infectious microorganisms, including those causing tuberculosis; thus, ^{68}Ga-UBI PET is intended to approve tracer sensitivity toward infection caused by *Escherichia coli* (EC) or *Staphylococcus aureus* (SA) in rodents and to

detect muscular infection due to *Mycobacterium tuberculosis* H37Rv (MTB) in guinea pigs and rabbits as "proof of target." Additionally, a justification of the biological effects of radiation (dosimetry) and further radiopharmaceutical optimization for robust, highly specific gallium-68 radiolabeling of NOTA-UBI are envisaged. **Methods:** An iThemba-manufactured 1.85-GBq ^{68}Ge/^{68}Ga generator provided gallium-68 for NOTA-UBI radiolabeling. Labeling efficiencies (%LE) in correlation with specific activity and tracer stability were assessed. The in vivo studies included three or more animals. Tracer selectivity and sensitivity were studied using Wistar rats (WR) following subcutaneous inoculation of either virulent clinical strain: SA-xen36 or EC-V-2603. New Zealand White rabbits (NZW) and guinea pigs (GP) were injected intramuscularly with MTB and with SA-25923 in the scruff to establish an (internal control) infection site, as it was formerly targeted by ^{68}Ga-UBI PET/CT. Healthy rabbits were studied for dosimetric evaluation. microPET and PET/CT image acquisition were conducted within 60 min after tracer injection, and 3D image analysis, by drawing volumes of interest, calculated targeted activity concentration (SUV) and target-to-nontarget (T/R) ratios. The bacterial burden (SA-xen36) was monitored by bioluminescence; moreover, infectious loci were nonspecifically verified by ^{18}F-FDG or ^{68}Ga-citrate, bacterial culturing, and immunohistological assessment from the dissected infection sites. **Results:** ^{68}Ga-UBI microPET achieved infection localization by means of targeting both types of bacteria host independently (for EC-V2603: r^2, 0.782; T/R, 4.44–6.95; for SA-xen36: r^2, 0.661; T/R, 3.23–5.85); tracer uptake was comparable to ^{18}F-FDG accumulation. The interclavicular reference area revealed low nonspecific uptake for ^{18}F-FDG < ^{68}Ga-UBI. ^{68}Ga-UBI sensitivity was approved by the tracer concentration, calculated in the infection site, to correlate with the bacterial burden, measured by SA-xen36 bioluminescence in WR (r^2, 0.705). Tracer selectivity was assured as bacterial inflammation was visualized by ^{18}F-FDG but not detected with ^{68}Ga-UBI because the presence of EC was eradicated by the immunocompetent animals at 7–8 days postinoculation. MTB thigh infection was localized successfully using ^{68}Ga-UBI PET/CT (for GP: T/R, 3.88–5.75; for NZW: T/R, 2.54–3.85), and a strong inflammatory response due to MTB infection was approved by ^{68}Ga-citrate imaging in NZW. The acute scruff infection caused by SA was better detected using ^{68}Ga-UBI PET/CT. Bacterial cultures and histological staining successfully confirmed the presence of MTB and SA. Varying the peptide amount of NOTA-UBI achieved high ^{68}Ga-UBI activity yields at the end of synthesis (r^2, 0.879; n = 11), with specific activities between 1 GBq/nmol (%LE, 33.9 ± 10.8; 220–550 MBq) and 0.1 GBq/nmol (%LE, 56.5 ± 6.3; 420–950 MBq), warranting sterile in-house kit-based production and potential application to humans. Targeted organs for dosimetric calculation were spleen<liver<kidneys<bladder wall, as observed over 120 min. **Conclusion:** The investigations support the approach that ^{68}Ga-UBI PET allows for the generic detection of bacteria, including the targeting of MTB, which may have an immediate impact on the development of novel anti-TB drugs supported by noninvasive imaging technologies. Further investigations will aim to reveal the feasibility, potential, and limitations of studying tuberculosis and other infectious diseases in humans.

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^{44}Sc and ^{177}Lu labeling of DOTA-PSMA DKFZ-617 for dosimetry and therapy of prostate cancer. E. Eppard[1], A. de La Fuente[2], S. Kürpig[1], F. Roesch[2], M. Essler[1]; [1]University Hospital Bonn, Bonn, Germany, [2]Institute of Nuclear Chemistry, Johannes Gutenberg University, Mainz, Germany

Objectives: With radiolabeling of the prostate-specific membrane antigen (PSMA) inhibitor Glu-NH-CO-NH-Lys (Ahx) using DOTA as a chelator, a broad pool of radionuclides becomes available for labeling. These possible variations allow the visualization of biological behavior over different periods of time, depending on the half-life of the radionuclide used (^{68}Ga $t_{1/2}$, 68 min; ^{44}Sc $t_{1/2}$, 3.9 h). Additionally, the usage of different imaging modalities or endoradiotherapies can be applied, depending on the employed radionuclide. **Methods:** DKFZ-PSMA-617 was obtained from ABX (Radeberg, Germany). ^{44}Sc was obtained from a ^{44}Ti/^{44}Sc generator in Mainz, where ^{44}Ti decays with a half-life of 60 d to no-carrier-added (n.c.a.) ^{44}Sc. Radiolabeling with ^{44}Sc was performed in 3 mL 0.25 M ammonium acetate buffer with varying amounts of ligand at 95°C. ^{177}Lu was obtained from IDB Holland, and labeling was performed in a gentisinic acid–sodium ascorbate solution with varying amounts of ligand at 95°C. Quality control was performed using radioHPLC and radioTLC. **Results:** ^{44}Sc-DKFZ-PSMA-617 and ^{177}Lu-DKFZ-PSMA-617 were effectively labeled at 95°C. Subsequent cartridge-based solid-phase extraction (C-18) resulted in a radiochemical purity of the final tracers of ≥98%. Stability studies and small-animal imaging with ^{44}Sc-DKFZ-PSMA-617 were performed. Radiochemical purity could be analyzed effectively using radioHPLC and radioTLC. **Conclusions:** The radiolabeling of DKFZ-PSMA-617 with the new generator-derived PET radionuclide ^{44}Sc was investigated in detail. ^{44}Sc-DOTA-PSMA was investigated in vitro and in vivo. Small-animal PET studies were performed to investigate pharmacological in vivo characteristics adequate for long-term (up to one day) molecular imaging studies. Also, radiolabeling of ^{177}Lu-DKFZ-PSMA-617 was optimized with regard to therapeutic applications.

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Ethanol postprocessing of ^{68}Ga eluates for preparation of ^{68}Ga-radiopharmaceuticals. E. Eppard[1], M. Wuttke[2], P. Nicodemus[2], F. Roesch[2]; [1]Department of Nuclear Medicine, University Hospital Bonn, Bonn, Germany, [2]Institute of Nuclear Chemistry, Johannes Gutenberg University, Mainz, Germany

Objectives: Postprocessing using a CEX cartridge in HCl–acetone media represents an efficient strategy for concentration and purification of ^{68}Ga-eluates. It assures the removal of ^{68}Ge and high labeling yields of injectable ^{68}Ga-labeled radiopharmaceuticals for routine medical applications. In an effort to overcome the use of an HCl–acetone solution, we have investigated the feasibility of replacing acetone with ethanol in the generator postprocessing protocol to combine the very efficient strategy for concentration and purification based on CEX with the superior properties of ethanol. Labeling of DOTATOC and PSMA^{HBED} with this method was investigated with and without a module system. **Methods:** A ^{68}Ge/^{68}Ga Obninsk generator was used, with a ^{68}Ga yield of 100 MBq and 85-kBq breakthrough of ^{68}Ge. Preconcentration and purification of the initial generator eluate were performed using several CEX resins. The distribution of ^{68}Ga and metallic impurities on the CEX column was investigated. The purified fraction was used for labeling DOTATOC and PSMA^{HBED}. **Results:** Using the HCl–ethanol system, up to 90% of the initially eluted ^{68}Ga activity was obtained in a 1-mL fraction of 90% EtOH–0.9 N HCl as an HCl–EtOH fraction within 4 min. Initial impurities eluted with ^{68}Ga were reduced. Due to the fact that the HCl–EtOH system has a lower pH than its acetone equivalent, buffer solutions are necessary. Radiolabeling yields of >98% can be achieved. In this case, product purification becomes obsolete. Also, labeling can be performed on module systems. **Conclusion:** Appropriate processing of ^{68}Ga on the basis of CEX chromatography is effective in HCl–EtOH media. It successfully removes the breakthrough of ^{68}Ge and allows the concentration of ^{68}Ga-eluates with higher yields than the established postprocessing method. The whole process guarantees safe preparation of injectable ^{68}Ga-DOTATOC (or other ^{68}Ga-labeled radiopharmaceuticals) for routine applications and can be successfully used in clinical environments.

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Ga-68-DOTA peptide imaging with new PET/CT systems: a potential tool in reducing the radiation burden. A. Esmail, F. Marafi, S. Dannoon; Kuwait University and Kuwait Cancer Control Center, Safat, Kuwait

Objective: Ga-68-DOTA–conjugated peptides are emerging new radiopharmaceuticals used for somatostatin receptor imaging. New PET systems with time-of-flight (TOF) options and new crystals should allow a similar image quality with a lower injected dose to be obtained when compared with old systems. The radiation exposure is to be estimated using different doses less than what is published in the guidelines with the emphasis not to lose image quality. **Methods:** All cases that were imaged for somatostatin receptor avidity using Ga-68-DOTA–conjugated peptides are reviewed in our institution. The product is licensed to be used in Kuwait as long it is FDA or CE certified and compounding it follows GMP guidelines. All cases were imaged with new PET/CT machines from GE (Discovery 690 and Discovery 710). Patients were injected with variable activities of Ga-68-peptides, depending on the elution yield from the Ga-68 generator supplied by ITG (Germany). Published guidelines recommend a dose of 100 MBq as a minimum and many times the yield did not allow

this dose to be reached for the number of the patients that are referred for the exam on the date of the test. Images were obtained after an uptake period ranging from 45 min to 90 min (depending on the workflow at the department and camera availability). Cases that were imaged more than one time (follow-up images) were selected. Images are acquired after a low-dose CT transmission scan for attenuation correction. Images of PET are done depending on the patient body mass index and this is done as low as 2 min per bed for BMI less than 33 and adding half a minute for BMI from 33 to 40. BMI of >40 are imaged with 3 minute per bed. All patients were asked to empty their bladder before going under the scan. Images were interpreted independently by two experienced nuclear medicine physicians for quality of images. Images were classified into three categories: suboptimal quality, adequate, and good quality for interpretation. This is based on the normal physiological distribution and number of lesions identified. The patient-administered activity and the estimated radiation exposure (from radiopharmaceutical) were estimated and compared with the published data. The values were blinded from the two readers. The dose and radiation burden for different studies were correlated with the quality of images obtained. **Research:** The only available published guideline for imaging tumors with PET/CT using Ga-68-DOTA–conjugated peptides is the European Association of Nuclear Medicine and Molecular Imaging (EANMMI). The published guideline in July 2010 recommends an injected radioactive dose of Ga-68 peptides to be ranging from 100 MBq (2.7 mCi) to 200 MBq (4.5 mCi), depending on the characteristic of PET system used. A minimum dose of 100 MBq (2.7 mCi) is recommended. These guidelines were published when the TOF machines were not widely available in the market. The radiation exposure of such a tracer ranges from 3.1–4.8 mSv depending on the conjugate used (NOC-TOC-TATE, arranged in the ascending order of exposure) when the maximum activity is administered. Our series of cases were searched and 8 patients were identified that met our selection criteria (at least two time point study using new PET system installed in the department). Patients identified received at a dose range of 29.6 (0.8 mCi) to 96.2 MBq (2.6 mCi). Image quality was compared for different activity injected for the same patient and the radiation exposure was estimated to be ranging from 0.68 mSv to 2.23 mSv. These estimated doses are at least 28% less than published data using the suggested doses. **Conclusions:** New PET/CT machines with the TOF option and new detection crystals allow the radiation exposure from the Ga-68–conjugated peptide to reach lower values without a drastic impact on image quality. This fact will give these new pharmaceuticals further advantages to be utilized in the field of somatostatin receptor imaging in neuroendocrine tumors. Although the number of cases in our identified population is small, this gives a proof of concept to image with lower doses using new PET systems. Phantom studies using Ga-68 radiotracers might help to verify the system resolution and image quality using very low doses in new PET systems and comparing them with old systems (old crystals and no TOF) that are still functioning in many diagnostic departments around the world.

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^{68}Ga-DOTATATE lyophilized ready-to-use kit developed as a diagnostic agent in pNET. L. Fugazza[1], E. Castaldi[1], L. D'Angeli[2], V. Muzio[1]; [1]Advanced Accelerator Applications, Colleretto Giacosa, Italy, [2]University of Turin, Colleretto Giacosa, Italy

Objectives: ^{177}Lu-DOTA-0-Tyr3-octreotate (^{177}Lu-DOTATATE), a somatostatin analogue that binds somatostatin receptors (sstr) overexpressed in neuroendocrine tumors (NETs) with a high affinity for sstr2, is currently undergoing phase III clinical study (NETTER-1) for midgut NETs. Conversely, ^{68}Ga-DOTATATE has been increasingly used for PET imaging and early diagnosis of sstr-positive tumors. We developed a GMP-grade lyophilized ready-to-use kit as a diagnostic agent for ^{177}Lu-DOTATATE. The kit is reconstituted with the eluate of a commercial ^{68}Ga generator without any purification step and generates a PET product that meets the current European Monograph specifications. We assessed the imaging performance of the ^{68}Ga-DOTATATE kit for tumor detection in a model of pancreatic cancer. **Methods:** Athymic nude mice were subcutaneously xenografted with rat pancreatic tumor cells (AR42J). When the tumor mass reached 200–500 mm^3, mice were injected with ^{68}Ga-DOTATATE. A PET scan and a biodistribution analysis were performed 30 min after radiotracer injection with a dynamic acquisition of 50 min. Organ biodistribution was determined at 30 min, 1 h, 2 h, and 4 h after radiotracer injection in a γ counter. **Results:** The ^{68}Ga-DOTATATE lyophilized kit was able to clearly detect the tumor mass through the PET scan. High tumor uptake was confirmed by γ counting at all time points. Tumor-to-kidney ratios (1.5–1.9 for all time points) and tumor-to-blood ratios (6.6, 19.1, 64.7, and 81.9 at 30 min, 1 h, 2 h, and 4 h, respectively) demonstrated the good diagnostic performance of the kit. **Conclusions:** The ^{68}Ga-DOTATATE kit is a useful, ready-to-use diagnostic agent in pNET with high diagnostic performance. The kit reconstitution procedure does not require any purification steps and allows for the standardized preparation of an injectable solution meeting pharmaceutical quality criteria.

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Preclinical evaluation of a novel integrin-targeting non-RGD small molecular radioligand, ^{67}Ga-/^{90}Y-FF58, for tumor imaging and radionuclide therapy. H. Fukunaga[1], A. Nagano[2], S. Oshikiri[2], M. Kajita[2], H. Kambara[2], K. Komatsu[1], S. Shinichiro[1], A. Hino[2], H. Kasahara[2]; [1]FUJIFILM Corporation, Kanagawa, Japan, [2]FUJIFILM RI Pharma Co., Ltd., Chiba, Japan

Objectives: The integrin $\alpha_V\beta_{3/5}$ transmembrane receptors overexpressed on numerous cancer types are potential tumor imaging and therapeutic targets. We have synthesized a novel $\alpha_V\beta_{3/5}$-binding non-RGD small molecule, FF58, exhibiting high tumor uptake and favorable pharmacokinetics for both tumor imaging and radionuclide therapy. Here we report on the radiosynthesis, biodistribution, and therapeutic efficacy of ^{67}Ga- and ^{90}Y-labeled FF58 in animal models. **Methods:** The integrin $\alpha_V\beta_3$–binding affinity of unlabeled FF58 was measured using ELISA via competitive displacement of vitronectin. Human glioblastoma U87MG and T98G cell lines were used in mouse xenograft models. A radioligand was injected into the tail vein of tumor-bearing mice, and the biodistribution was estimated by gamma-camera imaging and dissected organ counts. The antitumor efficacy of ^{90}Y-FF58 was assessed by tumor size and body weight. **Results:** The IC_{50} value of unlabeled FF58 was <0.1 nM. Preparation of ^{67}Ga-FF58 and ^{90}Y-FF58 yielded a radiochemical purity of >90%. High and selective tumor accumulation of radioligands was observed in the U87MG model over a period of 72 h or more. Significant inhibition of tumor growth by ^{90}Y-FF58 was observed in both the U87MG and the T98G models after either single or repeated administrations. **Conclusions:** ^{67}Ga- or ^{90}Y-FF58 exhibited high tumor uptake and antitumor efficacy in animal models. ^{68}Ga- or ^{90}Y-FF58 may also be a promising theranostic candidate for future clinical studies.

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Characterization and radiolabeling of PAMAM dendrimers with gallium-68: a novel theranostic targeting approach. A. Ghai, B. Singh; Department of Nuclear Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Objectives: Radiolabeling of polyamidoamine **(**PAMAM) dendrimers as imaging probes is less common but is viewed as a very promising molecular imaging approach for the detection of tumor angiogenesis. The objective of the present study was to standardize and optimize strategies for radiolabeling of generation four (G-4) of PAMAM dendrimers with gallium-68 (^{68}Ga) as potential positron emission tomography (PET) probes for imaging of tumor angiogenesis. **Methods:** G4 PAMAM dendrimers were conjugated with a bifunctional chelator, i.e., an *N*-hydroxysuccinimide-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) analogue. Purification of the desired formulations was done using a Sephadex G-25 column. A matrix-assisted laser desorption ionization (MALDI) technique was used to characterize and determine the molecular weight of the conjugates. Radiolabeling of the G4 PAMAM conjugate was done with ^{68}Ga. The radiolabeled ligand was further evaluated by in vitro and in vivo testing, and biodistribution studies were performed in BALB/c mice. **Results:** The radiolabeling efficiency of 95.0% was achieved at a conjugate concentration of 300.0 μg using sodium acetate buffer 4.0. The reaction time and temperature were standardized to 30 min and 90ºC, respectively. This radiolabeled formulation was found to have in vitro and serum stability for up to 4.0 h. Plasma protein binding was found to be 21.0% ± 3.4%. The animal biodistribution studies showed maximum uptake in the kidneys and bladder, and the data support the clearance of the radiolabeled conjugate through the renal route. **Conclusion:** PAMAM dendrimers could be conjugated

successfully with a bifunctional chelator (DOTA), and subsequent radiolabeling with ^{68}Ga could be achieved with reasonably high radiolabeling efficiency (>95.5%) and in vitro stability (up to 4 h). The potential of ^{68}Ga-radiolabeled dendrimers for the PET-based detection of tumor angiogenesis and drug loading and delivery to angiogenic sites shall be validated through further preclinical and clinical studies.

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The Indiana University experience in production of ^{68}Ga-DOTANOC under an expanded-access IND. M.A. Green, C.J. Mathias, J.W. Fletcher; Indiana University School of Medicine, Indianapolis, IN

Objective: The study aim was to provide the radiopharmaceutical ^{68}Ga-DOTANOC for use in the clinical PET/CT evaluation of patients with neuroendocrine tumors. **Methods:** Both the TiO_2-based Eckert & Ziegler (EZAG) ^{68}Ge/^{68}Ga generator and the SiO_2-based ITG generator have been employed to supply ^{68}Ga for the manual synthesis of ^{68}Ga-DOTANOC under Expanded Access IND #117255. Synthesis employed $^{68}Ga^{3+}$ in either 1.5 mL 0.1 M ultrapure HCl (fractionated elution with the EZAG generator) or 4.0 mL 0.05 M HCl (ITG generator without fractionation). In both cases, the eluate was buffered to ~pH 4.8 by the addition of ultrapure NaOAc and reacted with a commercial cGMP–DOTANOC conjugate (60 μg for the EZAG eluate; 30 μg for the ITG eluate). After heating for 10 minutes, the ^{68}Ga-DOTANOC product was isolated by C18 solid-phase extraction, washed, recovered in ethanol–saline, and then diluted with sterile saline to ≤5% ethanol prior to terminal sterilizing filtration. Quality control measures and release criteria followed the specifications of the published EANMMI Procedure Guidelines (*Eur J Nucl Med Mol Imaging.* 2010;37:2004–2010). **Results:** ^{68}Ga-DOTANOC was prepared for 73 clinical patient examinations (administered dose: 4.6 ± 0.6 mCi; 170 ± 22 MBq). ^{68}Ga-DOTANOC radiochemical purity averaged 98.6% ± 0.8% (ITLC-SG strips developed with 0.1 M HCl to quantify the levels of ionic ^{68}Ga and with 1:1 MeOH–1 M NH_4OH to quantify colloidal ^{68}Ga-hydroxide). Administered peptide doses averaged 43.3 ± 5.1 μg (n = 47) and 25.1 ± 5.5 μg (n = 26), respectively, using the EZAG and ITG generators. At dose expiration, ^{68}Ge breakthrough in the final product was at or near the background count rate, averaging 2.7 ± 3.5×10^{-7}% and 8.4 ± 7.6×10^{-6}% using the EZAG and ITG generators, respectively. **Conclusions:** ^{68}Ga-DOTANOC has been effectively produced using both the EZAG and the ITG generators, addressing a local clinical need for clinical assessment of the location and extent of disease in neuroendocrine cancer patients considering surgery.

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Zoledronic acid as a new theranostic tool? D. Haeusler, M. Tschokert, M. Zeilinger, M. Dumanic, S. Hayer, J. Kreiseder, J. Sommer, S. Kappel, W. Wadsak, M. Hacker, M. Mitterhauser; Medical University of Vienna, Vienna, Austria

Objectives: Zoledronic acid (ZOL) is known for its antitumor activities (*1*) and significant reduction of lung metastases in an orthotopic osteosarcoma (OS) model (*2*). Hence, we hypothesize that ZOL will add value as a theranostic tool because the gold standards for bone imaging lack sensitivity for the specific imaging of lung metastases. Because lung metastases decrease the 5-year survival rate of OS patients to 25%, a specific tracer for their visualization is crucial. **Methods:** ZOL was labelled with ^{99m}Tc and ^{153}Sm (*3*) (n = 6–10). Both tracers were examined for bone binding (*4*) (n = 6) and for plasma stability (human and mouse; n = 3). ^{99m}Tc-ZOL was applied to 10-μm cryotissues of lung metastases from OS patients (n = 2). Twenty MBq [^{99m}Tc]ZOL were administered to a wild-type mouse by retrobulbar injection; after 50 min of in vivo distribution, a 3D whole-body SPECT/CT scan (n = 1) was assessed. **Research:** Successful radiolabeling (98% ± 2% ^{99m}Tc-ZOL; 95% ± 2% ^{153}Sm-ZOL) allowed binding experiments with hydroxylapatite, amorphous calcium phosphate, human diaphysis, and human cancellous bone (40% ± 4%, 40% ± 1%, 18% ± 2%, and 28% ± 2% for ^{99m}Tc-ZOL, respectively; 95% ± 4%, 94% ± 9%, 78% ± 9%, and 85% ± 6% for ^{153}Sm-ZOL, respectively). Both tracers were stable for 4 hours in human and mouse plasma. ^{99m}Tc-ZOL was selectively displaced by unlabeled ZOL on tumor tissues (41.4% ± 7%; $P = 0.0016$; no uptake on control tissue). ^{99m}Tc-DPD was not displaced by unlabeled DPD (3.1% ± 4%). The first in vivo imaging of ^{99m}Tc-ZOL revealed excellent bone uptake. **Conclusion:** ^{99m}Tc-ZOL and ^{153}Sm-ZOL bound to bone specimens and were stable in plasma. ^{99m}Tc-ZOL uptake on lung metastasis tissues from OS patients was selective and displaceable; in contrast, ^{99m}Tc-DPD uptake was negligible. Hence, we hypothesize that the uptake of ^{99m}Tc-ZOL on lung metastases in vivo will be specific. These results suggest that ^{99m}Tc-ZOL and ^{153}Sm-ZOL could serve as promising new theranostic tools for OS. **References:** 1. Gronich. *Nat Rev Clin Oncol.* 2013. 2. Koto. *Cancer Lett.* 2009. 3. Haeusler. *J Labelled Comp Radiopharm.* 2013. 4. Mitterhauser. *Bone.* 2004.

*Second-place oral winner.

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Gallium-68 nanocolloid PET/CT for identification of sentinel lymph nodes in prostate cancer: first-in-man findings. M.S. Hofman[1,2], J. Doughton[3], S. Williams[2,3], P. Eu[1], R.J. Hicks[1,2]; [1]Centre for Molecular Imaging, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia, [2]The University of Melbourne, Melbourne, Victoria, Australia, [3]Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia

Objectives: Imaging of lymphatic drainage with PET/CT enables high-resolution and dynamic three-dimensional scanning with anatomic correlation. The aim of this study was to validate a gallium-68 nanocolloid in patients with prostate cancer. Identifying lymphatic drainage pathways may contribute to rational treatment of pelvic lymph nodes in high-risk prostate cancer. **Methods:** This was a pilot study to assess the feasibility of using a gallium-68 nanocolloid for PET/CT lymphoscintigraphy. Men who required gold fiducial placement for radiation therapy to the prostate were prospectively recruited in this pilot study. Iron oxide nanoparticles with a diameter of 20 nanometers were labelled with gallium-68 and injected transperineally into the prostate using transrectal ultrasound and template guidance at the time of gold fiducial implantation. Early and delayed imaging of the pelvis and whole body was performed. **Research:** Four patients have been recruited and imaged to date. Following intraprostatic injection of gallium-68 nanocolloid, sentinel and secondary-tier nodes were identifiable. These mirrored expected drainage pathways, including the visualization of iliac, pararectal, and presacral nodes and secondary-tier common iliac and retroperitoneal nodes. In one patient, a periprostatic drainage pathway to pelvic bone was identified. **Conclusion:** A novel gallium-68 nanocolloid has been developed and used for in-human evaluation of lymph node drainage in patients with prostate carcinoma. PET/CT imaging to assess pathways of metastatic spread is achievable and may contribute new information regarding the behavior of prostate cancer.

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Evaluation of DOTATOC PET/MRI combined with gadoxetate-enhanced MRI for the evaluation of neuroendocrine tumors. T. Hope, E. Nakakura, C.M. Aparici, H. VanBrocklin, M. Hernandez Pampaloni, J. Yee, E. Bergsland; UCSF, San Francisco, CA

Objectives: Gallium-68-labeled DOTATOC is a PET tracer used for the evaluation of somatostatin receptor–positive tumors. It has been shown to be sensitive for the detection of neuroendocrine tumors such as carcinoid. Gadoxetate disodium is a hepatobiliary contrast agent used in MRI. Hepatobiliary-phase images have been shown to be sensitive for hepatic metastases, particularly those from neuroendocrine tumors. To evaluate the combination of DOTATOC PET and gadoxetate (hepatobiliary-phase [HBP]) MRI, we imaged patients with known hepatic metastases from neuroendocrine tumors using the combined modality PET/MRI. **Methods:** Informed consent was obtained from all subjects, and approval was obtained through the local Committee for Human Research. Nine patients were imaged with both PET/CT and PET/MRI (4 females, 5 males; average age, 61 years). Each patient was injected with 5.0 (range, 3.4–5.6) mCi (185 [124–207] MBq) of ^{68}Ga-DOTATOC. The PET/CT scan was acquired 61 (52–77) minutes after the injection of ^{68}Ga-DOTATOC. A portal venous–phase CT scan was acquired after the injection of 150 mL of Omnipaque 350 (GE Healthcare, Waukesha, WI), which was used for attenuation correction. The PET protocol consisted of ten 3-minute bed positions, extending from the vertex to the midthighs. PET/MRI began an average of 112 (100–125) minutes after radionuclide injection. Imaging was performed on a 3.0-T time-of-flight PET/MRI scanner (GE Healthcare, Waukesha, WI).

First, whole-body PET/MRI was acquired with the following sequences at each bed position: MRAC, axial LAVA-FLEX, and axial 2D SSFSE. Subsequent to the completion of the whole-body PET/MRI acquisition, dynamic contrast-enhanced liver imaging was acquired using axial precontrast, two arterial and a portal venous phase using a LAVA-FLEX acquisition before and after the injection of 10 mL of gadoxetate disodium (Bayer Healthcare, Wayne, NJ). A whole-body postgadolinium LAVA-FLEX acquisition was then acquired at all six bed positions using the same scan parameters as in the precontrast PET/MRI acquisition. Finally, combined dedicated liver PET/MRI was acquired at a single bed position with the following sequences: axial and coronal SSFSE, axial echoplanar DWI (respiratory gated using bellows, NEX for b = 50 of 4 and NEX for b = 600 of 16), axial and coronal HBP LAVA, and axial navigated HBP LAVA. **Results:** PET/MRI acquisition took an average of 52 minutes. One hundred one liver metastases and 74 nodal metastases were noted. Additionally, there were two pancreatic lesions, two prostate lesions, and one bone metastasis. Ninety-nine percent of the liver lesions were detected on hepatobiliary-phase imaging, 83% on DWI, 46% on contrast-enhanced CT, 77% on single-bed-position PET from PET/MRI, and 63% on PET from PET/CT. The 15-minute single-bed-position PET acquired during PET/MRI detected more liver lesions than PET/CT ($P = 0.04$). HBP MRI outperformed all other imaging techniques (P values all < 0.05). Outside of the liver, all lesions visualized on CT were characterized on whole-body MRI. Image quality between PET/MRI and PET/CT for the whole-body acquisition was equivalent. **Conclusion:** DOTATOC PET/MRI is at least equivalent to PET/CT, with improved detection of hepatic lesions on hepatobiliary-phase imaging.

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Rapid ^{68}Ga radiolabelling of proteins in mild conditions exploiting a novel *tris*(hydroxypyridinone) bifunctional chelator. C. Imberti, M.T. Ma, P.J. Blower; Division of Imaging Sciences and Biomedical Engineering, King's College London, London, United Kingdom

Background: Established ^{68}Ga bifunctional chelators, such as derivatives of DOTA and NOTA, are not ideal for protein radiolabelling as they require heating and a low pH for efficient labelling, which may result in protein denaturation. *tris*(hydroxypyridinone) (THP) chelators based on CP256 (Berry et al., *Chem Commun.* 2011;47:7068–7070), however, can bind Ga^{3+} rapidly under extremely mild conditions and retain it in serum and in vivo over several hours. **Objectives:** The study aims were the synthesis of a new bifunctional THP derivative with an isothiocyanate group for protein conjugation via lysine side chains and its evaluation for $^{68}Ga^{3+}$ labelling of proteins under mild conditions. **Methods:** The phenylisothiocyanate THP chelator L^1 was synthesized and conjugated to the antibody trastuzumab following typical isothiocyanate conjugation and purification procedures (Cooper et al., *Nat Protoc.* 2006;1:314–317). Radiolabelling of the L^1–trastuzumab immunoconjugate was performed using an eluate obtained from an Eckert & Ziegler ^{68}Ge/^{68}Ga generator and neutralized with ammonium acetate (0.7 M). **Results:** Radiolabelling of the immunoconjugate was achieved in less than 5 minutes under mild conditions (25°C; pH 6–7). High specific activities (>850 MBq mg^{-1} when labelling 22.1 μg of immunoconjugate) were reached, with an excellent radiochemical yield (≥94%) and without the need for further purification steps. **Conclusions:** THP chelators show outstanding promise as ^{68}Ga bifunctional chelators for rapid and simple radiolabelling of heat- and pH-sensitive proteins at high specific activities for PET imaging.

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Unusual gallium transchelation behavior of *tris*(hydroxypyridinone) chelators in plasma and in vivo. C. Imberti, S. Nawaz, M.S. Cooper, J.D. Young, M.T. Ma, D.J. Berry, B.M. Patterson, G.E.D. Mullen, J.R. Ballinger, P.J. Blower; Division of Imaging Sciences and Biomedical Engineering, King's College London, St. Thomas' Hospital, London, United Kingdom

Objectives: *tris*(hydroxypyridinone) (THP) ligands chelate Ga^{3+} rapidly under unusually mild conditions (low concentration, neutral pH, and room temperature). We aimed to evaluate the ability of THP CP256 to chelate $^{67/68}$Ga in the presence of serum and apotransferrin and in vivo, to extract it from its complexes with transferrin and antibody–THP conjugates, and to determine the in vivo biodistribution of ^{68}Ga-CP256. **Methods:** Acetate-buffered ^{68}Ga- or ^{67}Ga-citrate was incubated with serum or apotransferrin; CP256 (10–30 μM) was then added. Speciation before and after the addition of CP256 and the serum stability of ^{67}Ga-CP256 were determined by size-exclusion chromatography. Trastuzumab–maleimide–THP labelled with ^{68}Ga was incubated with CP256, analyzing as before. ^{68}Ga-CP256 was injected i.v. into mice under dynamic nano-PET/CT. Acetate-buffered ^{68}Ga, followed at 1 h by CP256 (10 μg), was injected i.v. into mice under dynamic nano-PET/CT. **Results:** CP256 was efficiently labelled with ^{68}Ga preincubated with serum or apotransferrin. ^{67}Ga-CP256 was stable in serum for >7 days. CP256 was able to transchelate ^{68}Ga from its complex with trastuzumab–maleimide–THP; EDTA was not. ^{68}Ga-CP256 was rapidly cleared renally (whole-body half-life, <3 min). Acetate-buffered ^{68}Ga in mice showed typical retention in the blood pool with slow clearance to bone but, upon injection of CP256, was rapidly cleared renally, similar to ^{68}Ga-CP256. **Conclusions:** CP256 can be ^{68}Ga labelled in serum and can extract gallium from its complexes with transferrin and THP bioconjugates. In vivo it rapidly forms a complex with ^{68}Ga that behaves as a dynamic renal function imaging agent. This unusual transchelation behavior has potential novel uses in controlling the biodistribution and excretion of ^{68}Ga in molecular imaging.

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Comparison of ^{68}Ga-DOTATATE PET/CT with other functional imaging studies in head and neck paragangliomas: preliminary results. I. Janssen, C. Millo, A. Ling, C. Chen, P. Herscovitch, K. Pacak; National Institutes of Health, Bethesda, MD

Objective: The study aim was to compare the performance of ^{68}Ga-DOTATATE PET/CT with ^{18}F-DOPA, ^{18}F-DA, and ^{18}F-FDG in patients with head and neck paraganglioma (PGL). **Methods:** Six patients with case logic–confirmed head and neck PGLs (3 with SDHB, 1 with SDHD, 1 with an HIF2A mutation, and 1 sporadic case) underwent ^{68}Ga-DOTATATE, ^{18}F-DOPA, ^{18}F-DA, and ^{18}F-FDG PET/CT within 6 weeks. All definite head and neck foci localized with functional imaging modalities were presumed to be true-positive PGLs. The identified foci of abnormal uptake were divided into jugulotympanic (JT), vagale (V), and carotid body (CB) lesions on the basis of their anatomic area of occurrence. **Results:** A total of 13 head and neck lesions were found on the basis of ^{68}Ga-DOTATATE PET/CT: 8 lesions in the JT region, 3 in the V region, and 2 in the CB region. A total of 11 lesions were identified with ^{18}F-DOPA, with 6 in the JT region, 3 in the V region, and 2 in the CB region. A total of 6 lesions were identified with ^{18}F-DA, with 5 in the JT region, 1 in the V region, and none in the CB region. A total of 6 lesions were identified with ^{18}F-FDG, with 3 in the JT region, 1 in the V region, and 2 in the CB region. **Conclusion:** ^{68}Ga-DOTATATE appeared to be the most efficacious imaging tracer in the detection of head and neck PGL in our small patient cohort, suggesting that this could become the first-line functional imaging agent for localization of these tumors. Our results provide validation for the use of ^{177}Lu-DOTATATE or treatment with so-called "cold" somatostatin analogs for this group of patients, given that all detectable lesions expressed somatostatin receptors.

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Gallium-68-DOTA-octreotate PET/CT and outcomes of peptide receptor radionuclide therapy for pediatric patients with refractory metastatic neuroblastoma. G. Kong[1], M.S. Hofman[1,2], W.K. Murray[3], S. Wilson[3], P. Wood[4–6], P. Downie[4,7], L. Super[4,7], A. Hogg[1], P. Eu[1], R.J. Hicks[1,2,5]; [1]Centre for Cancer Imaging, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia, [2]Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia, [3]Department of Pathology, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia, [4]Monash Health Children's Cancer Centre, Victoria, Australia, [5]Translational Research Laboratory, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia, [6]Department of Paediatrics, Monash University, Victoria, Australia, [7]Children's Cancer Centre, Royal Children's Hospital, Melbourne, Victoria, Australia

Objectives: Pediatric patients with refractory metastatic neuroblastoma have limited treatment options. Neuroblastomas often express somatostatin receptors (SSTR), allowing ^{68}Ga-DOTA-octreotate (GaTATE) PET/CT

imaging and peptide receptor radionuclide therapy (PRRT) as a potential therapeutic option. We reviewed our experience with GaTATE PET/CT in assessing suitability for PRRT, correlated with patient tumor SSTR subtype 2 (SSTR 2) expression, and reported early outcomes of PRRT. **Methods:** GaTATE studies (eight patients; 2–9 years old) were reviewed with blinded scoring of disease sites and semiquantitative uptake analysis and compared with diagnostic ^{123}I- or posttreatment ^{131}I-MIBG studies to assess SSTR expression at known disease sites. Immunohistochemistry (IHC) for SSTR 2 was performed for five patient tumor samples. Four patients received PRRT. **Results:** GaTATE PET demonstrated high tumor-to-background ratios, with a median SUVmax of 6.7 (3.9–15.3); identified additional disease in 38% of patients (3/8); and upstaged 1 patient by detection of bone marrow involvement. Significant SSTR 2 expression was detected on IHC for all patients assessed. Six patients (75%) were deemed suitable for PRRT on imaging. Four patients received 17 PRRT cycles with palliative intent (10 ^{111}In-DOTATATE; 5 ^{177}Lu-DOTATATE; 1 combined ^{111}In-DOTATATE and ^{177}Lu-DOTATATE; 1 combined ^{177}Lu-DOTATATE and ^{90}Y-DOTATATE), with no significant toxicity attributed to PRRT. All had objective responses, but two are deceased due to progressive disease. The two survivors are 40 and 56 months from the commencement of PRRT. **Conclusion:** GaTATE PET was positive in a high proportion of patients with residual neuroblastoma, correlating with SSTR 2 detection on IHC, and showed a sufficient degree of SSTR expression for consideration of PRRT. It also identified additional disease sites when compared with MIBG imaging. PRRT appears to be safe and feasible, with responses observed in patients who had progressed on multimodality therapy. Future studies should consider incorporating this approach into therapy clinical trials.

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Progression-free survival and overall survival time in patients with GBM after ^{213}Bi-DOTA-substance P therapy. L. Krolicki[1], A. Morgenstern[2], J. Kunikowska[1], H. Koziara[3], B. Królicki[3], M. Jakuciński[4], C. Apostolidis[2], F. Bruchertseifer[2]; [1]Department of Nuclear Medicine, Medical University of Warsaw, Warsaw, Poland, [2]Institute for Transuranium Elements, European Commission Joint Research Centre, Karlsruhe, Germany, [3]Institute of Psychiatry and Neurology, Department of Neurosurgery, University of Warsaw, Warsaw, Poland, [4]Department of Nuclear Medicine, Brodnowski Hospital, Warsaw, Poland

Glioblastoma multiforme (GBM) has been demonstrated to have an NK-1 receptor system, and substance P can be used as a ligand for targeted therapy. Alpha emitters like ^{213}Bi offer the new potential for selective irradiation of tumors, with minimal damage to adjacent tissue. **Material and Methods:** Forty-two patients with glia tumors of grade III or IV after standard therapy were included in the study over two years. Following intracavitary or intratumoral insertion of 1-2 catheter systems, patients were treated with 1–8 doses of 2 GBq ^{213}Bi-DOTA-substance P (^{213}Bi-SP) at intervals of 2 months. ^{68}Ga-DOTA-substance P (^{68}Ga-SP) was coinjected with the therapeutic doses to assess biodistribution using PET/CT. The therapeutic response was monitored with MRI. The study was approved by the Ethical Committee of the Medical University of Warsaw. **Results:** Treatment with activity up to 13 GBq ^{213}Bi-SP was tolerated well, with only mild transient adverse reactions. Out of 42 evaluable patients, 13 of them are alive 3–26 months after the start of ^{213}Bi-SP therapy; 23 patients died due to progressive disease (n = 21) or non–treatment-related causes (n = 2). Follow-up of 6 patients was not available. The PFS (n = 28) from the start of radioisotope treatment was 3.7 months. The OS from the first diagnosis and the OS from the start of ^{213}Bi-SP therapy were 31.9 months and 8.5 months, respectively. Follow-up of therapeutic responses and toxicity has continued, and patient recruitment is ongoing. **Conclusions:** Treatment of recurrent GBM with ^{213}Bi-SP is safe and well tolerated. Targeted alpha therapy with ^{213}Bi-SP may evolve as a promising novel option for the treatment of recurrent GBM.

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Single-center experience over more than a decade analyzing 1,000 neuroendocrine neoplasm patients treated with single- or duo-radionuclide peptide receptor radionuclide therapy. H. Kulkarni, R.P. Baum, D. Kaemmerer, A. Petrovitch, M. Hommann, D. Hoersch; Zentralklinik Bad Berka, Bad Berka, Germany

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Objectives: The study aim was to assess the efficacy of PRRT using a single-radionuclide (SN-PRRT) approach or a combination of both (DUO-PRRT) Lu-177 and Y-90 in the same setting (tandem) or in sequence in 1,000 patients with NENs. **Methods:** We analyzed our database (containing 284 items per patient) for 1,000 patients (age, 4–85 years) with metastatic, progressive NENs and undergoing 1–9 cycles of PRRT at our center using Lu-177 (n = 331), Y-90 (n = 170), or both (n = 499). The median administered radioactivity was 17.5 GBq. Most patients (95.6%) underwent at least one previous other therapy (surgery in 86.8%, medical therapy in 55%, ablative therapy in 14.2%, and radiotherapy in 3.4%). **Results:** The median overall survival (OS) for all patients from the start of PRRT was 52 months (mo). The median OS varied according to the radionuclide used: for SN-PRRT, it was 24 mo with Y-90 (including patients with very high tumor load and short survival) and 55 mo with Lu-177, whereas for DUO-PRRT, it was 64 mo. According to the tumor grade, the median OS was 87 mo for G1, 55 mo for G2, and 28 mo for G3. Depending on the primary tumor origin, it was 45 mo for the pancreas, 77 mo for the small intestine, 55 mo for an unknown primary tumor, and 36 mo for lung carcinoids. The median progression-free survival (PFS) from the last therapy cycle was 22 mo, similar to those for pancreatic (23 mo) and small intestinal (25 mo) NENs. **Conclusions:** DUO-PRRT, combining Lu-177 and Y-90 in sequence or concurrently, seems to be more effective than single-radionuclide PRRT. Regardless of previous therapy, PRRT leads to a significant survival benefit in metastasized, progressive G1 or G2 NENs when compared with other treatment modalities.

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Theranostics of prostate cancer using Lu-177-labeled DOTAGA–based PSMA small molecules. H. Kulkarni[1], M. Weineisen[2], C. Schuchardt[1], M. Schottelius[2], H.-J. Wester[2], R. Baum[1]; [1]Zentralklinik Bad Berka, Bad Berka, Germany, [2]Technical University of Munich, Munich, Germany

Objectives: The study objective was to assess the safety and efficacy of peptide radioligand therapy (PRLT) with Lu-177-labeled DOTAGA-based PSMA small molecules (Lu-177 PSMA) in patients with metastasized castrate-resistant prostate cancer (mCRPC). **Methods:** PRLT with Lu-177 PSMA was performed in 30 mCRPC patients. Ga-68–PSMA-HBED-CC PET/CT was used for patient selection and follow-up. Multiple cycles (mean, 2.2; range, 2–4) were administered in 14 patients. The mean administered activity of Lu-177 PSMA per cycle was 5.6 ± 0.7 GBq (median, 5.8). The posttherapy response could not be assessed until now in 14 patients. Patient-specific dosimetry was carried out according to the MIRD scheme. **Results:** The metastases exhibited intense PSMA expression, demonstrated by baseline Ga-68–PSMA-HBED-CC PET/CT and high Lu-177 PSMA uptake on posttherapy planar and SPECT/CT images. A molecular response and a morphological response were observed in 8 patients and 4 patients, respectively. Stable disease was noted in 4 and 8 patients, according to molecular and morphological response criteria, respectively, whereas disease progressed in 2 patients. Organ and tumor doses were as follows: whole body, 0.02 ± 0.01 mGy/MBq; kidneys, 0.35 ± 0.14 mGy/MBq; and tumor lesions, 0.14–19.8 mGy/MBq. There was rapid clearance from blood, with a half-life of up to 42 hours. The treatment was well tolerated by all patients, without any significant adverse effects or alterations in any of the laboratory parameters or renal function (as determined by Tc-99m MAG3/TER). **Conclusion:** Due to high tumor uptake and fast renal washout and blood clearance, Lu-177 PSMA is safe and effective in castrate-resistant metastatic prostate cancer when used in combination with appropriate selection and follow-up of patients by Ga-68–PSMA-HBED-CC PET/CT.

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Role of Ga-68–PSMA PET/CT in recurring and metastatic prostate cancer. H. Kulkarni[1], H.-J. Wester[2], R.P. Baum[1]; [1]Zentralklinik Bad Berka, Bad Berka, Germany, [2]Technical University of Munich, Munich, Germany

Aim: The study aim was to investigate the role of Ga-68–PSMA-HBED-CC PET/CT in prostate cancer (PC) patients presenting with rising prostate-specific antigen (PSA). **Methods:** Ga-68–PSMA-HBED-CC PET/CT was performed in 84 PC patients (mean age, 61 ± 8 years; range, 48–86 years) with rising PSA; 81 presented with evidence of biochemical relapse (mean PSA, 10.1 ng/mL; range, 0.2–245) after prostatectomy and/or radiotherapy,

and 3 patients underwent primary staging. Contrast-enhanced PET/CT was performed 60 minutes after i.v. administration of 168 ± 15 MBq Ga-68–PSMA-HBED-CC. PET/CT was assessed visually and semiquantitatively (SUVmax) by a nuclear medicine physician and a radiologist with 10 years' experience, respectively. **Results:** Pathological findings were observed in 71 out of 84 patients (detection rate of 84.5%). Local residual/recurrent disease was demonstrated in 16 patients, pelvic lymph node metastases were demonstrated in 2 patients, and 3 patients exhibited initial bone marrow metastases (negative on CT). Multiple PSMA-positive metastases were observed in 23 patients; 12 with high uptake underwent radioligand therapy with a Lu-177-labeled PSMA ligand. **Conclusions:** Ga-68–PSMA-HBED-CC is a sensitive and specific PET tracer for the detection of prostate cancer recurrences and metastases. A high target-to-background ratio allows early and accurate detection of small lesions and bone marrow metastases (negative on conventional imaging). Ga-68–PSMA-HBED-CC PET/CT may be useful for the effective stratification of patients undergoing radioligand therapy with Lu-177-labeled PSMA ligands (theranostics).

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Evaluation of a peptide labeled with Ga-68 using two chelating agents. P. Kumar[1], S. Tripathi[1], C. Cheng[2], E. Wickstrom[2,3], M. Thakur[1,3]; [1]Department of Radiology, Thomas Jefferson University, Philadelphia, PA, [2]Biochemistry and Molecular Biology, Thomas Jefferson University, Philadelphia, PA, [3]Kimmel Cancer Center, Philadelphia, PA

Objective: Our laboratory has successfully designed, synthesized, and characterized a peptide that targets with high affinity (K_d, 3.1×10^{-9} M) VPAC1 receptor expressed on breast and prostate cancers. Using this peptide (TP-3805) labeled with Cu-64, we have imaged with high sensitivity and specificity breast and prostate cancers in humans. The long-term goal of this investigation is to label this peptide with gallium-68 and evaluate it in vitro and in tumor-bearing animals. To label this peptide with Ga-68, we have chosen two commonly used chelating agents DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and NODAGA (1,4,7-triazacyclononane-1-glutamic acid-4,7-diacetic acid). Here, we report preparation of the chelated peptide, radiolabeling with Ga-68, their stability and cell binding efficacy. **Methods:** The DOTA- and NODAGA-peptide conjugates were synthesized on solid phase and characterized by mass spectrometry. Ga-68-Cl_3 was eluted with 0.1 M HCl from a Ge-68/Ga-68 generator (Eckert & Ziegler, Germany). For radiolabeling the conjugated peptide with Ga-68, 300 µl of eluted Ga-68-Cl_3 (29.5 ± 4.2 MBq) and 20 µg of conjugated peptide (5.0 µg/µL in deionized water) were used. The labeling was performed using Na-acetate solution with different molarity (0.1, 1.0, and 1.9 M) and volume (100–400 µL) incubated at predetermined temperature (25, 50, 70, and 90ºC) for 30 min. The effects of pH (by changing the volume and molarity of Na acetate) and temperature were monitored, on the radiolabeling efficiency of both peptides. Labeling efficiency was determined by radio–high-performance liquid chromatography (HPLC) with a reverse-phase column (Zorbax, Agilent Inc.) eluted with a linear gradient starting 10% at 0 min reaching to 90% acetonitrile in aqueous 0.1% trifluoroacetic acid at 23 min. The in vitro stability (in normal saline) was examined by incubating the equal volume of radiolabeled peptide solution and normal (0.9%) saline for 2 h. The effect of metal ion impurity (Fe^{3+}) was studied by incubating an equal volume of 100 nM $FeCl_3$ solution with radiolabeled peptide solution at 37ºC for 2 h. Cell binding (in vitro) assay was performed in breast cancer cells T-47D, expressing VPAC-1 receptors. **Results:** As determined by mass spectrometry, the molecular weight of NODAGA-peptide was 3,718 (calculated M.W., 3,716) and DOTA-peptide was 3,787 (calculated M.W., 3,785). The purity of the peptides was 99.0%. Radio-HPLC retention time for both radio-complexes was 9.7 min and 3.5 min for free Ga-68. At pH 4–6, optimal radiolabeling (>95.0%) of the DOTA-conjugated peptide required higher (70°C–90ºC) temperature (n = 12) while the NODAGA-conjugated peptide needed incubation only at room temperature (n = 12). At pH 1–3, to obtain optimal radiolabeling of both conjugated peptides, temperatures of 90°C were required (n = 12). Both radiocomplexes showed high stability in normal saline and only 2% degradation was observed at 2 h. When the preparations were challenged with 100 nM $FeCl_3$ solution, 5% of degradation was observed at 2 h incubation at 37ºC. Cell binding (in vitro) assay showed higher uptake for Ga-68-NODAGA-peptide, 34.0% ± 0.8% as compared with 24.5% ± 0.9% for Ga-68-DOTA-peptide at 15 min. The uptake was nearly the same, 48.9% ± 3.9% for Ga-68-NODAGA-peptide and 45.2% ± 2.1% for Ga-68-DOTA-peptide, at 2 h of incubation at 37ºC. **Conclusions:** NODAGA-peptide showed more convenient radiolabeling features than that for DOTA-peptide. The radiolabeling of NODAGA-peptide can be accomplished conveniently at room temperature at pH 4.0. Ga-68-NODAGA-peptide also showed higher cell binding than the DOTA-peptide at 15 min. Further work is in progress. **Acknowledgments:** This work was supported by NIH, CA 3 RO1, and 157372 (MLT).

*Second-place poster winner.

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Long-term side effects in patients with disseminated neuroendocrine tumors who underwent tandem peptide receptor radionuclide therapy (PRRT) with ^{90}Y/^{177}Lu-DOTATATE. J. Kunikowska[1], R. Matyskiel[1], D. Pawlak[2], L. Królicki[1]; [1]Department of Nuclear Medicine, Medical University of Warsaw, Warsaw, Poland, [2]National Centre for Nuclear Research–Radioisotope Centre, POLATOM, Otwock-Swierk, Poland

PRRT with ^{90}Y and ^{177}Lu is a form of molecular targeted therapy for inoperable or disseminated neuroendocrine tumors (NEN). On the basis of the literature, ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE therapy is well tolerated, with moderate renal and haematological toxicity. The aim of the study was to observe long-term side effects with tandem PRRT. **Materials and Methods:** Well-differentiated progressive metastatic NEN in 52 patients were treated with 3–5 cycles of ^{90}Y/^{177}Lu-DOTATATE (3.7 GBq/m^2 body surface area; 1:1). Blood tests for hematology, kidney and liver function, and chromogranin A (CgA) were evaluated before therapy. All patients underwent CT scans and somatostatin receptor imaging (SRS; ^{99m}Tc-Tektrotyd or ^{68}Ga-DOTATATE). Mixed amino acid infusion over 8 hours was used for kidney protection. **Results:** Long-term follow-up was at a mean of 43 months (9–96 months). The progression-free survival (PFS) was 30.4 months. The median overall survival (OS) time was not reached. None of the patients had hand–foot syndrome. No renal toxicity grade 3 and 4 was observed. The baseline mean creatinine level was 0.92 ± 0.33 mg/dL, and the mean GFR was 84.7 ± 26.3 mL/min. In the follow-up, the mean GFR level at 12 months was 83.9 ± 25.2; at 24 months, 77.2 ± 31.1; at 36 months, 67.5 ± 9.7; at 48 months, 72.6 ± 11.2; at 60 months, 68.2 ± 15.1; and at 72 months, 62.4 ± 10.5. The mean GFR decline was 3.0 mL/min/year. Transient hematological toxicity (leucopenia and thrombocytopenia) was seen in 7 patients (13.5%). One patient (1.9%) developed myelodysplastic syndrome after receiving 29.6 GBq (standard treatment and 2 additional courses because of progression). No other long-term hematological toxicity of grades 3 and 4 was seen. **Conclusions:** Tandem radioisotope (^{90}Y/^{177}Lu DOTATATE) therapy for patients with disseminated or inoperable neuroendocrine tumors is effective and safe, considering the long-term side effects.

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Biodistribution and radiation dosimetry for the novel chemokine receptor CXCR4–targeting probe [^{68}Ga]pentixafor. C. Lapa[1], K. Herrmann[1,2], H.-J. Wester[3,4], M. Schottelius[3], J. Czernin[2], U. Eberlein[1], C. Bluemel[1], U. Keller[5], S. Knop[6], S. Kropf[4], A. Schirbel[1], A.K. Buck[3], M. Lassmann[1]; [1]Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany, [2]Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, UCLA, Los Angeles, CA, [3]Department of Pharmaceutical Radiochemistry, TUM, Munich, Germany, [4]Scintomics GmbH, Fürstenfeldbruck, Germany, [5]Medical Department of Hematology and Medical Oncology, TUM, Munich, Germany, [6]Division of Hematology and Medical Oncology, Department of Internal Medicine II, Würzburg University Medical Center, Würzburg, Germany

Aim: [^{68}Ga]pentixafor is a promising novel PET tracer for imaging the expression of the human CXCR4 receptor in vivo. Whole-organ distribution and radiation dosimetry of [^{68}Ga]pentixafor were evaluated. **Methods:** Five multiple-myeloma patients were injected intravenously with 90–158 MBq [^{68}Ga]pentixafor (mean, 134 ± 25 MBq) and dynamic PET/CT images were acquired immediately. Three dynamic whole-body sweeps were followed by four static scans at 30 min, 1 h, 2 h, and 4 h after administration of the radiopharmaceutical. Venous blood samples were obtained. Organ residence times were determined by integrating the corresponding volume-of interest time-dependent uptake using a dedicated computer code (NUKFIT). Organ

absorbed doses and the effective dose were calculated using OLINDA/EXM. **Results:** The effective whole-body dose based on 150 MBq [^{68}Ga]pentixafor was 2.3 mSv. The highest organ doses (for 150 MBq injected) were found in the urinary bladder wall (12.2 mGy), spleen (8.1 mGy), kidneys (5.3 mGy), and heart wall (4.0 mGy). Corresponding absorbed organ doses were as follows: liver, 2.7 mGy; red marrow, 2.1 mGy; testes, 1.7 mGy; and ovaries, 1.9 mGy. The corresponding effective dose was 2.3 mSv. **Conclusion:** [^{68}Ga]pentixafor exhibits a favorable dosimetry and delivers a radiation dose to organs that is even lower than that of [^{18}F]FDG or ^{68}Ga-labeled somatostatin receptor ligands.

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Adaptation of SPECT/PET procedure for fast and effective visualization of infection and inflammation with $^{67/68}$Ga-citrate. A.A. Larenkov, M.V. Zhukova, A.S. Lunev, A.B. Bruskin, O.E. Klementieva, G.E. Kodina; Burnasyan Federal Medical Biophysical Center, Moscow, Russia

Objectives: ^{67}Ga-citrate was used for scintigraphic imaging of infectious and inflammatory focal sites since 1971. The mechanism of Ga-citrate accumulation in inflamed tissues still is not entirely clear. It is believed that after intravenous injection, Ga-citrate enters in transchelation reaction, and it binds to the blood plasma transferrin. ^{67}Ga-citrate has a good sensitivity to the centers of inflammatory processes and infectious and inflammatory diseases, but it has some limitations for clinical practice due to the relatively long time required to obtain a clear images. Studies of various scientific and medical centers around the world were aimed at assessing the suitability of diagnostic ^{68}Ga-citrate for PET imaging of infectious and aseptic inflammation focal sites. At the same time, nuclear-physical properties of ^{68}Ga do not allow (in spite of a number of publications) to implement high-quality visualization of inflammation focal sites: in the first hours after the administration the most of activity is detected in the blood. Thereby, only blood vessels are clearly visible in the tomograms. **Methods:** We have developed a procedure that allows a quick and high-quality visualization of infection and inflammation focal sites using ^{68}Ga-citrate to be carried out. The blood transferrin blockade was performed with ferric compounds (complexes of Fe(III)) just before (15 min) or simultaneously with the administration of ^{68}Ga-citrate. **Results:** Experimental data show that this procedure allows visualization of the lesions of inflammatory processes at one hour after administration. **Conclusion:** Hereby the blocking agent can be introduced initially into the freeze-dried composition for ^{68}Ga-citrate synthesis to obtain a quick and high-quality visualization of infection and inflammation focal sites using ^{68}Ga-citrate (and ^{67}Ga-citrate). During the study, the technology for producing the lyophilized composition for the synthesis of the ^{68}Ga-citrate radiopharmaceutical (Tsigalin) with blocking agent was designed and validated. The stages of preclinical studies were performed comprehensively. Start of the clinical trials is expected. **Acknowledgment:** This work was financially supported by the Ministry of Education and Science of the Russian Federation (State Contract 14. N08.12.0018).

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Preliminary results of ^{177}Lu-DOTATATE radionuclide therapy in patients with medullary thyroid cancer. F.P.P. Lobo Lopes[1,2], F. Vaisman[1,2], L. de Souza Machado Neto[1], P.H.R. de Castro[1,2], D.A. Bulzico[1], B. Vilhena[1], M. Carneiro[1], R. Corbo[1,2]; [1]INCA–National Cancer Institute, Rio de Janeiro, Brazil, [2]Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Background: Medullary thyroid cancer (MTC) is a rare but potentially life-threatening disease with limited therapeutic options. As a neuroendocrine tumor, MTC expresses somatostatin receptors, and therefore, somatostatin-labeled radiopharmaceuticals could be used to treat patients with MTC. **Objective:** The aims of this study were to evaluate tumor shrinkage after ^{177}Lu-DOTATATE treatment, to analyze the impact on quality of life as accessed by the SF-36 questionnaire, and to demonstrate a possible prognostic role for ^{111}In-DTPA-octreotide uptake in patients with MTC. **Patients and Methods:** Patients with progressive MTC underwent evaluation using ^{111}In-DTPA-octreotide. Patients who demonstrated ^{111}In-DTPA-octreotide uptake were treated with 4 cycles of 7,400 MBq (200 mCi) of ^{177}Lu-DOTATATE and were evaluated using CT scans over 8–12 months after the treatment. **Results:** Of the 16 patients initially enrolled, 9 (56.25%) had lesions that were observed in the ^{111}In-DTPA-octreotide scans and were eligible for therapy with ^{177}Lu-DOTATATE. Three patients had a partial response, 3 patients were classified as having stable disease, and 1 patient had progressive disease. All responders indicated improvement in quality of life 6–12 months after therapy. No limiting or grade 3 and 4 side effects were observed during or 8–12 months after the treatment. **Conclusions:** Treatment with ^{177}Lu-DOTATATE seems to be an alternative therapy for somatostatin receptor–positive tumors, with very mild adverse effects and quality-of-life improvement, at least during a short-term period. Further studies are needed to determine long-term benefits and to identify which patients are more likely to respond to this modality of therapy.

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New bifunctional *tris*(hydroxypyridinone) chelators for rapid labelling with gallium-68: conjugates with SSTR2- and αvβ3-targeting peptides. M.T. Ma[1], C. Cullinane[2], P. Roselt[2], C. Imberti[1], R.J. Hicks[2], P.J. Blower[1]; [1]Division of Imaging Sciences and Biomedical Engineering, King's College London, St. Thomas' Hospital, London, United Kingdom, [2]Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia

Background: We have shown that *tris*(hydroxypyridinone) ligands rapidly complex $^{68}Ga^{3+}$ quantitatively at room temperature, at very low concentration, over a wide pH range (*Chem Commun*. 2011;47:7068). **Objectives:** To synthesize and evaluate labelling and biodistribution of conjugates of new isothiocyanate-functionalized *tris*(hydroxypyridinone) chelators with tumor-targeting peptides. **Methods:** Two *tris*(hydroxypyridinones), each with a pendant isothiocyanate group, were synthesized and conjugated to amine groups of Tyr^3-octreotate for SSTR2 targeting (**1**) and monovalent and trivalent cyclic-(RGDfK) derivatives (e.g., **2**) for αvβ3 targeting. An eluate from an iThemba Labs 1.8-GBq ^{68}Ge/^{68}Ga generator was processed on a cation-exchange cartridge, eluted in 90% ethanol–0.9 N HCl (*J Nucl Med.* 2014;55:1023), and added to each bioconjugate before neutralizing with ammonium acetate. Biodistribution was assessed in balb/c nude mice bearing U87MG (αvβ3) or AR42J (SSTR2) tumors, by PET at 1 and 2 h postinjection, after which animals were killed and tissues/organs harvested and counted. Coinjection of unconjugated peptide (400 μg per animal) with each radiotracer, followed by scanning and biodistribution 1 h postinjection assessed specificity of the radiotracers. **Results:** All conjugates were labelled with $^{68}Ga^{3+}$ in ≥95% radiochemical yield and high specific activity (60 MBq nmol^{-1}) at 25°C and formulated to pH 6–7 in <5 min. Biodistribution showed tumor-specific uptake and retention of target receptor affinity. Excretion was rapid and predominantly renal. Coinjection of unconjugated peptide substantially reduced tumor uptake in all cases. **Conclusions:** The new bifunctional *tris*(hydroxypyridinone) chelators enable easy preparation of bioconjugates, and rapid radiolabelling with $^{68}Ga^{3+}$ under mild conditions without subsequent purification. The simplicity and efficiency of labelling at very low concentrations under mild conditions brings the possibility of kit-based ^{68}Ga tracer production without complex automated synthesis typical of multistep PET radiochemistry.

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Biological behavior of ^{68}Ga-DOTA-minigastrin (CP04): preliminary results. M. Maurin, P. Garnuszek, U. Karczmarczyk, R. Mikołajczak; National Centre for Nuclear Research–Radioisotope Centre, POLATOM, Otwock-Swierk, Poland

Objectives: The CP04 minigastrin analogue [DOTA-$(DGlu)_6$-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH_2] is a CCK2R-targeting vector (*1*). We selected this molecule to investigate the influence of radiometal (^{68}Ga, ^{90}Y, or ^{177}Lu) on its physicochemical and biological properties. Earlier, we synthesized cold CP04 complexes with these metals in order to determine the spatial structure of the conjugates. Herein the preliminary biological assessment of ^{68}Ga-CP04 is presented. **Methods:** To 20 μL of CP04 (1 mg/mL) and 70 μL of 2.5 M CH_3COONa, 200 μL of ^{68}Ga eluate (200 MBq) from the ^{68}Ge/^{68}Ga generator (iThemba) was added, followed by 12 min incubation at 90ºC. It was then diluted with 710 μL of ascorbic acid (50 mg/mL; pH 4.5). Radiochemical purity was checked by radio-HPLC method (Kinetex 150/4.6 mm; 25% AcN/0.1% TFA; 1 mL/min). Immunodeficient Rj:NMRI-Foxn1^{nu}/Foxn1^{nu} (male; 18–25 g) mice were subcutaneously inoculated in the flanks with suspensions of freshly harvested A431-CCK2R(+) cells and

A431-CCK2R(−) cells (2 mln in 0.3 mL) in the presence of MatrixGel. The tumors were allowed to grow for 2–3 weeks. Biodistribution was checked at 1 h after i.v. injection of ^{68}Ga-CP04 (100 µL; 12 MBq; 0.75 µg of peptide) in the tail (n = 5) with the focus on uptake in A431-CCK2R(+) and A431-CCK2R(−) tumors, as well as in kidneys and stomach. **Results and Conclusions:** Radiochemical purity of ^{68}Ga-CP04 was greater than 90%. HPLC revealed peaks that could be attributed to the form with oxidized methionine (ca. 6%) and to free ^{68}Ga (at the level of 2%). In vivo very fast clearance with urine (ca. 90 %ID after 1 h) was observed. The highest uptake was in kidneys (3.5 %ID/g). In CCK2R-positive tumor the uptake (1.7 %ID/g) was over 3 times higher than in the negative one (0.5 %ID/g) ($P < 0.05$). Further comparative evaluation is in progress. **Acknowledgment:** This project was financed by funds from the National Science Centre (Poland), allocated on the basis of decision number DEC-2011/03/B/ST5/02734. **Reference:** 1. Laverman P, Joosten L, Eek A, et al. *Eur J Nucl Med Mol Imaging.* 2011;38:1410–1416.

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Radiolabelling of CDP1-NODAGA with ^{68}Ga(III)chloride as a potential imaging agent for host-dependent and -independent inflammation. A. Mdlophane[1], T. Ebenhan[2,3], B.B. Mokaleng[2], M.M. Sathekge[2], J.R. Zeevaart[4]; [1]The South African Nuclear Energy Corporation, North West Province, South Africa, [2]University of Pretoria & Steve Biko Academic Hospital, Pretoria, South Africa, [3]School of Health Sciences, University of KwaZulu–Natal, Durban, South Africa, [4]Department of Science and Technology, North West University, North West Province, South Africa

Objectives: The identification of inflammation and infection at early stage of the disease is critical for a favorable outcome. Hence, there is need for reliable and reproducible noninvasive, more accurate diagnostic procedures. A cathelicidin peptide (CDP1) functionalized with NODAGA was selected to evaluate its potential to image host-dependent and -independent inflammation. We set out to develop a labelling protocol for ^{68}Ga-CDP1-NODAGA and to optimize its labelling efficiency. **Methods:** ^{68}Gallium(III) chloride (^{68}Ga) was eluted by eluate fractionation from an SnO_2 matrix–based ^{68}Ge/^{68}Ga generator (1.85 GBq; iThemba LABS, South Africa) using 10 mL of 0.6 N HCl. A 2-mL eluate fraction was adjusted to pH 3.5 using 2.5 M sodium acetate buffer. Lyophilized CDP1-NODAGA powder was divided in ready-to-use aliquots of 0.15–0.25 mg which were freshly reconstituted in deionized water yielding 1 µg/µl stock solutions. Volumes of 150 µl buffered ^{68}Ga (50–55 MBq; % ^{68}Ga-to-buffer ratio, 23/87) were complexed with 0.5–12 nmol CDP1-NODAGA, incubated (5–15 min at ambient temperatures and additional 5–15 min at 95°C), and subsequently purified from unbound ^{68}Ga using a Sep-Pak light C18-cartridge unit, desorbing the product with rising percentages of ethanolic saline solutions (5%–90%). The radioactive yield was calculated from the decay-corrected product activity in relation to the sum of significant activities contained in all other fractions (residual reaction mixture and other cartridge purging liquids) or materials (plastic ware, residual in the C18 unit). The percentage of product radiolabeling (%PR) and the presence of colloidal ^{68}Ga complexes were determined using instant thin-layer chromatography silica gel paper with 0.1 M citrate or 1 M ammonium acetate–methanol, 1:1 (v/v), as mobile phases, respectively. The purified radiolabelled product was kept for 120 min at 37°C to justify its integrity, preliminarily. **Results:** A high %PR (72–91) was recorded at room temperature for CDP1-NODAGA, which became versatile at concentrations of <1–3 nmol; further incubation at 95°C.

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A DOTA-based bisphosphonate with an albumin-binding moiety for delayed body clearance in bone-targeting radiotherapy. M. Meckel, N. Pfannkuchen, M. Miederer, F. Rösch; Johannes Gutenberg University, Mainz, Germany

Objectives: Radiolabeled bisphosphonates (BP) are commonly used in diagnosis and therapy of bone metastases. In many cases blood clearance is fast and only 30%–50% of the injected activity is retained in the skeleton. A longer blood circulation may enhance accumulation of the compounds in the bone metastases. Therefore, a modified macrocyclic BP derivative with an additional binding entity to human serum albumin (HSA) was synthesized and evaluated in vitro and in vivo. **Methods:** The theranostic bisphosphonate BPAMD was compared with the novel albumin-binding BP DOTAGA(428-D-Lys)M^{BP} (ABBP). Both tracers were labeled with ^{68}Ga and evaluated in binding studies to artificial bone material as well as to HSA. The compounds were further compared in in vivo microPET and ex vivo organ distribution studies in healthy Wistar rats over a time period of 3 h p.i. **Research:** Binding studies revealed a consistent affinity to apatite of both the albumin-binding BP (81.3% ± 2.2%) and the original compound (81.6% ± 0.5%). [^{68}Ga]ABBP showed a distinguished binding of 88.1% ± 5.9% to HSA compared with 28.8% ± 1.1% for [^{68}Ga]BPAMD. In vivo microPET and ex vivo organ distribution studies resulted in significant longer blood concentration levels (SUV_{blood}, 2.59 ± 0.72 and 0.06 ± 0.01, respectively). Skeletal accumulation of the modified compound increased strongly over time, while the accumulation of the non-modified BPAMD stayed constant. Ratios of the femur epiphyseal plate to the diaphysis showed to be more favorable for [^{68}Ga]ABBP with a ratio of 2.9 compared with 1.9 for [^{68}Ga]BPAMD. **Conclusion:** The modification of BPAMD toward an albumin-binding BP results in a novel compound that conserves the activity of both functional groups within one molecule. Thus, blood retention is significantly longer for the albumin-binding DOTA-BP. The better bioavailability results in better ratios between high and low metabolic bone sections. Further studies with the therapeutic nuclide ^{177}Lu have to determine the therapeutic potential of these novel tracers.

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A DOTA-zoledronate conjugate for PET diagnosis and endoradiotherapy of bone metastases. M. Meckel, N. Pfannkuchen, M. Miederer, F. Roesch; Johannes Gutenberg University, Mainz, Germany

Objectives: Bisphosphonates (BP) are commonly used in the treatment of bone disorder diseases, whereby zoledronic acid is the most potent bisphosphonate drug. Conjugates of BP with macrocyclic chelators open new possibilities in bone-targeted radionuclide imaging and therapy. Endoradiotheraphy with ^{177}Lu- or ^{225}Ac-labeled macrocyclic BP could have great potential subsequent to PET examinations using ^{68}Ga-labeled analogs in the treatment of painful skeletal metastases. **Methods:** Two new DOTA-BP, DOTAM^{PAM} and DOTAM^{ZOL}, were successfully synthesized, based on the established pharmaceuticals pamidronate and zoledronate, respectively. The ligands were labeled with ^{68}Ga, purified, and compared in in vitro and in vivo studies against [^{18}F]NaF and a known simple DOTA-BP conjugate (BPAPD) in healthy Wistar rats. Furthermore DOTAM^{ZOL} was labeled with ^{177}Lu and evaluated in vivo. **Research:** The new ligands reached an RCY of 80%–90% in 15 min with ^{68}Ga. After resin purification the purity of all studied bisphosphonates was higher than 98%. The tracers showed low uptake in soft tissue, a fast renal clearance, and a high accumulation in bone, 1 h p.i. The best compound was [^{68}Ga]DOTAM^{ZOL} (SUV_{Femur}, 5.4 ± 0.6) followed by [^{18}F]NaF (SUV_{Femur}, 4.8 ± 0.2), [^{68}Ga]DOTAM^{PAM} (SUV_{Femur}, 4.5 ± 0.2), and [^{68}Ga]BPAPD (SUV_{Femur}, 3.2 ± 0.3). Best blood-to-bone ratios were obtained for [^{18}F]NaF (97.4) and [^{68}Ga]DOTAM^{ZOL} (11.5). [^{177}Lu]DOTAM^{ZOL} was received with an RCY of 98%–99%. It provided a blood to bone ratio of 45.7. After 60 min p.i. the estimated activity in the skeleton was 42.7 %ID for [^{68}Ga]DOTAM^{ZOL} and 47.7 %ID for [^{177}Lu]DOTAM^{ZOL}. **Conclusion:** The ^{68}Ga-labeled DOTA-bisphosphonate compounds showed a promising uptake profile and similar distribution kinetics. Bone accumulation was highest for [^{68}Ga]DOTAM^{ZOL}. [^{177}Lu]DOTAM^{ZOL} also revealed bone uptake, which makes DOTAM^{ZOL} a promising bone-targeting tracer for the combination of diagnosis and therapy.

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Preclinical characterization of a novel ^{68}Ga-labeled DOTA-depsipeptide–based imaging agent for noninvasive detection of infection and inflammation. B.B. Mokaleng[1], T. Ebenhan[1,2], J.D. Venter[3], S. Ramesh[2], H.G. Kruger[2], B. Marjanovic-Painter[4], J.R. Zeevaart[5], M.M. Sathekge[1]; [1]University of Pretoria & Steve Biko Academic Hospital, Pretoria, South Africa, [2] Catalysis and Peptide Research Unit, University of KwaZulu–Natal, Durban, South Africa, [3]Tuberculosis Intervention Unit, Medical Research Council, Pretoria, South Africa, [4]The South African Nuclear Energy Corporation, North West Province, South Africa, [5]Preclinical Drug Development Platform, Department of Science and Technology, North West University, North West Province, South Africa

Objectives: Bacterial infection can be controlled by early diagnosis and monitoring of the disease using scintigraphic imaging. The need for infection-selective tracer to overcome the diagnostic limitations with unspecific radiopharmaceuticals continues to be explored with antimicrobial peptides (AMPs). This study explores depsipeptides, a class of natural antimicrobial cyclic peptides, which include one or more ester bonds as part of their amide backbone showing a wide spectrum of biological activity and are therefore relevant for drug discovery. The main goal was to evaluate the biodistribution and selectivity of a radiolabeled ^{68}Ga-DOTA-depsipeptide derivative (GG-ITLVPLP) using PET/CT imaging of healthy rabbits and animals bearing sterile inflammation (turpentine oil induced) and acute staphylococcal and mycobacterial thigh (TB-) infection. **Methods:** DOTA-GG-ITLVPLP was radiolabeled with gallium-68 obtained from SnO_2-based ^{68}Ge/^{68}Ga generators. ^{68}Ga-DOTA-GG-ITLVPLP was formulated in saline for injection. Ex vivo studies were done using a BALB/c mice model injecting *S. aureus* (1×10^8 colony-forming units) and sterile inflammation of the same animals; dissection was performed 2 days (n = 5) and 6 days (n = 6) later, respectively. All animals were sacrificed 60 minute postinjection with ^{68}Ga-DOTA-GG-ITLVPLP (24.5 ± 7.73 MBq). For PET/CT imaging New Zealand rabbits were allocated into 3 groups: (1) two healthy, (2) three rabbits bearing 1×10^8 *S. aureus* (right thigh muscles) and sterile inflammation (contralateral thigh muscles), (3) three rabbits with a muscular inoculum of *Mycobacterium tuberculosis* (thigh muscle) and *S. aureus* (scruff region). Image acquisition was conducted 3 days postinoculation; animals underwent ketamine–medetomidine anesthesia before injection of ^{68}Ga-DOTA-GG-ITLVPLP (116 ± 14 MBq). Infection and inflammatory tissues were tested with histopathological (hematoxylin–eosin and Ziehl–Neelsen) staining, postmortem to confirm bacterial presence. **Results:** There was a reproducible labeling efficiency of 67% ± 3.7% (n = 26). The in vivo study on healthy animals showed high activity in the kidneys and bladder indicating rapid renal excretion and minimum activity in the heart, liver, triceps, and quadriceps. Ex vivo, the major activity was recovered within 60 minutes in urine (58% ± 16.8%; range, 31%–89%); further activity was found in the body carcass and a minimum in kidneys, bladder, liver, and heart. The total tissue %ID/g from infected mice sacrificed at 60 minutes postinjection amounted to 0.21 ± 0.05 (day 2) and 0.24 ± 0.11 (day 6) for *S. aureus* ($P = 0.55$) and 0.16 ± 0.04 (day 2) and 0.21 ± 0.13 (day 6) for sterile inflammation ($P = 0.39$). PET/CT images showed similar target-to-nontarget ratios of ^{68}Ga-DOTA-GG-ITLVPLP (infected quadriceps/noninfected triceps) at 5 and 60 min postinjection in healthy reference muscle tissue (1.2 ± 0.11 and 1.2± 0.24); in comparison, *S. aureus*–infected muscles showed insignificant uptake, whereas ratios concerning inflammation were 2.6 ± 0.3 ($P < 0.05$) and 2.8 ± 2.3. The corresponding values in mycobacterial infected muscles amounted to 2.6 ± 0.4 and 2.8± 0.2 ($P < 0.01$). **Conclusion:** The results demonstrate that both sterile inflammation and mycobacterial infection can be targeted by ^{68}Ga-DOTA-GG-ITLVPLP. PET/CT imaging with ^{68}Ga-DOTA-GG-ITLVPLP could be explored further for localization of infection and inflammation.

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^{68}Ga-DOTATATE uptake in patients with neuroendocrine tumors. F. Moradi[1], A. Barkhodari[1], M. Jamali[1], R. Minamimoto[1], B. Schneider[2], F.T. Chin[2], E.S. Mittra[1], A. Iagaru[1]; [1]Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Stanford University, Stanford, CA, [2]Molecular Imaging Program at Stanford, Department of Radiology, Stanford University, Stanford, CA

Objective: The high sensitivity of ^{68}Ga-DOTATATE PET/CT results in identification of somatostatin receptor expression in a variety of lesions and normal structures in patients with known neuroendocrine tumors (NET). We evaluated the range of standardized uptake values (SUV) in normal tissues as well as benign, indeterminate, and malignant lesions in this patient population as a potential aid for image interpretation. **Materials and Methods:** 57 patients (mean age ± SD, 56.5 ± 12.7; 24 males) with confirmed diagnosis of NET underwent ^{68}Ga-DOTATATE PET/CT. SUV_{mean} and SUV_{max} was measured in 37 normal anatomical structures for each patient. Abnormal uptake was divided into benign, indeterminate, and malignant categories based on imaging characteristic, clinical follow-up, and pathology. **Results:** Intense physiologic uptake (SUV_{max}, >7) was observed in spleen, renal parenchyma, adrenal glands, pituitary gland, and stomach (decreasing order). Moderate uptake (3–7) was present in the prostate, jejunum, pancreas, ileum, and colon. Mild uptake (1–3) was present in the uterus, rectum, skeleton, gonads, and nasopharynx. Salivary glands and thyroid uptake was highly variable (0–11.4). Physiologic uptake correlated poorly with blood-pool or bladder activity. Ranges of uptake in benign, indeterminate, and malignant lesions were determined. Physiologic uptake (pancreas, duodenum, splenule, and prostate) mimicked pathology in 4 patients. **Conclusion:** ^{68}Ga-DOTATATE uptake in normal and abnormal structures is highly variable in patients with NET. Anatomic and clinical correlation may be necessary to characterize foci of intermediate uptake.

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Development of a ^{68}Ga-ranatensin analog for bombesin receptors in PET molecular imaging. C. Morgat[1–3], R. Varshney[4], J. Schulz[2,3], C. Savona-Baron[2,3], D. Vimont[2,3], C. Riès[2,3], S.S. Bertrand[2,3], M. Allard[1–3,5], A.K. Mishra[4], P. Fernandez[1–3], E. Hindié[1–3]; [1]Service de Médecine Nucléaire, CHU de Bordeaux, Bordeaux, France, [2]Université de Bordeaux–INCIA, Talence, France, [3]CNRS–INCIA, Talence, France, [4]Division of Cyclotron and Radiopharmaceutical Sciences, Institute of Nuclear Medicine and Allied Sciences, New Delhi, India, [5]EPHE, Bordeaux, France

Objectives: Overexpression of Gastrin-Releasing Peptide Receptor (GRPR) has been demonstrated in several human cancers such as prostate cancer and breast cancer. For breast cancer targeting little information is available as to GRPR expression in various breast cancer cell lines. Then, a new DOTA-substituted ranatensin analog, DOTA-RV_15, was developed for GRPR imaging. **Methods:** GRPR has been investigated using Western Blot and immunofluorescence in various breast cancer cell lines (MCF-7, MDA-453, MDA-468, SKBR3, T47D, and ZR75.1) and in the PC3 prostate cancer cell line. DOTA-RV_15 was synthesized, labeled with $^{nat/68}$Ga, and investigated in vitro (calculation of LogP value using HPLC-UV, pharmacological characterization using calcium imaging, and plasmatic stability assessed by radioHPLC). **Results:** PC3 cells exhibited the highest immunopositivity for GRPR. Among breast cancer cell lines, MCF-7 and ZR75.1 (ER-positives) expressed the highest amount of GRPR. After synthesis and HPLC purification DOTA-RV_15 was coordinated to ^{nat}Ga to obtain cold reference and then radiolabeled with ^{68}Ga with good specific radioactivities (2–4 GBq/μmol) and radiochemical purities (>99%). The log *P* value was −3.04 ± 0.33. ^{nat}Ga-DOTA-RV_15 clearly abolished bombesin-induced calcium release in PC3 cells. Finally, >90% of intact ^{68}Ga-DOTA-RV_15 was found after 45 minutes. **Conclusion:** These results suggest a relevant role of GRPR in ER-positive breast cancer cells. The peptide was successfully radiolabeled with ^{68}Ga. Data reveal the hydrophilic nature of our compound, meaning that it should show preferential renal excretion and low hepatobiliary excretion. Calcium imaging demonstrates that ^{nat}Ga-DOTA-RV_15 is a GRPR antagonist. The superiority of GRPR-based antagonists for molecular imaging has been previously reported in prostate cancer, and one can expect that similar superiority will be found with ranatensin analogs. ^{68}Ga-DOTA-RV_15 might therefore be considered as a promising candidate for PET imaging of ER-positive breast cancers. IC_{50} experiments and microPET imaging are currently ongoing.

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Investigation of the radiochemical stability of ^{68}Ga- and ^{177}Lu-labeled high-affinity DOTATATE (DOTA-3-iodo-Tyr3-octreotate). D. Mueller, C. Breunig, M. Baehre, A. Odparlik; University Hospital Halle, Saxony–Anhalt, Germany

Objectives: Radiolabeled HA-DOTATATE (DOTA-3-iodo-Tyr3-octreotate) is increasingly used for diagnosis and treatment of neuroendocrine tumors (NET). HA-DOTATATE is not governed by patent restrictions, is commercially available and therefore is an attractive alternative to other somatostatin ligands. The objective of our study was to investigate the radiochemical stability of ^{68}Ga- and ^{177}Lu-labeled HA-DOTATATE in clinical practice. **Methods:** HA-DOTATATE was labeled with ^{68}Ga using the NaCl-based labeling procedure. ^{68}Ga-HA-DOTATATE was stabilized using ascorbic acid. The labeling of HA-DOTATATE with ^{177}Lu was carried out in sodium acetate buffer under presence of 2,5-diydroxybenzoic acid (gentisic acid) as a radical scavenger. The radiochemical purity was determined by radio-HPLC (RP-18; gradient: water–acetonitrile). The radiolabeled peptides were stored at room temperature. **Results:** The radiolysis of the ^{68}Ga-labeled peptide could not be observed, and ^{68}Ga-HA-DOTATATE was stable within four hours.

Because of the half-life of ^{68}Ga, the activity of the radiopharmaceutical after more than 4 h is usually lower than the minimum patient dose. The radiolysis of ^{177}Lu-HA-DOTATATE could be detected after 12 h and was significantly observed after 24 h. The concentration of the radiolabeled peptide was then lower than 95%. Within 48 h the concentration of radiolysis products increased to 35% of the total activity. **Conclusion:** Our results show that at room temperature ^{68}Ga-labeled HA-DOTATATE is stable for 4 h and ^{177}Lu-HA-DOTATATE can be used within 12 h after the labeling.

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Clinical efficacy of PET/CT with ^{68}Ga-DOTATOC for detecting suspected or unknown primary neuroendocrine tumors: the Japan experience. Y. Nakamoto, K. Sano, T. Ishimori, K. Togashi; Graduate School of Medicine, Kyoto University, Kyoto, Japan

Objectives: It has been reported that PET/CT using ^{68}Ga-DOTATOC has higher diagnostic performance for detecting neuroendocrine tumors (NETs). The purpose of this study was to investigate the clinical usefulness of DOTATOC PET/CT in detecting clinically-suspected NET lesions. **Methods:** A total of 43 patients were retrospectively analyzed. Thirteen patients underwent a DOTATOC PET/CT scan for detecting unknown primary tumors after histopathological confirmation of NET (group A), 7 patients for detecting suspected recurrence by a rising hormone level after surgery for NET (group B), and the remaining 23 patients for detecting unknown primary tumors due to high hormone levels (insulin [n = 5], gastrin [n = 9], adrenocorticotropic hormone [n = 6], 5-hydroxyindoleacetic acid [n = 2], and chromogranin A [n = 1]) (group C). The detection rate was evaluated according to their situation. **Results:** In group A, primary tumors were suspected by DOTATOC PET/CT in 7 of 13 patients (gastrointestinal NET in 6 patients and prostatic cancer in 1 patient), but prostatic cancer was not confirmed by histopathology, i.e., false-positive. In group B, DOTATOC PET/CT depicted suspected lesions in 6 of the 7 patients (nodal metastasis in 5 patients and liver metastasis in 1 patient). In group C, DOTATOC PET/CT did not reveal any abnormalities in this population. **Conclusion:** DOTATOC PET/CT was useful for detecting NETs, especially when recurrence was suspected due to high hormone levels after surgery for NET or primary tumors were suspected after histopathological confirmation of NET. On the other hand, no relevant information was obtained in patients who had no history of NET simply when hormone levels were high.

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Labelling and in vivo biodistribution of ^{68}Ga-labelled *tris*(hydroxypyridinone)–conjugated anti-PSMA single-chain antibody fragment in a mouse model of human prostate cancer. S. Nawaz[1], F. Kampmeier[1], G. Mullen[1], J.R. Ballinger[2], P.J. Blower[1]; [1]King's College London, London, United Kingdom, [2]Guy's Hospital–Guy's & St. Thomas' Trust Foundation, London, United Kingdom

Objectives: The monoclonal antibody J591 is specific for an extracellular epitope of PSMA, the most studied antigen for imaging prostate cancer. We aimed to evaluate ^{68}Ga labelling and in vivo biodistribution of a new scFv fragment derived from J591 incorporating a Cys conjugated to the new *tris*(hydroxypyridinone) (THP) maleimide chelator YM103. **Methods:** J591c(scFv) was expressed in HEK293T cells, purified by metal ion affinity chromatography and size exclusion chromatography (SEC) and conjugated with YM103. The conjugate was purified by SEC and characterized by mass spectroscopy. The eluate of a ^{68}Ga generator (IGG100; E&Z) was preconcentrated on a cation-exchange cartridge and incubated with 10 µg YM103-J591c(scFv) in NH_4OAc buffer (pH 7). Labelling was assessed by SEC and iTLCsa, stability in serum by SDS-PAGE and PSMA-affinity using Du145 and Du145-PSMA cell lines. The same cells were grown as xenografts in male SCID mice for imaging after IV injection of 7 MBq (10 µg) ^{68}Ga-YM103-J591c(scFv) using Nano PET/CT (Mediso). **Results:** At protein concentrations of >0.25 µg/mL, labelling efficiency exceeded 99% within 1 min at room temperature and pH 7. There was no loss of radiolabel in serum over 6 h. Binding studies in PSMA+ cells indicated a K_d of 32 nM. In mice the tracer showed rapid clearance from all organs except kidneys and bladder. Tumor uptake was 4.12 and 0.45 %ID/g in PSMA+ and PSMA– tumors, respectively (Student t test, $P < 0.01$). **Conclusion:** The THP bifunctional chelator allows rapid and efficient labeling of YM103-J591c(scFv) with ^{68}Ga. The labelled product is stable in serum, selectively binds to PSMA positive cells in vitro and in vivo, and warrants further evaluation for imaging PSMA expression in PCa.

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Labelling and preclinical evaluation of NOTA cyclo-RGD dimers labelled with Ga-68 for imaging of integrin receptors. D. Niculae, C. Tuta, F. Puicea, M. Mihon, R. Leonte, A. Silisteanu; Horia Hulubei National Institute for Physics and Nuclear Engineering, Bucharest, Romania, Politehnica University, Bucharest, Romania

Objectives: The $\alpha_v\beta_3$ integrin receptor, expressed on tumor cell membranes, can be preferentially targeted by peptides containing the RGD sequence. DOTA-E-[c(RGDfK)$_2$] and NOTA-SCN-Bn-E-[c(RGDyK)$_2$] were labelled with Ga-68 and tested for radiolabelling yield, purity, stability, in vitro binding, ex vivo biodistribution, and in vivo imaging. **Methods:** The radiolabelling was performed using an automated system with inline quality control. A Ga-68 eluate from a tin oxide–based Ge-68/Ga-68 generator, purified and concentrated to 600 MBq in 0.2 mL water on an anionic exchanger, was used to label DOTA/NOTA–derivatized RGD peptides. Elution, concentration, labeling, and purification procedures were performed in 25 min. The ex vivo biodistribution was tested in tumor-bearing animal models (Walker 256, Guerin, melanoma, and AR42J). The affinity of DOTA/NOTA cyclo-RGD dimers for tumor cell surface receptors (HT29, AR42J, and A431) was determined by real-time quantification. **Results:** Nanomoles of peptides were labeled with high yields. NOTA-SCN-Bn-E-[c(RGDyK)$_2$] was labelled at room temperature in less than 20 min, and no postlabelling purification was required. The biodistribution pattern of ^{68}Ga-NOTA-SCN-Bn-E-[c(RGDyK)$_2$] in Walker and melanoma models showed high tumor uptake. The blood clearance was fast, and the renal elimination was more rapid than in the case of ^{68}Ga-DOTA-E-[c(RGDfK)$_2$]. High tumor-to-background ratios were observed. Binding to receptors was achieved in the first 3 min of incubation. PET/CT scans highlighted tumor uptake at 30 min postinjection. **Conclusion:** Radiolabelling with Ga-68 of very promising candidates for imaging targets of interest in cancer diagnosis and therapy follow-up, such as $\alpha_v\beta_3$ receptors, was successfully adapted on the automated module, reducing the reaction time and operator exposure. The preclinical biological evaluation of ^{68}Ga-DOTA-E-[c(RGDfK)$_2$] and ^{68}Ga-NOTA-SCN-Bn-E-[c(RGDyK)$_2$] showed high and stable tumor uptake.

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Shortcut to high-affinity Ga-68 and Cu-64 radiopharmaceuticals: one-pot click chemistry trimerization on the TRAP platform. J. Notni[1], Z. Baranyai[2], D. Reich[1], A. Vagner[2], M. Weineisen[1], I. Toth[2], H.-J. Wester[1]; [1]Technische Universität München, Garching, Germany, [2]University of Debrecen, Debrecen, Hungary

Objectives: Due to its 3 carbonic acid groups available for bioconjugation, the TRAP chelator is destined for the synthesis of trimeric bioconjugates for radiolabelling. We optimized a protocol for bioorthogonal TRAP conjugation via Cu(I)-catalyzed Huisgen cycloaddition of terminal azides and alkynes (CuAAC), aided by determination of the kinetic stability of Cu(II)–TRAP complexes. **Methods:** TRAP derivatives for CuAAC, TRAP(alkyne)$_3$ and TRAP(azide)$_3$, were obtained by amide coupling of propargylamine and 3-azidoprop-1-ylamine, respectively. Thermodynamic and kinetic properties of Cu(II) complexes were determined by UV spectrophotometry, evaluating NOTA–EDTA for competitive demetallation of Cu(II) complexes of TRAP and TRAP conjugates. A trimer of PSMA-targeting DUPA-Pep was synthesized using TRAP(alkyne)$_3$, 3.3 eq DUPA-Pep-azide, 10 eq Na ascorbate, and 1.2 eq Cu(II)-acetate. Its PSMA affinity (IC_{50}) was determined in competition assays on LNCaP cells, and pilot PET imaging was performed with the Ga-68-labeled compound on LNCaP-xenografted nude mice. **Results:** Formation constants ($\log K_{ML}$, 19.1/17.6) and dissociation rates (k, $38\cdot10^{-6}/7\cdot10^{-6}$ s^{-1} at 298 K and pH 4) for Cu(II) complexes of TRAP and TRAP conjugates showed that the latter possess lower thermodynamic stability but higher kinetic inertness. However, transchelation occurred at pH 2–3 within hours to days at room temperature, enabling the removal of Cu(II) after click coupling by direct addition of NOTA trihydrochloride to the reaction mixture. In contrast, an extrapolated

dissociation half-life of >100 hours at 37°C and pH 7 confirmed the suitability of TRAP bioconjugates for application in Cu-64 PET. ^{68}Ga-TRAP(DUPA-Pep)$_3$ showed 18-times-higher affinity than the DOTAGA monomer (IC_{50}, 2 ± 0.1 vs. 36 ± 4 nM), resulting in markedly improved PET contrast. **Conclusion:** The kinetic stability profile of Cu(II)–TRAP conjugates allows for simple Cu(II) removal after click functionalization but also enables application in Cu-64 PET, thus broadening the scope of application for TRAP.

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Ga-68-Aquibeprin and Ga-68-Avebetrin for complementary, selective PET imaging of integrin subtypes $\alpha_5\beta_1$ and $\alpha_v\beta_3$. J. Notni[1], F. Hofman[1], K. Steiger[2], D. Reich[1], T. Kapp[1], F. Rechenmacher[1], H. Kessler[1], H.-J. Wester[1]; [1]Technische Universität München, Garching, Germany, [2]Helmholtz Zentrum München, München, Germany

Objectives: Currently, the clinical value of $\alpha_v\beta_3$ integrin mapping is not well defined, mainly due to unknown expression patterns of different integrin subtypes over time and the multiple roles of $\alpha_v\beta_3$ in tumor biology. The possibility of selective in vivo addressing of integrins $\alpha_5\beta_1$ and $\alpha_v\beta_3$ could significantly contribute to a better understanding of this area. **Methods:** Aquibeprin was obtained by Click-Chemistry trimerization of a $\alpha_5\beta_1$-selective pseudopeptide on the TRAP platform. Integrin subtype affinity profiles were determined in ELISAs on immobilized integrins. The Ga-68-labelled compounds were used for small-animal PET, employing M21 (human melanoma) xenografted nude mice. Expression densities of β_3 and α_5 in M21 slices were determined by immunohistochemistry. **Results:** With $\alpha_5\beta_1/\alpha_v\beta_3$ affinities (IC_{50}) of 0.083 ± 0.013/620 ± 23 nM for Ga-68-Aquibeprin and 39 ± 10/0.22 ± 0.05 nM for Ga-68-Avebetrin, the tracers show complementary selectivity and, furthermore, possess similar lipophilicity (log*D*, –4.2 and –3.9, respectively). Accordingly, dynamic PET scans show comparably fast renal blood clearance and very low unspecific binding. Fast and irreversible tumor uptake correlated well with immunohistochemically determined integrin densities (high β_3/moderate α_5 expression). Selectivity of $\alpha_5\beta_1$ imaging was illustrated by unchanged Ga-68-Aquibeprin uptake in M21 upon blockade with Avebetrin (5 mg/kg). **Conclusion:** Virtually identical, favorable pharmacokinetics, high affinity, and complementary subtype selectivity of Ga-68-Aquibeprin and Ga-68-Avebetrin allow for independent in vivo quantification of integrins $\alpha_5\beta_1$ and $\alpha_v\beta_3$, for the first time enabling meaningful studies of the temporal expression patterns of both integrin subtypes by PET.

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Feasibility of PSMA targeting therapy using Lu-177-labeled nanoparticles in xenografted mouse model. S.W. Oh[1,2], S.H. Moon[2], G.J. Cheon[2], J.M. Jeong[2], D.S. Lee[2]; [1]Boramae Medical Center, Seoul National University, Seoul, Korea, [2]College of Medicine, Seoul National University, Seoul, Korea

Objectives: Feasibility of prostate-specific membrane antigen (PSMA) targeting therapy using ^{177}Lu-labeled multifunctional nanoparticles was investigated in a xenografted mouse model. **Methods:** Nanoparticles with iron-oxide core (IO) were encapsulated with PSMA targeting glutamate-urea-lysin (GUL) probe and radiolabeling probe (DOTA). In vitro characterization of PSMA-targeting nanoparticles (DOTA-IO-GUL) including labeling efficiency, purity, and stability were performed, and the targeting efficacy of DOTA-IO-GUL was evaluated in PSMA-positive/negative cancer cell lines. ^{177}Lu-DOTA-IO-GUL was intravenously administered in a xenografted mouse model of PSMA-positive/negative prostate cancers. Therapeutic effects were evaluated by serial measurement of tumor size and animal PET/CT imaging. **Results:** The PSMA-targeting nanoparticles were successfully synthesized, and they were stable and safe in in vitro conditions. The selective internalization of the PSMA-targeting nanoparticles was demonstrated in both in vitro and in vivo conditions. The ^{177}Lu-labeled PSMA-targeting nanoparticles reduced the sizes of PSMA-positive prostate cancers, not PSMA-negative prostate cancers. **Conclusion:** ^{177}Lu-labeled PSMA-targeting radionuclide therapy based on multifunctional nanotechnology could be a potential candidate for a novel therapeutics for advanced/metastatic prostate cancer.

*First-place oral winner.

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Performance of the IGG100 gallium-68 generator. A. Orzechowski, L. Tegelman, I. Taskaeva, A. Raboy, J. Hothcock; Eckert & Ziegler Isotope Products, Valencia, CA

Objectives: Eckert & Ziegler Isotope Products has been manufacturing the IGG100 gallium-68 generator for over six years. The objective of the current work is to measure and monitor detailed IGG100 gallium-68 generator performance data, focusing on performance specifications. **Methods:** Measured performance specifications for the IGG100 are elution efficiency, germanium-68 breakthrough, titanium leakage, metal impurities, and elution profile. HPGe gamma-ray spectrometry system/GENIE2000 software was used for Ge-68 breakthrough measurements. A metals screen was performed by ICP-MS on an eluate of each generator to measure metal impurities. Elution efficiency for each generator was calculated from a set of minimum six elutions, assayed for Ga-68 in an ion chamber and compared with the Ge-68 on the column. **Research:** Detailed performance data have been collected for more than 400 generators at beginning of life. Several in-house generators, as well as two generators at end of life, have been studied over an extended period of time to determine whether the performance characteristics are stable over the generator's recommended one-year lifetime and beyond. **Conclusion:** The aggregate data are consistent from one generator to another, and create a profile of typical IGG100 performance and normal range of variation. Over the life of the generator Ge-68 breakthrough remains stable and below European Pharmacopeia limit. Elution efficiency and elution profile also remain stable over the generator's working life. Titanium is always present in the eluates at low levels. Other transition metals that could interfere with Ga-68 labeling are not present in significant amounts.

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In vitro assessment of Ga-67 as an Auger-emitting therapeutic radionuclide. M.F. Othman, S.Y.A. Terry, P.J. Blower; Division of Imaging Sciences and Biomedical Engineering, King's College London, St. Thomas' Hospital, London, United Kingdom

Background: Despite its desirable half-life and high-energy Auger electrons, ^{67}Ga therapy has been neglected due to lack of suitable chelators and targeting molecules. The advent of ^{68}Ga PET has improved molecular targeting with radiogallium, inviting re-evaluation of therapy with ^{67}Ga. **Objective:** To compare the toxicity of internalized ^{67}Ga and ^{111}In in 3 cancer cell lines (DU145, HCC1954, and MDA-MB-231). **Method:** Lipophilic ^{67}Ga-oxine and ^{111}In-oxine were prepared in 1% ethanol in saline. Cell uptake (during 2 h) and retention (up to 72 h) were determined in all cell lines in HBSS medium. Cells were treated for 1 h with 0–20 MBq/mL of the complexes alongside non-radioactive controls with standardized ethanol and oxine concentrations, then washed, seeded, and grown in HBSS for 72 h. Viability was measured with trypan blue. Clonogenic assays were carried out by culturing for 10–14 days before fixing and crystal violet staining. **Results:** Cellular uptake was 8%–13% for ^{67}Ga-oxine and 73%–78% for ^{111}In-oxine in all cell lines. No significant uptake was seen with ^{67}Ga-citrate or ^{111}In-chloride. Retention at 72 h was 43% for ^{67}Ga and 50% for ^{111}In. ^{67}Ga was more toxic than ^{111}In (IC_{50}, 0.09 Bq/cell for ^{67}Ga and 0.17 Bq/cell for ^{111}In, as determined by a trypan blue assay; 0.03 Bq/cell and 0.1 Bq/cell, respectively, as determined by a clonogenic assay). No significant toxicity was seen with ^{67}Ga-citrate or ^{111}In-chloride. **Conclusion:** Oxine complexation enabled rapid nonspecific uptake in cells, but ^{67}Ga-oxine was inefficient compared with ^{111}In-oxine. ^{67}Ga is more toxic than ^{111}In at equivalent internalized activity per cell. ^{67}Ga can kill cancer cells at achievable intracellular concentrations and deserves evaluation for radionuclide therapy, in the context of a theranostic pairing with ^{68}Ga.

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Preclinical evaluation of ^{68}Ga-DOTA-NT20.3 as a PET imaging agent for neurotensin receptor 1 expression in a model of exocrine pancreatic adenocarcinoma. A. Prignon[1], C. Provost[1], J.-N. Talbot[2], A. Gruaz-Guyon[3]; [1]Plateforme LIMP, Paris, France, [2]APHP, UPMS, Paris, France, [3]INSERM, Paris, France

Objectives: Pancreatic ductal adenocarcinoma (PDA) grows extremely rapidly, and early diagnosis allowing therapeutic surgical resection is rarely

possible. Positron emission tomography-computed tomography (PET-CT) imaging with ^{18}F-fluorodeoxyglucose has several limitations, and differentiating between PDA and focal mass–forming pancreatitis is still a major clinical problem (*1,2*). ^{68}Ga-DOTATOC PET-CT is becoming the method of reference for the detection and staging of pancreatic neuroendocrine tumors (pNETs), but exocrine pancreatic cancers do not express sufficient amounts of the somatostatin receptors. PDA expresses a high density of neurotensin receptor 1 (NTSR1) as compared with normal human pancreas, chronic pancreatitis, and endocrine pancreatic tumors (*3*). Recent studies suggest that increased expression of NTSR1 contributes to the progression of PDA (*4*), and NTSR1 was recently identified as a prognosis marker in PDA (*5*). In our previous study, we demonstrated, in nude mice grafted with a human colon carcinoma model, that ^{68}Ga-labelled DOTA-conjugated neurotensin analogues were suitable radiotracers for imaging neurotensin receptor–positive tumors (*6*). We decided to evaluate the best candidate of these analogues (DOTA-NT20.3) as a PET tracer for human ductal pancreatic carcinoma imaging. **Methods:** DOTA-NT20.3 peptide was radiolabelled with gallium-68 using an R&D Synchrom module (Raytest, Germany). HPLC quality control was performed, and radiochemical purity was assessed using ITLC. ^{68}Ga-DOTA-NT20.3 dynamic PET imaging was performed over 50 min immediately after injection to determine in vivo biodistribution of the tracer in healthy organs and to quantify its elimination in kidneys and urinary bladder in female (n = 3) or in male (n = 3) nude mice. Data were expressed as %ID (percentage injected dose)/organ per frame, and the decay-corrected mean time–activity curves (TACs) were extracted for each target organ. Male athymic nude mice (n = 4) were subcutaneously inoculated in the right shoulder with AsPC1 cells (4×10^6), a human pancreatic adenocarcinoma cell line. PET imaging was performed to evaluate the in vivo biodistribution and tumor uptake of the tracer. SUVmax intensity was reported as the mean ± SD at each time point for tumor, kidneys, and a "nontumor" region that corresponded to a background close to the tumor area. The tumor-to-nontumor ratios were calculated. At 1 h after injection of ^{68}Ga-DOTA-NT20.3 and after PET imaging, the mice were sacrificed; the main organs and tissues were dissected, washed, weighed, and counted in a gamma counter. Tissue uptake was calculated and expressed as the percentage injected dose corrected for decay per gram of tissue (%ID/g). The residence time of ^{68}Ga-DOTA-NT20.3 in each target organ was calculated on the basis of whole-body PET imaging of mice and compared with the residence time based on the ex vivo 1-h biodistribution. Dosimetry extrapolation to humans was calculated using OLINDA software. A blocking experiment was performed with a 400-fold excess of unlabeled non–DOTA-NT20.3 peptide (n = 3 mice). Ten-minute static PET images were acquired at 45 min postinjection (p.i.), and animals were sacrificed at 1 h p.i. for the measurement of tumor uptake. Tumor-to-nontumor ratios were calculated, and tumor uptake (%ID/g) was compared with values obtained in the absence of non–DOTA-NT20.3 peptide at the same time point (n = 4 mice). **Research:** DOTA-NT20.3 peptide was radiolabelled in 30 min. The overall decay-corrected radiochemical yield (RY) was 76%–85%. The radiochemical purity after purification of the reaction mixture was ≥99% using analytical HPLC, and a specific activity (SA) of 9.9 ± 0.9 MBq/nmol of peptide was achieved. The retention time (RT) was 6.5 min for ^{68}Ga-DOTA-NT20.3 in HPLC, and the rate of flow (Rf) was 0.6 for ITLC. Normal mice and AsPC1 tumor–bearing mice were characterized by a rapid delivery of ^{68}Ga-DOTA-NT20.3 up to 2 min p.i. into the blood compartment, maximal renal excretion between 5 and 10 min p.i., and elimination by the urinary bladder reaching 55–61 %ID in 50 min p.i. No uptake was observed in other organs, especially in the pancreas, the target organ. No significant difference in radiotracer biodistribution was found between female and male mice. High-contrast images were obtained and showed intense tracer uptake in tumors expressing NTRS1. The optimal frame of ^{68}Ga-DOTA-NT20.3 imaging was between 40 and 50 min after injection. The SUVmax in the tumor was 1.1 ± 0.2, and the uptake ratio (tumor-to-nontumor) was 4.2 ± 1. ^{68}Ga-DOTA-NT20.3 ex vivo biodistribution, investigated 1 h p.i., showed moderate kidney retention (5.38 ± 0.54 %ID/g) and low activity in the pancreas (0.22 ± 0.03 %ID/g) and remaining organs, consistent with findings on PET imaging. Uptake in the AsPC1 tumor was rapid and high, with 5.28 ± 0.93 %ID/g. The NTSR1 specificity of the ^{68}Ga-DOTA-NT20.3 tracer was tested in a blocking study with the coadministration of unlabeled non–DOTA-NT20.3 peptide. The tracer uptake in AsPC1, calculated as the tumor-to-nontumor ratio from PET imaging 45 min p.i., was reduced significantly, from 3.7 ± 1.1 to 1 ± 0.1, and ex vivo tumor uptake 1 h p.i., from 5.8 ± 0.8 to 1.6 ± 0.3 %ID/g. Residence times based on whole-body PET imaging of mice were in accordance with residence times based on ex vivo 1-h biodistribution. **Conclusion:** ^{68}Ga-DOTA-NT20.3 has a favorable pharmacokinetics and biodistribution profile, which results in high-quality PET images. ^{68}Ga-DOTA-NT20.3 seems to be a good candidate for PET imaging of overexpression of NTSR1 in the human ductal pancreatic carcinoma model.

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Development of GalioMedix kit to prepare ^{68}Ga-DOTATATE injection solution for PET imaging of neuroendocrine tumors. D. Ranganathan[1], N. Wagh[1], S. Thamake[2], I. Tworowska[2], J. Puente[2], A. Delpassand[2], E. Delpassand[2]; [1]Radio-Isotope Therapy of America (RITA) Foundation, Houston, TX, [2]RadioMedix Inc., Houston, TX

Objectives: The purpose of this work was to develop a sterile, lyophilized kit formulation based on direct reconstitution of ^{68}Ga eluate from the generator to prepare ^{68}Ga-DOTATATE injection solution for PET imaging of neuroendocrine tumors. **Method:** Two separate formulations were developed to be compatible with the 50-mCi Isotope Technologies Garching (ITG) generator and Eckert & Ziegler generator. The following parameters were optimized in each formulation: pH, temperature, time, and reaction volume to evaluate the incorporation of the radionuclide to DOTATATE. Further the formulation was freeze-dried and evaluated to meet its desired specification for an injection solution. **Results:** GalioMedix, a preformulated GMP kit, gives consistently high radiochemical yields (>95%) when tested up to 45 mCi of ^{68}Ga activity and a volume up to 4.5 mL for the ITG generator at 90°C. The resulting labeled solution meets all the requirements for ^{68}Ga-DOTATATE injection solution (pH, osmolarity, endotoxin, and sterility). To date the GalioMedix kits are stable (6 months) and the stability of GalioMedix kits are monitored on an ongoing basis. **Conclusion:** The GalioMedix kit–based approach for the preparation of ^{68}Ga-DOTATATE satisfies the necessity of a standardized pharmaceutical product with controlled quality and wide availability.

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A preclinical comparative study of ^{68}Ga-labeled DOTA–, NOTA–, and HBED-CC–chelated PSMA-targeted radiotracers. S. Ray, Z. Chen, M. Pullambhatla, R.C. Mease, M.G. Pomper; Johns Hopkins University, Baltimore, MD

Objectives: Prostate-specific membrane antigen (PSMA) is an increasingly important target for imaging and therapy of prostate cancer. We previously reported two PSMA-targeted, ^{68}Ga-labeled, DOTA-chelated radiotracers conjugated to the PSMA-targeting moiety, H_2N-Lys-(CH2)3-Glu-urea-Lys. We chose DOTA because it can chelate both imaging and therapeutic nuclides. The goal of this study is to investigate our previous lead radiotracer, ^{68}Ga-SRV100; a new radiotracer, ^{68}Ga-SRVI68, which employed the NOTA chelator; and ^{68}Ga-DKFZ-PSMA-10, which is currently in clinical trials. **Methods:** Multistep syntheses were employed in preparing ^{68}Ga-SRV100 and ^{68}Ga-SRVI68 using well-established methods. DKFZ-PSMA-10 was purchased from a commercial vendor. PSMA inhibition constants (K_i) were evaluated by competitive binding assay. In vivo characterization was performed by PET-CT and by biodistribution assays using PSMA+ PC3 PIP and PSMA– PC3 flu tumor-bearing male mice. **Research:** Radiotracers were synthesized in high radiochemical yield (~95%–99%) and purity (>99%) with specific activities >168 GBq (4.05 mCi/μmol). Whole-body

PET-CT images enabled visualization of PSMA+ PC-3 PIP tumor as early as 30 min postinjection. ^{68}Ga-SRVI68 demonstrated the highest tumor uptake at 42.2 ± 6.7 percentage of injected dose per gram (%ID/g) at 1 h, and fastest rate of clearance from all tissues including tumors. ^{68}Ga-SRVI68 demonstrated the lowest blood and normal tissue uptake, including PSMA− PC3 flu tumor (PSMA+ tumor/kidney at 2 h postinjection, 0.6). ^{68}Ga-SRV100 and ^{68}Ga-DKFZ-PSMA-10 demonstrated similar uptake and retention in PSMA+ PC3 PIP tumors, with tumor/kidney ratios of 2.1 and 0.2 at 2 h. **Conclusion:** ^{68}Ga-SRVI00, designed to serve as a PSMA-targeted theranostic, and ^{68}Ga-SRV68, designed for imaging, demonstrated the highest tumor-to-normal tissue ratios in this series suggesting their potential for clinical translation.

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Detection of relapsing protate cancer with PET/CT: noninferiority of Ga-68-labeled PSMA-binding peptide to C-11 choline in extraprostatic relapse. S. Reske[1], G. Glatting[2], M. Gottstein[1]; [1]University of Ulm, Ulm, Germany, [2]Heidelberg University, Mannheim, Germany

Objectives: C-11 choline is established for imaging relapsing prostate cancer (rPCa). Recent reports indicated improved imaging of rPCa with a Ga-68-labeled PSMA-binding peptide (HBDE) compared with F-18 choline (Cho). Here we studied the assessment of localization and disease extent of rPCa with HBDE PET/CT using Cho as a reference method. **Methods:** One hundred twenty-eight patients with rPCa were examined on the same day under identical conditions starting with Cho and followed by HBDE PET/CT 3 h later with a state-of-the-art technique. PET/CT scans were anonymized and read by 2 experienced readers. Target-to-background ratios of the most prominent lesions were determined. Both readers were blinded to clinical data and previous imaging results. The primary treatment was radical prostatectomy in 105 patients and radiation therapy and/or androgen deprivation (ADT) in 23 patients. At PET/CT, done 6.3 a (median, 47 d–20 a) after the primary treatment, 45 patients had no specific treatment, 6 patients had chemotherapy, and the remaining patients had ADT and/or various alternative therapies. The PSA at PET/CT was 8.3 ± 25.7 ng/mL (mean ± SD). **Research:** Cho detected significantly more local relapses. The UICC stage, as determined by Cho vs. HBDE, was not different in all stages of extraprostatic disease. **Conclusons:** Cho better detected local relapse than HBDE. The stage of extraprostatic relapsing PCa was determined equally well by both methods independent of tumor stage. HBDE might improve assessment of the extent of nodal, skeletal, and visceral relapse. Lesion contrast with HBDE is very high for many lesions, opening important avenues for targeted therapy with radiolabelled PSMA-binding peptides.

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Preparation of ^{68}Ga radiopharmaceuticals in a South African hospital radiopharmacy. S. Rubow, A. Africander, A. Ellmann; Stellenbosch University and Tygerberg Hospital, Tygerberg, South Africa

Objectives: Our aim was to establish and validate a reliable radiolabelling routine with ^{68}Ga according to GRP principles at the Western Cape Academic PET/CT Centre. **Methods:** ^{68}Ge/^{68}Ga generators from iThemba Labs (South Africa) and kits for ^{68}Ga-peptide labelling from ABX (Germany) were used. Protocols for generator elution manually or with a Scintomics automated unit were established. Acceptance criteria for the validation were specified a priori. A manual ^{68}Ga DOTANOC synthesis routine based on the Scintomics/ABX kit for cationic purification was validated in 4 trial runs. Quality control included testing for sterility, endotoxins, labelling yield, radiochemical purity by ITLC (all) and HPLC (n = 3), half-life determination, and pH of the product. Operator radiation exposure was monitored. **Results:** During all validation runs, the final product was sterile, endotoxin free, and contained <5% free ^{68}Ga. Average decay-corrected labelling yield was 50% (validation) and 63% (successful clinical batches). ^{68}Ge breakthrough in eluates increased with generator age, but this was not reflected in the labelled product. Of 30 postvalidation productions, 3 batches failed due to buffer impurities and 1 due to a blocked filter. Procedure and shielding modifications decreased radiation exposure to the operator from 0.08 to 0.02 μSv/MBq eluate for manual synthesis. Problems included malfunctioning of the synthesis unit, eluant leakage, and chemical impurities in a buffer solution. **Discussion:** The synthesis unit's disposable manifolds and tubing and sterile consumables and reagents support GRP principles. When we had problems with our synthesis unit, we therefore based our manual procedure on the same kits and method. **Conclusion:** Validation showed that ^{68}Ga DOTANOC suitable for administration to patients can be prepared at our Centre. Careful attention to detail and rigorous quality assurance protocols are essential if complex radiolabelling procedures are to be done in a hospital radiopharmacy.

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^{177}Lu-DOTATATE posttherapeutic imaging: is it really the truth and nothing but the truth? Z. Saad[1], R. Sajjan[2], M. Aldridge[2], M. Moran[2], J. Bomanji[2]; [1]Cambridge University Hospitals, NHS Foundation Trust, Cambridge, United Kingdom, [2]University College London Hospitals, NHS Foundation Trust, London, United Kingdom

Objective: PRRT of somatostatin receptor positive tumors is currently performed using DOTA-chelated somatostatin analogues such as DOTA DPhe[1] Tyr3-octreotate (DOTATATE) radiolabelled with either lutetium (^{177}Lu) or yttrium (^{90}Y). The advantage of ^{177}Lu is it emits both γ and β radiation, allowing posttherapeutic imaging. The aim of this study was to investigate the usual and unusual distribution patterns of ^{177}Lu-DOTATATE, especially free ^{177}Lu, which can contribute to false-positives, potentially affecting the stage and outcome of the disease. **Methods:** A qualitative (visual) review of 242 scans was carried out in consecutive 80 patients (age range, 6–78 years) who received ^{177}Lu-DOTATATE therapy following ^{68}Ga-DOTATATE PET/CT study. All patients received 7.4 GBq (±10%) × 4 fractions of ^{177}Lu-DOTATATE, each at least 8 weeks apart. Both high-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC) were performed to check if ^{177}Lu was properly labelled with DOTATATE as suboptimal labelling leads to free ^{177}Lu, which acts as calcium mimic and is accumulated in bone with unwanted bone/bone marrow radiation. Whole-body anterior and posterior images coupled with SPECT/CT were acquired the following day to assess and document uptake of ^{177}Lu-DOTATATE. **Results:** A total of 3 studies (2 adult and 1 pediatric) demonstrated significantly intense skeletal activity that was not evident on baseline ^{68}Ga-DOTATATE PET/CT scanning prior to the ^{177}Lu-DOTATATE posttherapeutic scan. The dilemma was to distinguish between a true progression and technical artefact. We found no protocol deviations in these discrepant cases; however, radiopharmaceutical labelling efficiency was below 99.5% (typically above 99.5%) and administered therapeutic activities were between 7.7 GBq–7.9 GBq in these three studies. After excluding dedifferentiation and other mechanisms potentiating receptor/ligand errors, atypical labelling efficiency with high burden of activity was identified as a source that incorporated enough free ^{177}Lu (non–DOTA-labelled) in bones to resemble disease progression. Close clinical surveillance was carried out with subsequent posttherapeutic scans in 2 patients showing resolution of intense bony uptake. Subsequent radionuclide therapy of the third patient is still awaited. **Conclusion:** Knowledge of varied factors contributing to atypical distribution pattern, mimicking progression of disease, is of paramount importance to nuclear physicians as it influences the management plan in these patients. Poor labelling of ^{177}Lu-DOTATATE should be considered before suggesting disease progression where high bone uptake is seen on a ^{177}Lu-DOTATATE posttherapy scan in the absence of bony disease on a ^{68}Ga-DOTATATE PET/CT scan.

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Peptide receptor radionuclide therapy and theranostics beyond neuroendocrine tumors and into the next decade. S. Satz[1], R.P. Baum[2], M.M. Sathekge[3]; [1]Advanced Imaging Projects, LLC, Lake Worth, FL, [2]Zentralklinik, Bad Berka, Germany, [3]University of Pretoria & Steve Biko Academic Hospital, Pretoria, South Africa

Objectives: The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumors (NETs) is aimed at enabling the implementation of a novel therapy for treatment of NETs in nuclear medicine facilities globally. The objective of this paper is to review the status of PRRNT for a spectrum of additional diseases and the future application of theranostics in the next decade. **Methods:** This systemic review was based on PRISMA guidelines. Databases searched included Pubmed, Medline, Scopus, Web of Science, Cochrane Controlled

Trials Register, Clinicaltrials.gov, EU Clinical Trials Registry, and Google Scholar. **Research:** Seven trials for NETs are registered in Clinicaltrials.gov. Twenty-nine trials appear using ^{177}Lu, including 1 comparing PRRT with interferon. Several trials using ^{90}Y for PRRNT are listed. Only 1 controlled phase 1 dose escalation clinical trial has been conducted in children and young adults with somatostatin receptor positive tumors using ^{90}Y. PRRNT is being used to diagnose and treat HIV/AIDS, tuberculosis and several pediatric diseases, preclinically and early phase trials. A search of Pubmed resulted in 19 PRRNT patient studies in India, 24 in China, and preclinically in Korea. One hundred twelve diagnostic studies are listed including a score of cardiac ones. The EU Clinical Trials Registry lists 4 PRRNT studies, 4 using ^{177}Lu and 21 using ^{90}Y. **Conclusion:** In addition to somatostatin receptor targeting, there are other sites that are in or on a cell surface that can be targeted to bind with a specific molecule, antigen, hormone, antibody, peptide, or peptidomimetic, including integrins such as Theranost-RGD, VEGF, EGFR, gastrin-releasing, transmembrane glycoprotein, or other receptor using PPRNT. Radionuclides and pairs for PRRT include ^{90}Y, ^{177}Lu, ^{213}Bi and ^{18}F, ^{68}Ga, ^{95}Zr, ^{124}I, ^{44}Sc, ^{86}Y, ^{64}Cu, ^{15}O, and ^{11}C and ^{76}Br. In addition to malignancies, the potential application of PRRT includes cardiovascular, neurological, and infectious diseases, including tuberculosis and HIV/AIDs, as well as rare and childhood diseases.

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Radiochemical evaluation of DATA-based chelators with ^{68}Ga. J. Seemann[1], B. Waldron[1], D. Parker[2], F. Roesch[1]; [1]Johannes Gutenberg University, Mainz, Germany, [2]Durham University, Durham, United Kingdom

Objectives: The relatively new class of DATA chelators for ^{68}Ga, based on the 6-amino-1,4-diazepine-triacetic acid core, has been introduced recently. Compared with established chelators based on the cyclen scaffold (i.e., DOTA derivatives), these novel compounds enable quantitative radiolabelling rapidly at room temperature. However, a detailed examination of the radiochemical characteristics of these ligands has not been carried out. **Methods:** Four DATA-chelators (DATAm, DATAp, DATAPh, and DATAPPh) were radiolabelled at three amounts of substance (5, 7, and 10 nmol) and four pH values (4, 5, 6, and 7) using acetone-postprocessed ^{68}Ga. Stability of the radiotracers in the presence of *apo*-transferrin was tested over 2 h at 37°C. A comparison of lipophilicity was performed using the shake flask and analytical radio-HPLC methods. **Research:** All chelators were labelled to >98% at room temperature within 10 min using 10 nmol of precursor over the pH range 4–7. Reducing the amount to 7 nmol, chelators bearing propionates showed slower reaction kinetics but still achieved quantitative RCYs after 15 min. RCYs of DATAp and DATAPh dropped to <95% using 5 nmol. At pH 4, RCYs were slightly lower compared with the reactions performed at pH 5. A considerable drop in RCYs was observed at pH 6 with an increase at pH 7. All chelators showed a stability of 96.8% ± 2.6% over 2 h in *apo*-transferrin. Lipophilicity data obtained with the shake flask and HPLC method were consistent and indicate DATAm to be the most hydrophilic derivative (log*P*, −4.0 ± 0.2) and DATAPPh to be the least hydrophilic compound (log*P*, −2.3 ± 0.1). **Conclusion:** The DATA chelators form stable complexes with ^{68}Ga in quantitative yields over a wide pH range using only 5–10 nmol of precursor. As radiolabelling can be performed at room temperature, these chelators provide superior characteristics over current standards and are promising candidates for further investigation toward conjugation to targeting vectors and kit-type formulations.

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Can we predict patient's dosimetry from blood kinetics and animal biodistribution data of ^{177}Lu-and ^{153}Sm-EDTMP therapy used for pain palliation in extensive bone metastases? S. Sharma[1], A. Ghai[1], A. Koul[2], B.R. Mittal[1], B. Singh[1]; [1]Department of Nuclear Medicine and PET, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [2]Department of Biophysics, Panjab University, Chandigarh, India

Aim: To evaluate if the multiple-points blood kinetics and animal biodistribution data following administration with ^{177}Lu- and ^{153}Sm-labeled EDTMP can be used to derive the patient's dosimetry. **Methods:** The ready to label and lyophilized EDTMP cold kits and ^{177}Lu (as Lu_2Cl_3) and ^{153}samarium (as $SmCl_3$) were procured from the national supplier (BRIT; BARC, Mumbai, India). The radiolabeling was carried out in house and prior to administration in animals, the radiolabeled preparations (^{177}Lu-EDTMP and ^{153}Sm-EDTMP) were tested for radiolabeling efficiency, radiochemical purity, and sterility. Forty-two male adult balb/c mice (weight, 25–35 g) were used in the present study. The mice were divided into two groups (21/group, 7 time points, and 3 mice/time point), i.e., GI and GII, respectively. Each animal of GI and GII was injected intravenously (tail vein) with 3.6 MBq either of ^{153}Sm-EDTMP (GI) or of ^{177}Lu-EDTMP (GII). Blood samples from each animal were withdrawn at time intervals of 0.5 h, 3 h, 6 h, 24 h, 48 h, 96 h, and 168 h following radioactivity administration. The radioactivity in the blood samples was counted using well-type gamma counter and the activity was expressed as %ID/mL. The animal biodistribution data in various organs (bone, liver, lungs, kidneys, brain, stomach, intestine, and colon) as a function of time was analyzed to evaluate the residence times of each of the two therapeutic radionuclides used. This information was further used to derive the whole-body absorbed dose and dose received at the bone surface in humans by using the computer algorithm (OLINDA 1.1). **Results:** The radiolabeling efficiency for each radiolabeled preparation was ≥97.0%. Both the radiopharmaceuticals exhibited rapid blood clearance with ≤1.0% of the radioactivity remaining at 30 min. The animal biodistribution data demonstrated the highest bone uptake (47.0%) for ^{153}Sm-EDTMP at 24 h, which decreased to 18.1% at 96 h. Likewise, for ^{177}Lu-EDTMP, the maximum bone uptake (46.0%) was seen at 48 h, which declined to 17.1% at 96 h. The organ distribution data analysis exhibited that total-body doses in humans from ^{153}Sm-EDTMP and ^{177}Lu-EDTMP were 0.0345 mSv/MBq (effective dose, 0.0255 mSv/MBq) and 0.0228 mSv/MBq (effective dose, 0.0124 mSv/MBq), respectively. The whole-body dose and the bone dose from ^{153}Sm and ^{177}Lu derived from the animal biodistribution data provided an excellent agreement with the reported values. Likewise, the absorbed dose to various other organs/tissue was also derived. **Conclusion:** It is thus highlighted that multiple-point blood kinetics and animal biodistribution data may provide good estimation for predicting dose delivered to whole body or bone following ^{153}Sm-EDTMP or ^{177}Lu-EDTMP therapy in patients with bone metastases. The findings may provide important supportive data for grant of regulatory permission, especially to the newer therapeutic radionuclides being introduced in to the clinical practice. However, these preliminary findings need further preclinical and clinical validation.

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Deviation in the predefined calibration factors of the dose calibrators and the associated inaccuracy in the radioactivity measurements of beta-gamma emitters. S. Sharma[1], B. Singh[1], A. Koul[2], B.R. Mittal[1]; [1]Department of Nuclear Medicine and PET, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [2]Department of Biophysics, Panjab University, Chandigarh, India

Objectives: To determine if the predefined calibration factors of the dose calibrators can provide accurate radioactivity measurements of beta-gamma emitters used in routine therapeutic nuclear medicine procedures. **Methods:** Two models of dose calibrators were used in the present study for radioactivity measurements of ^{153}Sm (EDTMP) and ^{177}Lu (EDTMP). A known (precalibrated) activity of each of the two beta emitters received by us from our national supplier for administration to the patients with extensive bony metastases for bone pain palliation was used for experiments. **Results:** When we used the manufacturers' provided dial setting of 450 × 10, each of the dose calibrators underestimated the radioactivity of ^{177}Lu by about 9.0%. Dial settings of 403 × 10 and 408 × 10 for CRC-15R and CRC-ultra dose calibrators, respectively, were calculated experimentally by using the iterative approach. The radioactivity measurements made at these settings provided an excellent agreement with the specified values. Likewise, a dial setting of 230 for each of the two dose calibrators was calculated for ^{153}Sm, which provided a good agreement between the experimentally derived radioactivity values and the certified values. A deviation of ±5.0% was observed when radioactivity of ^{177}Lu and ^{153}Sm was measured over a wide range (4.0 MBq–2.1 GBq) for time intervals equivalent to 4.5 half-lives of each of the two radionuclides. A deviation of ±5% was observed when radioactivity was counted in different dilution volumes and in syringes of varying size. **Conclusion:** These variations could lead to a cumulative error of about 20.0% toward the inaccuracy in the radioactivity measurements of the beta-gamma emitters and thus predefined

calibration factors of the dose calibrators may require experimental resetting of these parameters and periodic checking to provide accurate radioactivity estimates of beta-gamma emitters in a given clinical setting.

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Physiological organ distribution pattern of ^{68}Ga-DOTATATE in disease-free NET patients: a semiquantitative analysis. B. Singh, A. Watts, B.R. Mittal; Department of Nuclear Medicine and PET, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Objectives: The aim of this study was to describe the normal physiological distribution of ^{68}Ga-DOTATATE using standardized uptake values. **Methods:** ^{68}Ga-DOTATATE PET/CT data of 161 patients were analyzed and the data of 65 patients (34 M, 31 F; median age, 37.0 y) who were found to be disease-free were included in the study. The reconstructed axial PET images were used to determine the SUV as a normal physiological range over different organs. **Results:** Visual assessment of the reconstructed ^{68}Ga-DOTATATE PET/CT data revealed increased uptake of the radiotracer in pituitary, salivary, thyroid glands, liver, spleen, adrenals, and kidneys. A semiquantitative analysis of the data indicated that the highest mean ± SD values of SUVmax were observed for spleen (25.6 ± 8.1) followed by kidneys (14.24 ± 4.00), adrenals (10.6 ± 4.2), liver (10.2 ± 3.3), pituitary (5.5 ± 2.5), pancreatic head (4.2 ± 2.0), thyroid (3.2 ± 1.4), and parotids (2.3 ± 1.2). A wide variation in SUV was seen in head of pancreas with an apparently increased physiological uptake (SUV > 7.0) of the radiotracer in 7/65 (11%) patients. A significantly higher uptake of the radiotracer was seen in liver (P = 0.02) and kidneys (P = 0.01) in elder (more than the median age of 37 years) patients. Female patients demonstrated significantly (P < 0.05) higher SUV in pituitary, thyroid, parotids, spleen, and kidneys as compared with males. **Conclusions:** The information of the varied physiological uptake range of ^{68}Ga-DOTATATE over different organs may help in differentiating tumor sites/recurrence from the physiological uptake of the radiotracer. The high uptake of the radiotracer in 11% of patients in the present study was more likely to be physiological but certainly requires more caution while reporting such scans. Likewise, significant age- and sex-related variations in the uptake of the radiotracer over majority of the organs should also be considered, which could be of special significance when using ^{68}Ga-DOTATATE PET imaging in response evaluation.

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First results with the novel theranostic NTR1 antagonist ^{177}Lu-3BP-227 in ductal pancreatic adenocarcinoma patients. C. Smerling[1], C. Schuchardt[2], H. Kulkarni[2], C. Haase[1], F. Osterkamp[1], U. Reineke[1], R.P. Baum[2]; [1]3B Pharmaceuticals GmbH, Berlin, Germany, [2]THERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging, Zentralklinik, Bad Berka, Germany

Objectives: Neurotensin receptor 1 (NTR1) is an ideal target for targeted radiotherapy of ductal pancreatic adenocarcinoma. Using ^{177}Lu-3BP-227, a novel NTR1 antagonist, we determined the organ and tumor kinetics and estimated the mean absorbed dose to normal organs and tumor lesions in pancreatic adenocarcinoma patients. Patients with appropriate tumor uptake and biodistribution were identified as candidates for a therapeutic administration of ^{177}Lu-3BP-227. **Methods:** Three patients with confirmed ductal adenocarcinoma of the pancreas and no other treatment options received 1.2–1.5 GBq ^{177}Lu-3BP-227. One patient received a second dose of 6.4 GBq ^{177}Lu-3BP-227 intraperitoneally. Planar whole-body images (and SPECT/CT) were acquired up to 165 hours postinjection. Dosimetry was performed according to the MIRD scheme and using OLINDA/EXM software to estimate the dose to whole body, normal organs, and metastases. **Research:** Administration of ^{177}Lu-3BP-227 was well tolerated without any significant adverse effects. The whole-body uptake showed a biexponential decline, and the maximum renal uptake was 4% IA. Specific uptake was found in metastatic lesions with absorbed doses of 33 to 63 mSv/MBq. ^{177}Lu-3BP-227 showed an exceptional retention in the tumor lesions with half-lives of 73–135 h. A posttherapy CT scan of the patient receiving consecutively the 6.4 GBq dose showed a response at tracer-avid tumor lesions. **Conclusion:** ^{177}Lu-3BP-227 exhibited a rapid clearance from blood with specific accumulation and long retention in the primary tumors and metastases, and therefore holds promise in the theranostic treatment of this highly malignant cancer.

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Resource and logistical realities associated with a Ga-68 radiopharmaceutical economy. J. Sunderland, D. Dick; University of Iowa, Iowa City, IA

Objectives: To identify and model the relevant variables and challenges associated with a distribution model based upon a relatively low-activity generator system with a long-lived parent (Ge-68) and short-lived daughter (Ga-68). To model and assess the viability of several pharmacy models (hospital-centric, distribution-centric, mobile) as a function of generator strength, frequency of elution, synthesis yield, and distribution time. **Methods:** A distribution-based radiopharmaceutical economy utilizing long-lived, low activity generators (<200 mCi) with short-lived ($t_{1/2}$, <2 hours) daughter products has not previously been attempted. A model of global Ge-68 production capabilities was made based upon available reaction cross-section data and published IAEA production capabilities. Current estimated production capacity was scaled up in units of additional Ge-68/Ga-68 generators per month (50, 100, and 200 mCi) per additional 30 MeV cyclotron. A model of [Ga-68]radiopharmaceutical production with appropriate variables (generator size, number of generators per facility, elutions per day, synthesis time, radiochemistry yield, DOT packaging/transport time, and calibrated activity) was created to calculate the number patient doses that could be produced and imaged per workday. **Conclusion:** Multiple models utilizing a range of higher- and lower-activity generators tailored to patient demand likely presents the most efficient use of Ge-68 resources. One size does not fit all. Recycling of Ge-68 generators postexpiration for reuse in subsequent generators will significantly enhance worldwide capacity if the practice is universal. Lower injected doses will also substantially increase the number of studies that can be performed per day. While the constraints due to the long half-life of the parent and short half-life of the daughter make the business model complex (e.g., less than 10 doses per day per 100-mCi generator), there are viable models for a Ga-68 economy.

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Gallium labeling in capillary. D. Szikra[1], G. Máté[1], G. Nagy[2]; [1]Department of Nuclear Medicine, University of Debrecen, Debrecen, Hungary, [2]Scanomed Ltd., Debrecen, Hungary

Objectives: Microfluidics gain increasing application in PET radiochemistry. Numerous examples can be found for ^{11}C and ^{18}F labeling, but not for ^{68}Ga. The aim of this work was the development of an automatized synthesis system for systematic optimization of labeling conditions. **Methods:** A "microfluidic" synthesis system was constructed from HPLC parts and PEEK capillaries. Gallium and chelator solutions were injected into the stream of water, pumped by two HPLC pumps. The reagents were mixed and heated in a capillary reactor and the reaction mixture is captured in the loop of a HPLC injector and injected onto a column, enabling on-line analysis of the product. **Research:** The reaction of ^{68}Ga and HEPES buffered NOTA and NOPO chelators were examined in 1–9 pH and 100–0.01 μM concentration range. Optimal labeling conditions were determined from the 3D plots of labeling yields plotted in the function of chelator concentration and pH. The labeling yields were reproducible (RSD, <1%; n = 5), and the results were in good agreement with manual labeling experiments. Production experiments were conducted among the optimal reaction conditions and resulted in >98% yield and >99% radiochemical purity. The labeling conditions were successfuly applied for peptide-chelator conjugates: NODAGA-$(RGD)_2$ and NOPO-RGD were labeled with similarly good yield and purity. **Conclusion:** The constructed system was able to provide useful data for the determination of optimal labeling conditions in a short time. It has a high potential in testing new chelators.

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Uptake of ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC in primary neuroendocrine tumors, metastases, and normal liver tissue: is there a significant difference? M. Todorovic-Tirnanic[1], M.M. Gajic[1], R.P. Baum[2]; [1]Department of Inorganic and Analytical Chemistry, University of Belgrade, Belgrade, Serbia, [2]Zentralklinik, Bad Berka, Germany

Objectives: The study aim was to compare two frequently used Ga-68-labeled somatostatin (agonist) analogues with different affinities for human somatostatin receptor (hsstr) subtypes 2, 3, and 5 (DOTATOC exhibits a much higher affinity for hsstr 3 and 5 but has somewhat lower binding to hsstr 2). As hsstr expression on tumor cells correlates significantly with the standardized uptake value (SUVmax) of ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC, the aim of this study was to compare the in vivo distributions of the two radiopharmaceuticals by determining their SUVmax in normal liver and in primary tumors and metastases in patients with gastroenteropancreatic (GEP) neuroendocrine tumors (NET). **Methods:** Seventy-six PET/CT studies in 38 patients (selected from 800 patients with GEP NET; 1 duodenal, 18 pancreatic, 2 cecal, 12 ileal, 3 jejunal, 1 mesenteric, and 1 in the appendix) with clinically, biochemically, and morphologically stable diseases were analyzed. ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC PET/CT was performed at consecutive controls. The time to acquisition after injection was identical for both studies (±10 min). SUVmax for both radiopharmaceuticals in the primary tumor; in liver, lymph node, soft-tissue, and bone metastases; and in normal liver tissue were determined, and mean SUVmax were compared. **Results:** Overall, 225 metastases (98 liver, 67 lymph node, 43 bone, and 17 soft-tissue) and 18 primary NET were analyzed on both ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE PET/CT studies, along with normal liver tissue. The mean SUVmax in the TATE/TOC groups were as follows: normal liver, 6.8 ± 1.7/6.9 ± 1.8; liver metastases, 15.4 ± 9.4/17.9 ± 11.4; lymph node metastases, 12.0 ± 9.5/15.2 ± 13.3; bone metastases, 7.5 ± 5.7/9.9 ± 8.0; soft-tissue metastases, 15.3 ± 16.4/17.3 ± 18.8; and primary tumors, 20.4 ± 13.7/24.23 ± 20.1. A highly significant difference (TOC higher than TATE) was found for primary tumors (P = 0.008) and liver (P = 0.000) and lymph node (P = 0.000) metastases, whereas the uptake of ^{68}Ga-DOTATOC was significantly higher in bone metastases (P = 0.011). In soft-tissue metastases, the accumulation of ^{68}Ga-DOTATOC was higher (the mean difference in SUVmax was 2.0), but it did not reach the level of significance. In normal liver, the mean difference in mean SUVmax was only 0.07 (not significant). Both radiopharmaceuticals accumulated more in primary tumors than in metastases. The highest mean SUVmax for metastases were seen in the liver and in soft-tissue metastases (without a significant difference compared with the primary tumor), intermediate in lymph nodes (significantly lower than in the primary tumor), and the lowest in bone metastases. Normal liver tissue exhibited the lowest uptake of both radiopharmaceuticals (significantly lower than in primary tumors and metastases in the liver, soft tissue, and lymph nodes). **Conclusion:** ^{68}Ga-DOTATOC has significantly higher uptake in primary GEP NET and their metastases than ^{68}Ga-DOTATATE. Both radiopharmaceuticals exhibited the highest uptake in primary tumors, which was 3-fold (^{68}Ga-DOTATATE) to 3.5-fold (^{68}Ga-DOTATOC) higher than in normal liver tissue. For both radiopharmaceuticals, liver and soft-tissue metastases demonstrated the highest uptake among the metastases, lymph node lesions were intermediate, and bone metastases showed the lowest accumulation. There was no significant difference between DOTATOC and DOTATATE accumulation in normal liver tissue. The higher uptake of ^{68}Ga-DOTATOC in primary tumors and metastases could be beneficial when a theranostic approach is considered.

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Tuning the chemical properties of AAZTA as Ga(III)-binder ligand. I. Tóth[1], A. Vágner[1], E. Brücher[1], L. Tei[2], Z. Baranyai[1]; [1]University of Debrecen, Debrecen, Hungary, [2]Dipartimento di Scienze dell'Ambiente e della Vita Università del Piemonte Orientale, Alessandria, Italy

Objectives: Although the ^{68}GaDOTATOC shows remarkably good diagnostic parameters, the accessibility of ^{68}Ge/^{68}Ga generators (*1*) renewed interest for new bifunctional ligands. The metal binding entity of such a ligand has to form thermodynamically stable and kinetically inert complex with Ga(III), and it should be (easily) conjugated to a biological vector for selective delivery. All requirements are fulfilled by the semimacrocyclic AAZTA ligand (*2*). Here we propose a cyclohexyl derivative, Cy-AAZTA, as metal binder of Ga(III). **Methods:** The equilibrium properties of Cy-AAZTA with several metal ions were studied by pH potentiometry, UV-VIS-, ^{1}H- and ^{71}Ga-NMR. The kinetic inertness of Ga(Cy-AAZTA) complex was studied by following the exchange reaction with Cu^{2+} ion in the presence of citrate ion. The kinetics of the ligand exchange reaction with transferrin was also studied in the presence $NaHCO_3$. **Results:** The stability constants of the Cy-AAZTA complexes with several metal ions are 1.5 log$K$ units smaller compared with AAZTA. The formation of Ga(Cy-AAZTA)(OH) complex is detected at pH of >6.0. The transmetallation reaction of Ga(Cy-AAZTA) complex takes place by slow dissociation of the Ga(III)-complex followed by a fast reaction between Cu^{2+} and the ligand. The rate of the ligand-exchange with transferrin at pH of 7.4 is independent of the transferrin concentration. It means that the rate-determining step is the dissociation of the complex. The increased inertness of Ga(Cy-AAZTA) can be explained by the stereochemical rigidity of the Cy-AAZTA ligand. **Conclusion:** High stability, fast formation, and slow dissociation of Ga(Cy-AAZTA) represent promising properties of Cy-AAZTA ligand to the complexation of Ga isotopes for in vivo applications. **References:** 1. Glenson GI. *Int J Appl Radiat Isot.* 1960;8:90–94. Rufini V, Calcagni ML, Baum RP. *Semin Nucl Med.* 2006;36:228–247. 2. Baranyai Z, Uggeri F, Maiocchi A, et al. *Eur J Inorg Chem.* 2013;1:147–162.

*First-place poster winner.

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Synthesis of cyclene-phosphonic acid derivatives and preliminary investigation of Ga^{3+} binding by NMR and TLC. G.S. Tsebrikova[1], V.E. Baulin[1,2], I.P. Kalashnikova[1,2], V.V. Ragulin[2], V.O. Zavelsky[2], A.Y. Maruk[3], O.E. Klementyeva[3], G.E. Kodina[3], A.Y. Tsivadze[1]; [1]Frumkin Institute of Physical Chemistry and Electrochemistry, Moscow, Russia, [2]Institute of Physiologically Active Compounds, Chernogolovka, Russia, [3]Burnasyan Federal Medical Biophysical Center, Moscow, Russia

Objectives: Searching for new easy prepared ligands for fast and efficient ^{68}Ga binding is an actual problem. Cyclene-phosphonic acid derivatives are traditionally considered as promising components of bone imaging radiopharmaceuticals. **Methods:** Cyclene-phosphonic acid derivatives 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis(methylenephosphonic acid) (**1**), ((1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetrakis(ethane-2,1-diyl))tetraphosphonic acid (**2**), ((1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetrakis(propane-3,1-diyl))tetraphosphonic acid (**3**), and 1,4,7,10-tetraazacyclododecane-1-(2-pyridylmethyl)-4,7,10-*tris*(methylenephosphonic acid) (**4**) were synthesized through a short and efficient synthesis. For Ga^{3+}-binding estimation with **1–4**, the ligand interaction with $Ga(NO_3)_3$ was studied by ^{1}H, ^{31}P, and ^{13}C NMR spectroscopy. The yield of the labeling reaction of compounds **1–4** with ^{68}Ga was determined by thin-layer chromatography (TLC). **Results:** The changes observed in NMR investigations give the evidence of fast and effective Ga^{3+} complexation with ligands with a quantitive yield. As an example, the interaction of Ga^{3+} with **1** at pH 7.5–8 leads to a reduction of the free ligand signal and to the appearance of two new narrow peaks of the Ga complex. The influence of the buffer solution nature, pH, concentration of the ligand, and reaction temperature on the yield of ^{68}Ga labeling was examined in different chromatography systems. **Conclusion:** Ligands for efficient binding of ^{68}Ga were synthesized. An NMR procedure for preliminary testing of PET candidates was investigated. Biodistribution studies on small animals will be accomplished soon. **Acknowledgment:** This work was financially supported by the Russian Foundation for Basic Research (Grant No. 14-03-00100_a).

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Initial evaluation of ^{68}Ga-DOTA-en-pba as a PET imaging reporter. T. Tsotakos[1], S. Geninatti-Crich[2], C. Tsoukalas[1], S. Xanthopoulos[1], M. Paravatou-Petsotas[1], A. Gaitanis[3], C.D. Anagnostopoulos[3], S. Aime[2], R. Jiménez[4], K. Djanashvili[4], P. Bouziotis[1]; [1]Radiochemical Studies Laboratory, Institute of Nuclear and Radiological Sciences, Technology, Energy, and Safety (I.N.Ra.S.T.E.S.), N.C.S.R. "Demokritos," Athens, Greece, [2]Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy, [3]Biomedical Research Foundation of the Academy of Athens (BRFAA), Athens, Greece, [4]Biocatalysis and Organic Chemistry, Delft University of Technology, Delft, The Netherlands

Objectives: Alterations in glycosylation, caused by an increased expression of sialyltransferases, of cell surface proteins and lipids is frequently associated with tumorigenic and metastatic processes. The result is glycosylation of exposed glycans with anionic monosaccharide sialic acid residues (Sia). Numerous studies have demonstrated that Sia are relevant biomarkers of metastatic activity of tumors, and that the amount of Sia expression on cancer cells correlates with the prognosis of patients. Subsequently, probes that can

non-invasively visualize Sia in vivo present particular research interest. Phenylboronic acid can selectively form five- and six-membered cyclic boronate esters with the exocyclic polyol function of Sia. DOTA conjugated to the targeting vector (phenylboronic acid moiety) is a versatile chelator that allows labeling of the molecule with trivalent metals such as Gd^{3+} for MR imaging or radioactive tracers for PET/SPECT imaging. The aim of our study was the radiolabeling and preliminary ex vivo and in vivo evaluation of a phenylboronic acid derivative DOTA-en-pba with the PET tracer ^{68}Ga. **Methods:** For a typical preparation of ^{68}Ga-labeled DOTA-en-pba, the imaging reporter (50 µg) was mixed with sodium acetate buffer, pH 3.6, and 200 µL of ^{68}Ga eluate (~80 MBq) were consequently added. The mixture was then incubated for 1 h at 90°C. Radiochemical purity was determined by HPLC, using a gradient system for elution. In vitro stability of ^{68}Ga- DOTA-en-pba was assessed in saline and serum, up to 3 h. In vitro cell binding experiments were performed on B16 melanoma cells, in order to assess the targeting capability of ^{68}Ga-DOTA-en-pba to the sialic acid residues found on tumor cells. The in vivo behavior of the radiolabeled compound was evaluated in athymic SCID mice bearing B16 melanoma tumor. Each mouse received 6.8 nmol/1 MBq ^{68}Ga-labeled DOTA-en-pba, which was administered intravenously via the tail vein. The biodistribution study was performed at 30, 60, and 120 min postinjection. Imaging studies were performed on a nanoScan PET/CT imaging system. **Results:** The imaging reporter DOTA-en-pba was successfully labeled with gallium-68 at high radiochemical purity (≥98%) after heating at 95ºC for 20 min. The radiolabeled complex was stable in saline at RT up to 3 h. Serum stability studies showed that the complex remained almost completely intact after 3 h incubation. Further assessment was not possible, due to the short half-life of Ga-68. Biodistribution studies in B16 tumor-bearing SCID mice showed significant blood clearance at the time points studied. The excretion route was primarily via the urinary tract, as no significant liver and intestinal uptake is observed. Apart from the kidneys, no major uptake in all analyzed tissues is observed (≤2% ID/g from 30 min p.i.). Uptake in the tumor peaked at 60 min p.i. (6.36 ± 2.41 %ID/g) and decreased at 120 p.i. (2.96 ± 0.77 %ID/g). However, the tumor-to-blood ratio increased from 60 to 120 min (1.8 and 3.9, respectively), showing a clear differentiation between the affected and the non-affected tissue. The acquired PET images were in accordance with the ex vivo biodistribution results. **Conclusion:** The complexation of paramagnetic gadolinium ions to the imaging reporter DOTA-en-pba permits its monitoring by MRI. We have shown that DOTA-en-pba can also be easily labeled with the positron emitter Ga-68, thus leading to a potential dual-modality PET/MRI imaging agent.

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Clinical impact of ^{68}Ga-DOTATATE in patients with neuroendrocrine tumors. M. Tuncel, S. Kilickap, E. Akdemir; Hacettepe University, Ankara, Turkey

Objectives: The introduction of ^{68}Ga-DOTA-peptide PET-CT for the evaluation of neuroendocrine tumors (NETs) has significantly improved the diagnostic workup and showed higher sensitivity and specificity than conventional imaging (CI) modalities (ultrasound, CT, endoscopy, and MRI) and somatostatin receptor scintigraphy (SRS). However, the clinical impact of ^{68}Ga-DOTA-peptide PET-CT in patient management has yet to be determined. We aimed to evaluate the impact of ^{68}Ga-DOTATATE PET-CT in our patients with NETs. **Methods:** The clinical and imaging data of 51 consecutive patients (20 males, 31 females; age range, 19–80; mean, 55 years) with a diagnosis of known NET (5 carcinoid, 2 pheochromocytoma, 2 paraganglioma, 3 medullary thyroid carcinoma, and 2 poorly differentiated and 37 well-differentiated gastroenteropancreatic NET) were studied. All patients underwent ^{68}Ga-DOTATATE PET-CT imaging for staging (n = 5), restaging (n = 40), and suspected recurrence (n = 6). PET-CT scans were obtained 60 min after the intravenous injection of about 148 MBq (120–185 MBq) of ^{68}Ga-DOTATATE using a dedicated PET-CT tomograph (Discovery ST; GE Healthcare) from the skull base to the midthigh. PET scan emission images were recorded for 3 min per bed position in the 3D mode using the Discovery ST. All images were corrected for scatter, randoms, dead time, and decay. Low-dose CT was used for attenuation correction and anatomic localization. The number, size, localization, and SUVmax of the lesions were noted, and ^{68}Ga-DOTATATE PET-CT results were compared with CI results from a median of 22 days (range, 2–60) without therapy. For the evaluation of PET studies, any area with an intensity greater than background that could not be identified as physiologic activity (pituitary gland, spleen, liver, adrenal glands, and head of the pancreas) was considered to indicate tumor tissue. As a standard of reference, clinical and imaging follow-up data were used (14 mo; range, 9–48 mo). Both PET-CT and CI images were interpreted together by a medical oncologist in another session to determine the clinical impact of ^{68}Ga-DOTATATE PET-CT. **Results:** In 10 patients, ^{68}Ga-DOTATATE PET-CT detected additional lesion sites (13 lesion sites in 10 patients) not detected by CI (3 endobronchial, 5 lymph node, 2 intestinal, and 3 bone; median SUVmax, 7 [3–16]; lesion size, 10 mm [5–20]). In lesion sites detected by both modalities, PET-CT detected more lesions than CI (total lesions, 353 for CI and 488 for PET-CT; $P < 0.001$). The SUVmax of lesions were higher in patients in whom more lesions were seen by PET-CT (median SUVmax, 5.5 vs. 20; $P < 0.0001$). Twelve patients referred for restaging were interpreted as having no evidence of recurrent or residual disease by both PET-CT and CI (95% diagnostic CT, 5% MRI). In 16 patients, although detecting malignant lesions, ^{68}Ga-DOTATATE PET-CT had no clinical impact over CI. ^{68}Ga-DOTATATE PET-CT changed clinical management in 23/51 patients (45%): peptide receptor radionuclide therapy (PRRT) was chosen for 2 patients instead of surgery due to systemic disease, PRRT was chosen for 1 patient instead of local ablative therapy for the liver due to systemic disease, 2 patients underwent surgery instead of follow-up with a somatostatin analogue, PRRT was considered as systemic therapy in 8 patients due to high (tumor/liver SUVmax, >2.5) radiotracer uptake, and PRRT was prevented in 10 patients due to radiotracer uptake lower than liver. **Conclusion:** ^{68}Ga-DOTATATE PET-CT had a major clinical impact in 45% of patients with NETs. It detected more lesions than CI, especially in patients with high radiotracer uptake. Our results indicate the use of ^{68}Ga-DOTATATE PET-CT as a mandatory procedure to guide patient management.

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Characterization of ^{68}Ge/^{68}Ga ITG GmbH generators and their long-term validation. I. Tworowska[1], M. Schultz[2], D. Ranganathan[1], S. Thamake[1], E. Delpassand[1], K. Zhernosekov[3], S. Marx[3]; [1]RadioMedix Inc., Houston, TX, [2]University of Iowa, Iowa City, IA, [3]ITM Isotopen Technologie, Garching, Germany

Objectives: There is a growing interest in the use of generator-produced gallium-68 (^{68}Ga) for clinical and research applications. The goal of this study was to validate the efficacy and reliability of ^{68}Ge/^{68}Ga generators ITG GmbH on the basis of long-term QC of ^{68}Ga-eluate and the generator's performance during the preparation of 200 doses of ^{68}Ga-DOTATATE. **Methods:** We evaluated 3 different generators loaded with 1,110 MBq of ^{68}Ge. The ^{68}Ge/^{68}Ga generators were eluted manually using 0.05 N HCl by fractioned elution (1 mL) or by collecting the entire 4-mL volume. The amounts of ^{68}Ga eluted from the generator and ^{68}Ge content in the final dose were monitored over a period of 10 months. Several anion-exchange and cation-exchange resins have been tested to determine their efficacy for ^{68}Ga preconcentration. The QC validation of eluate included RCY of elution, ^{68}Ge breakthrough, metal content, sterility, and radiochemical yields of absorption and desorption of ^{68}Ga from resins. **Research:** The generators loaded with 1,110 MBq of ^{68}Ge produced activity of 932–954 MBq of ^{68}Ga. The yield of ^{68}Ga elutions was 84%–86% (decay-corrected). The percentage adsorption of ^{68}Ga concentrated on the ion-exchange-resins was >81% for all of the tested resins. The % desorption of ^{68}Ga from these resins varied from 54% to 83%, with the highest yield achieved for the StrataSCX. Overall, all of examined resins can be applied for preconcentration of ^{68}Ga if it is required because of the kinetics of labeling-reaction. There is no need to purify ^{68}Ga eluate to achieve acceptable radiochemical QC objectives for the production of clinical doses of Ga-DOTATATE using the ITG generator. The guaranteed shelf-life of the ITG generators is 12 months, RCP of eluate >95% Ga^{3+} and RNP >99.9% of Ga^{68}, and endotoxin level <100 EU/eluate. ^{68}Ge content was 0.0026 ± 2E–03% on average. **Conclusion:** The reliable performance profile of the ITG GmbH ^{68}Ge/^{68}Ga generator, the low level of ^{68}Ge content, and the absence of metal content in the eluate simplify the protocol for research and clinical dose preparation.

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Case report: glioblastoma imaging and therapy with $^{64}CuCl_2$. G. Valentini[1], P. Panichelli[1], C. Villano[2], G. Pigotti[1], D. Martini[1], B. Giacobbi[1], D. Coccetti[1]; [1]ACOM S.p.A., Montecosaro, Località Cavallino, Italy, [2]U.O.C. Medicina Nucleare Ospedale Civile "Spirito Santo," Pescara, Italy

Glioblastoma is one of the most malignant and aggressive types of brain tumors, with an average life expectancy of less than 15 months. Our aim was to demostrate the capability of $^{64}CuCl_2$ to obtain both diagnosis and therapy with PET/CT imaging for radiotargeted molecular therapy in patients with glioblastoma. We introduced this new product for the following reasons: as shown in previous experimental data, glioblastoma needs copper for cellular metabolic activities, and ^{64}Cu is able to link to DNA and destroy tumor cells thanks to its Auger effect. In fact, it is characterized by high linear energy transfer (LET) in a small spatial region that can crash the cell. We report a particular case of a 71-year-old man with a cerebral craniotomy (November 2010) for a glioblastoma in the left Rolandic region. In spite of surgery, the patient showed severe epilepsy, with difficult gait (lower-limb palsy), nonfluent speech, and urinary incontinence. Moreover, he had no exact and real thought movement nexus. He underwent complete radiation therapy and a partial chemo treatment due to his pharmaceutical intolerance. Prior to the patient's consent, $^{64}CuCl_2$ PET/CT was evaluated in four different treatments, planned every 3 months. Two to 3 hours after an 80-mCi dose injection, PET/CT acquisition was performed according to the cerebral protocol (15-min length with 128 × 128 matrix) (Biograph 6 Truepoint PET/CT; Siemens). $^{64}CuCl_2$ scans showed a marked volume reduction along all three sections (axial, coronal, and sagittal): 1.42 cm, 2.6 cm, and 1.5 cm. Also verified was the capability of $^{64}CuCl_2$ to cross the blood-brain barrier (BBB) and to link cellular DNA. The patient's life expectancy has been carried up to 15 months after tumor diagnosis with enhanced quality of life. Actually, the man is able to walk, to chew and swallow, and to speak, and his epilepsy crises are shorter, milder, and few and far between. These results are very promising, but we need to extend this study to other patients to evaluate the real usefulness of $^{64}CuCl_2$ in glioblastoma diagnosis and therapy, mainly in pediatric populations, in which it would be possible to obtain three-times-greater efficacy.

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Performance characteristics of ITG Ge-68/Ga-68 generator and establishment of INDs for ^{68}Ga-DOTATOC and ^{68}Ga-PSMA-HBED-CC: the NYP–Weill Cornell Medical Center Experience. S. Vallabhajosula, A. Amor-Coarasa, J. Babich; New York Presbyterian Hospital–Weill Cornell Medical College, New York, NY

Objectives: Several $^{68}Ge/^{68}Ga$ radionuclide generators (Ga-68 generator) are commercially available and use TiO_2, SnO_2, or derivatized SiO_2 as column material. They are all eluted using hydrochloric acid (of varying concentration) and thus provide cationic ^{68}Ga species ready for radiopharmaceutical syntheses. Isotope Technologies Garching GmBH (ITG) developed a generator that utilizes pyrogallol-derivatized SiO_2 as an adsorbent allowing for very dilute HCl (0.05 N) to efficiently elute Ga-68 ready (no prepurification) for peptide labeling. We evaluated the performance of this generator and established protocols and quality measures for the preparation of ^{68}Ga-labeled peptides intended for clinical studies under IND. **Methods:** A 50-mCi (1.85 GBq) ITG Ga-68 generator utilizes an IQS-Fluidic labeling module that is self-shielded for the generator and the radiochemical manipulations. The entire system is compact and was readily housed in a laminar flow cabinet to provide an ISO class-5 environment. Ga-68 elution yields and Ge-68 breakthrough were determined for elutions of 4–6 mL of 0.05 N HCl. ^{68}Ga-DOTATOC (25 μg) and ^{68}Ga-PSMA-HBED-CC (5 μg) were synthesized using GMP kits. Complete batch-release quality-control specifications were established for IND submission and IRB approvals. **Results:** Over a 6-month period, Ga-68 elution yields were >80%, and Ge-68 breakthrough was <0.001%. The total synthesis time of Ga-68-labeled peptides was ~1 h, including initial setup and all quality-control release testing. The radiochemical purity of both peptides determined by HPLC analysis was >98%. The final sterile, pyrogen-free formulation was provided in physiological saline with 10% ethanol. **Conclusions:** The ITG Ga-68 generator contained within the IQS-Fluidic labeling module is compact, self-shielded, and easy to operate using simple manual techniques. The system provides radiolabeled peptides with high RCP with acceptable Ge-68 levels. Both IND radiolabeled peptides are approved for clinical research studies.

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PET/CT imaging of neuroendocrine tumors with the use of radiolabeled peptide analogues: the role of ^{68}Ga-DOTATATE. M. Vangu, N. Mkhize, L. Louw, K. Purbhoo; University of the Witwatersrand, Johannesburg, South Africa

Objectives: Neuroendocrine tumors (NETs) are today known as a heterogeneous group of different tumors that arise from neuroendocrine cells. The diagnosis of these tumors is nowadays enhanced by the presence of some neuroendocrine markers, and particularly the presence of chromogranin A. Furthermore, functional imaging plays an important role on the management of patients with NETs, particularly for diagnosis, staging, and restaging. Currently, the role of PET tracers for functional imaging in patients with NETs is well recognized. ^{68}Ga- DOTATATE is one of the most prominent radiopharmaceuticals that is used in imaging neuroendocrine lesions that may overexpress somatostatin receptors. **Methods:** We retrospectively reviewed imaging of patients referred from September 2010 to October 2014 who underwent PET/CT imaging with ^{68}Ga-DOTATATE for the diagnosis, staging, or restaging of NETs. All images were evaluated visually and the maximum standardized uptake value (SUVmax) was used for quantification of the tumor activity. **Results:** There were 133 patients, 85 were females (63.91%) and 48 were males (36.09%), and their ages ranged from 4 to 85 years old (mean, 53.32 ± 15.03). The indications for referral were as follows: diagnosis (36%), staging (22%), and restaging (42%). Positive imaging findings were seen in 56% of patients, negative findings in 42%, and equivocal findings were seen in 2% of patients. No significant correlation ($P = 0.06$) was found between positive biomarkers and positive imaging findings (chi-square and Fisher exact tests). The detailed analysis of the findings showed that 79% of patients with NETs had positive findings against only 20% for those with suspected NETs. **Conclusions:** ^{68}Ga-DOTATATE PET/CT imaging appears to be a good metabolic imaging modality in patients with known NETs. In this review, the imaging modality did not perform well when there was only a suspicion of NET.

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Joining the theranostics league: preliminary data from the Johannesburg early experience. M. Vangu, K. Purbhoo, N. Mkhize, L. Louw, N. Malan; University of the Witwatersrand, Johannesburg, South Africa

Objectives: The management of patients with inoperable or metastasized neuroendocrine tumors (NETs) with the use of radiolabelled somatostatin analogues is increasingly gaining popularity. Promising results are obtained with ^{177}Lu- DOTA-D-Phe1-Tyr3-Thr8-octreotide (DOTATATE) in terms of both tumor regression and reduction of hormonal overproduction. The term theranostics has been coined to represent the combined diagnosis and therapy that uses somatostatin analogues for personalized management of patients who are selected to undergo peptide receptor radionuclide therapy (PRRT). **Methods:** Since November 2013, we have introduced the use of ^{177}Lu-DOTATATE and administered 11 cycles in seven patients with NETs, and one patient has already received four cycles. By the end of February 2015, we expect to administer 17–19 cycles, excluding potential treatment in new patients who will be referred for PRRT. All patients undergo ^{68}Ga-DOTATATE prior to PRRT and their renal functions and hematological status are assessed. The Karnofsky performance score (KPS) and the ECOG scale are included in the selection of patients for PRRT. Gamma imaging following each cycle of PRRT is done to confirm the uptake of ^{177}Lu-DOTATATE in the previously detected lesions at the time of therapy and also to allow dosimetry. Follow-up imaging with ^{68}Ga-DOTATATE is performed after the second and the fourth cycles. Different from other centers, we give all our patients oral lysine an hour before the administration of ^{177}Lu-DOTATATE in an attempt to protect their kidneys. **Results:** We will present the preliminary data of early experience in Johannesburg on PRRT in NETS and demonstrate the feasibility for this personalized therapy at any geographic location when standards and resources permit. Analysis of the following will be presented: KPS and ECOG status, total dose administered, tumor uptake on ^{177}Lu-DOTATATE gamma imaging, presence or absence of side effects, and the status and numbers of visualized lesions on sequential ^{68}Ga-DOTATATE imaging. **Conclusion:** A conclusion will be drawn from the analysis of the results.

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Lutetium-177 (^{177}Lu) dosimetry in patients treated for neuroendocrine tumors (NETs) in Johannesburg, South Africa. B. Van Wyk, M. Vangu, K. Purbhoo; University of the Witwatersrand, Johannesburg, South Africa

Objectives: Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE is an important option in the treatment of neuroendocrine tumors (NETs). However the absorbed dose to the tumor is limited by the irradiation of the kidney and red marrow. The kidney especially is a major concern, and this is due to the variations in patients' maximal specific and non-specific kidney uptake and washout. The gamma-decay scheme of ^{177}Lu allows for immediate imaging. This is very important as one may take patient images after injection and perform the kidney dosimetry. **Methods:** This is a retrospective and prospective study in nine patients, five females and four males (age, 36–68; mean age, 54.2). The dose usually administered is 740 MBq, and each patient is planned to receive four to six cycles at three-month intervals. Practically a patient may receive up to six cycles of 740 MBq each, as determined by the treating physician. Seven of the nine patients have already received at least one therapeutic dose (one with completion of the traditional four cycles). Patients will undergo whole-body ^{177}Lu-DOTATATE scanning, and SPECT acquisition will also be used whenever possible. We will determine the kidney dose as well as any difference when using these two imaging acquisition techniques. **Results:** The TAC (obtained from using data from Image J) of all patients will be drawn using the trapezoidal method and the kidney dose determined using the S-factor from the OLINDA program. Results of the doses received by the first five patients have shown an average dose of 0.15 Gy to the kidney. The full data on the nine patients will be presented at the congress. **Conclusion:** We expect to present the results on our limited study for the determination of the kidney dosimetry in patients receiving single or multiple cycles of PPRT with ^{177}Lu-DOTATATE in Johannesburg, South Africa.

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^{68}Ga-based homodimeric barbituates: a potential diagnostic ligand for GABA receptor imaging. R. Varshney, S. Rangaswamy, A.K. Mishra; Division of Cyclotron and Radiopharmaceutical Sciences, Institute of Nuclear Medicine and Allied Sciences, New Delhi, India

Objective: The functional expression of $GABA_A$ receptors has been implicated in the pathogenesis of a wide range of neurological and psychiatric diseases, i.e., epilepsy, anxiety, depression, schizophrenia etc. Phenobarbital, thiopentalbarbital, and pentobarbital are found to possess good affinity and are selective for $GABA_A$ receptors. Out of the 3 barbitals, pentobarbital has been found to possess more affinity for apoferritin, is more flexible, and is less polar, which in turn enhances its affinity for GABA receptors. We have developed a novel PET radioligand ^{68}Ga-DO3A-EPB. **Methods:** Diethyl-2-ethylmalonate was derived using 5-bromovaleronitrile to give diethyl-2-(4-cyanobutyl)-2-ethylmalonate with the yield of 97%. The condensation reaction between malonate derivate and urea yielded pentobarbital with a good yield of 88%. Two units of pentobarbital were conjugated with glutamic acid, and the amine part of glutamic acid was functionalized with 2-bromoethyl-4-methylbenzenesulfonate to give a final ligand. This bis derivative was conjugated with DO3A using bromoacetylbromide to yield 2,2′,2″-(10-(2-((1,5-bis((5-(5-ethyl-2,4,6-trioxohexahydropyrimidin-5-yl) pentyl)amino-1,5-dioxopentan-2-yl)amino-2-oxo-ethyl)-1,4,7-triyl) triaceticacid (DO3A-EPB) with a 78% yield. The radiolabeling efficiency was found to be >97%, and the stability in serum indicated that ^{68}Ga remained bound to the conjugate under physiological conditions. **Results:** The synthesized ligand has been characterized by different spectroscopic techniques (NMR and mass). Radiolabelling efficiency was achieved at more than 97%, and the radioconjugate did not exhibit any dissociation under physiological conditions. The biological evaluation is under progress. **Conclusion:** A homodimeric ligand system with reasonable pharmokinectics for GABA receptors was designed and developed. The stability and suitability as a radioimaging agent holds a promising future in imaging GABA receptors for the treatment of neuropathological disorders.

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^{68}Ge/^{68}Ga generators and tracer production. I. Velikyan; PET Centre, Centre for Medical Imaging, Uppsala University Hospital, Uppsala, Sweden

The blossoming of ^{68}Ga utilization is reflected in the exponential growth of the publications, and the potential scope is rather extensive covering targeted, pretargeted, and nontargeted imaging. Targeted imaging in oncology provides tumor-type specific noninvasive diagnosis with precise localization of lesions. Most importantly it has the potential for pretherapeutic quantification of receptor status, uptake kinetics, and dosimetry that enables accurate selection and planning as well as monitoring response to the therapy resulting in personalized medicine and, in particular, radiotheranostics. Clinical intrapatient studies with variable amounts of the injected ^{68}Ga-agents demonstrated importance of individualized patient management. Diagnostic imaging, e.g., of insulinoma, prostate cancer, bone metastases, lung malignancies, invasive ductal carcinoma, and pulmonary embolism, were proven feasible using various ^{68}Ga-based imaging agents. The majority of the radionuclides commonly used in PET, SPECT, and radiotherapy are metal elements sharing coordination chemistry. The key feature of ^{68}Ga is its production in a generator system. It should be mentioned that the generator production is one of the reasons why Tc-99m stands for 80% of all nuclear medical procedures worldwide. Another reason is that the labelling coordination chemistry allows for kit formulation. The vast experience of Tc-99m might be translated to ^{68}Ga with the added value of higher sensitivity, resolution, quantification, and dynamic studies. The majority of the therapeutic radionuclides are also metals thus allowing for the radiotheranostic development wherein the pretherapeutic imaging and radiotherapy are conducted with the same vector molecule exchanging the imaging and therapeutic radionuclides. The advantages of ^{68}Ga are multiple. It is available from a long shelf-life generator that is simple in use and is a steady source of the radionuclide for medical centers without cyclotrons or remote from distribution sites. Moreover, it is a source of the enrichment of radio-pharmaceutical arsenal at centers equipped with cyclotrons. The high positron emission fraction and half-life of 68 min provides sufficient levels of radioactivity for high-quality images while minimizing the radiation dose to the patient and personnel. It requires a short scanning time and allows for repetitive examinations. In modern generators ^{68}Ga is obtained in ionic form compatible with subsequent highly reproducible and straightforward labelling chemistry. The diversity of ^{68}Ge/^{68}Ga generators currently available on the market is a result of an over six-decade journey starting with the first liquid-liquid extraction generator system and simple radiopharmaceuticals for clinical application. Further development was directed toward column-based generators providing cationic ^{68}Ga with the first commercial one around 2000 that together with the advent of SST ligands contributed to the progress of the ^{68}Ga/PET. The first generator of pharmaceutical grade appeared on the market in 2014, and more generators are on their way to the market and marketing authorization acquisition. Historically there have been two basic Ge-Ga separation methods: liquid-liquid extraction and column technology. The latter is most widely used with various sorbents either inorganic or organic. The relation of the Ge-68 decay and ^{68}Ga accumulation is described by secular equilibrium regulating the frequency of the elution and tracer production. Such parameters as separation specificity, radiation resistance, and chemical stability of the column material, eluate sterility and Ge-68 content, eluent type and elution profile are considered in the development of the generators. ^{68}Ge/^{68}Ga generator meets the criteria of an ideal generator in terms of efficient separation, physical half-life of parent allowing rapid daughter regrowth, and stable granddaughter with no radiation dose to the patient. However, long shelf-life may raise concern with regard to radiolytic stability of column material, sterility of the eluate, and Ge-68 waste management. These aspects were investigated. The use of the generator should meet GMP requirements. The currently available document to adhere to is the Ph. Eur. monographs. The limit of Ge-68 breakthrough of 0.001% defined in the monograph was estimated assuming high and infinite accumulation of the radionuclide in sensitive organs such as bone marrow. However, experimental evidence from organ distribution of ^{68}Ge(IV) in rats with subsequent extrapolation and estimation of human dosimetry parameters indicated the possibility of at least a 100-fold enhancement of the limit. This finding together with the absence of Ge-68 complexation with DOTA derivatives and binding to plasma proteins may facilitate the development of kit-type preparation of ^{68}Ga-based imaging agents. However, currently the production process of ^{68}Ga-tracers falls under the GMP manufacturing category rather than registered radiopharmaceutical preparation and thus both generators with and without marketing authorization should be considered for clinical use. Such disadvantages as large ^{68}Ga eluate volume, contamination with long-lived parent nuclide ^{68}Ge, and also metal cations that might compete ^{68}Ga in the complexation reaction were overcome by either fractionation or concentration/purification of the generator eluate. A common advantage of the concentration/purification methods is the possibility of using several tandem generators or eluates from several generators with the same final volume but enhanced

^{68}Ga amount and generator shelf-life. Various buffers and radical scavengers were investigated for the improvement of the production outcome. Metal cation and Ge-68 content can also be reduced by regular elution and elution prior to the synthesis. The preelution is especially important in order to reduce the content of the ^{68}Ga decay product and stable Zn(II) that continuously accumulates in the generator column. The influence of various metal cations on ^{68}Ga complexation with various chelators was studied and development of chelators with high specificity toward Ga(III) was considered. However, the choice of the chelator is essential not only from the efficient chemistry point of view but also in the context of the radiotheranostics wherein the chelator that is suitable for both imaging and therapeutic radionuclides might be more preferable. The selection of the synthesis procedure depends on the requirement of the tracer in terms of specific radioactivity that in turn depends on the application. A number of in vitro, ex vivo, and in vivo preclinical as well as clinical studies indicated the necessity of specific radioactivity optimization for the relevant in vivo performance in terms of accurate quantification, target uptake, and image contrast. The advantages of the automated production are multiple. A number of standard, custom made or in-house built synthesizers based on either stationary tubing systems or disposable cassette systems were developed. Cassettes for the production of various ^{68}Ga-tracers for clinical use are commercially available. In conclusion, the market of generators and automated synthesis systems is expanding. The development of kit-type preparation is feasible. ^{68}Ga has proved its potential to facilitate development of clinically practical PET and worldwide promote the PET technique for earlier better diagnostics and individualized medicine. Production automation may provide the possibility for harmonized and standardized multicenter clinical studies that in turn will accelerate the introduction of new radiopharmaceuticals as well as their regulatory approval. The diversity and clinical applications of ^{68}Ga-based agents are expanding offering benefits of high sensitivity, resolution, quantification, and personalized medicine.

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Biological evaluation of Ga68-labeled click conjugate for targeting of metastatic melanoma. N.K. Wagh[1], S. Thamake[2], J. Reedy[3], D. Ranganathan[1], E.S. Delpassand[1,2], M.K. Schultz[3], I. Tworowska[1,2]; [1]Radio-Isotope Therapy of America (RITA) Foundation, Houston, TX, [2]RadioMedix Inc., Houston, TX, [3]University of Iowa, Iowa City, IA

Objective: Glucose is the preferred energy substrate for cellular metabolism. Cancerous cells grow and multiply faster than normal cells, resulting in higher demand for glucose as a source of energy. Cancerous cells show higher glycolytic rate in the metabolic process than normal cells. The higher uptake of glucose in tumor cells is regulated through glucose transporters (GLUT), especially through GLUT1. Our objective is to evaluate glucosamine click conjugate to target cancer cells through GLUT1 transporter. **Methods:** Glucosamine click conjugate (RMX-GC-08) was synthesized by a two-step process according to a protocol described previously (*1*). The structure was validated using LC-MS and ESI. RMX-GC-08 was radiolabeled with gallium 68 (^{68}Ge/^{68}Ga generator; ITG GmBH, Germany), purified using C18 Sep-pak resin, and analyzed using ITLC and radio-HPLC prior to in vitro studies. In vitro competitive uptake and internalization studies of the radioconjugate was assessed using the human melanoma cancer cell, B16, MeWo, and A351 cell lines at various time points and concentration of GLUT1 competitors. **Research:** The analysis of RMX-GC-08 conjugate by rHPLC (Rt, 28 min) and LC-MS mass spectroscopy confirmed the identity of the product. RMX-GC-08 was obtained in 31% yield with more than 95% purity on analytic HPLC. Radiolabeling of RMX-GC proceeded with 100% radiochemical yield and with specific activity of 0.5 ci/mg. The uptake studies confirmed GLUT1-specific accumulation of radiotracer in cancer cells with uptake ranging from 4.5–8 %ID/mg during the first 2 h of incubation. The RMX-GC uptake was decreased in the presence of GLUT1 competitor (glucose, glucosamine, cytochalasin B) by 40%–80% depending on concentration of agent and time of incubation. Time-dependent accumulation (2–4 h) of radiotracer showed at least a 2-fold increase of the uptake of Ga68-RMXGC-08. Preliminary biodistribution of RMX-GC-08 in the B16 melanoma xenograft mouse model showed tumor retention of 4.3 ± 0.7 %ID/g at 1 h with a tumor/muscle ratio of 2.02. **Conclusion:** On the basis of the in vitro studies RMX-GC-08 shows higher uptake in melanoma cancer cell line with highest values for MeWo cell line. These results provide a crucial starting point for optimizing glucosamine click conjugates for targeting tumor cells that express GLUT1 transporters and their further validation as theranostic agents. **Acknowledgment:** This work was supported by NIH/NCI grant 1R43CA186364-01. **Reference:** 1. Thamake S, Ranganathan D, Tworowska I, Delpassand E. In vivo validation of novel GLUT-1 targeting click-conjugates [abstract]. *J Nucl Med.* 2013;54:1081.

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^{68}Ga-DATATOC: synthesis, radiolabeling, and first in vivo studies. B. Waldron[1], J. Seemann[1], R. Bergmann[2], J. Nagel[1], F. Roesch[1], J.P. Sinnes[1]; [1]Johannes Gutenberg University, Mainz, Germany, [2]Helmholtz Center, Dresden-Rossendorf, Germany

Objectives: ^{68}Ga-DOTATOC is currently used as the industry standard for diagnostic imaging of NETs and its metastases. Radiolabeling can be performed manually and automated at 95°C. In order to approach the application of ^{68}Ga following a kit-type procedure, a DATA-based chelator (6-amino-1,4-diazepine-triacetate) was used in the study as it has shown to radiolabel under very mild conditions. Conjugation with TOC to afford a DOTATOC analog may enable radiolabeling of the peptide at room temperature. **Methods:** DATATOC was synthesized in a seven-step synthesis. Radiolabeling with ^{68}Ga was performed manually at room temperature, and stability was assessed in human serum. An automated setup was also examined, using the Modular-Lab eazy (Eckert & Ziegler, Berlin, Germany). First in vivo studies using MPC-mCherry tumor–bearing mice were performed and compared with DOTATATE. **Research:** Radiolabeling was performed at room temperature using N_2 solution, NaOAc buffer, and 14 nmol DATATOC. An RCY of 96.3% ± 1.2% was obtained within 3 min. Stability was tested in human serum over a period of 2 h (Δ, 1.3%). Automated labeling with a 23 nmol precursor achieved quantitative complexation of ^{68}Ga. In vivo PET/CT studies with ^{68}Ga-DATATOC indicate a high specific uptake in the tumor region after 10 min (SUV of 3.73 ± 1.49). In a blocking study with OC, the SUV in the tumor was reduced to 0.45 ± 0.15. In addition, ^{68}Ga-DATATOC showed high stability in mouse plasma with 93.7% of the tracer remaining intact after 120 min. Compared with ^{68}Ga-DOTATATE a faster renal excretion of the tracer was observed. **Conclusion:** DATATOC can be labeled with ^{68}Ga in a manual or automated setup rapidly at room temperature, offering significant advantages over similar DOTA-based derivatives. Furthermore, first in vivo studies confirm excellent targeting and excretion characteristics for the novel tracer. With the perspective toward a kit-type formulation, the superior characteristics of this new compound pave the way for a new generation of ^{68}Ga radiopharmaceuticals.

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Characterization of SST2-receptor binding and toxicological profile of OPS202 (Nodaga-JR11) diastereomers. B. Waser[1], J.C. Reubi[1], H. Bouterfa[2], H. Mäcke[3], J. Kaufmann[2]; [1]Division of Cell Biology and Experimental Cancer Research, Institute of Pathology, University of Bern, Bern, Switzerland, [2]OctreoPharm Sciences GmbH, Berlin, Germany, [3]Department of Nuclear Medicine, University Hospital Freiburg, Freiburg, Germany

Objectives: The specific binding capacities of the two diastereomers of the antagonist (*S*)-OPS202, (*R*)-OPS202 and the mixture (*R*/*S*)-OPS202 (OPS202 = Nodaga-JR11) to the somatostatin receptor subtype sst2 are characterized. The experiments are planned to compare the receptor-binding profiles of the single diastereomeres as well as the mixture. In addition (*S*)-OPS202, (*R*)-OPS202 and (*R*/*S*)-OPS202 were assessed in an extended single-dose toxicity study administered in Wistar rats to indicate the existence of possible hazards likely to arise from a short-term exposure. **Methods:** The diastereomeric mixture of (*R*/*S*)-OPS202 originating from the synthesis of the JR11 peptide moiety with the enantiomeric mixture of the Nodaga(tBu3) prochelator has been separated by chromatographic methods. The binding affinities (IC_{50} values) for the control somatostatin-28 and the three samples (*S*)-OPS202, (*R*)-OPS202, and (*R*/*S*)-OPS202 were measured on the human somatostatin receptor subtype sst2A. CCL39 cells stably expressing human sst2 were used and cells grown as described previously. Cell membrane pellets were prepared, and receptor autoradiography was performed on pellet sections mounted on microscope slides. For each of the tested compounds, complete displacement experiments with the

universal somatostatin radioligand 125I-[Leu8,DTrp22, Tyr25]-somatostatin-28 (SS-28) using 15,000 cpm/100 mL and increasing concentrations of the unlabeled peptide ranging from 0.1 to 1,000 nM were performed. The unlabeled, universal somatostatin-28 was run as a control in parallel, using the same increasing concentrations. IC_{50} values were calculated after quantification of the data with a computer-assisted image processing system. Tissue standards that contained known amounts of isotope, cross-calibrated to tissue-equivalent ligand concentration, were used for quantification. The single-dose toxicity study comprised four treatment groups (n = 10) of Wistar rats, a vehicle group, and three test item groups, which underwent i. v. treatment with (*S*)-OPS202, (*R*)-OPS202, and (*R*/*S*)-OPS202 and a dose of 1.43 mg/kg API in 3mL/kg applied volume. **Research:** The compounds (*R*)-OPS201, (*S*)-OPS202, and (*R*/*S*)-OPS202 showed IC_{50} values of 4.3 ± 0.6 (n = 4), 6.2 ± 1.2 (n = 4), and 6.0 ± 0.5 (n = 4)] compared with reference compound SS-28 (IC_{50}, 2.3 ± 0.3; n = 4). The toxicological study showed no mortality in either group, and no test-item-related clinical findings were observed throughout the study period. In addition, a negative influence on body weight and food consumption was not noted, nor was there any influence on parameters of hematology, clinical chemistry, coagulation, organ weight, and histopathological findings. **Conclusions:** The single diastereomers (*R*)-OPS202 and (*S*)-OPS202 as well as the mixture (*R*/*S*)-OPS202 display a similar high affinity to the sst2 receptor in only marginally higher IC_{50} values than the reference compound SS-28. In the toxicological study no difference between the two diastereomers was observed in any parameter determined. The dose of 1.43 mg/kg OPS202 given either as a mixture or as separated diastereomers once intravenously is within the no-observed-adverse-effect-level. A different asymmetric environment of the chelator Nodaga does not influence the sstr-binding profile or the toxicological behavior of the bioactive moiety in the antagonistic compound OPS202 showing a clear potential for the translation as PET tracer into the clinic.

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Impact of ^{68}GA-DOTATATE PET/CT on the management of neuroendocrine tumors: the referring physician's perspective. E.M. Wolin[1], K. Herrmann[2], J. Czernin[2], P. Gupta[2], M. Barrio[2], A. Gutierrez[2], C. Schiepers[2], S. Mosessian[2], M.S. Allen-Auerbach[2]; [1]Markey Cancer Center, School of Medicine, University of Kentucky, Lexington, KY, [2]David Geffen School of Medicine, UCLA, Los Angeles, CA

Background: Somatostatin receptor imaging with ^{68}Ga-DOTATATE PET/CT (DOTATATE) is increasingly used for managing patients with neuroendocrine tumors. **Objective:** The objective of this study was to determine referring physicians' perspectives on the impact of DOTATATE on the management of neuroendocrine tumors. **Methods:** A set of 2 questionnaires (pre-PET and post-PET) was sent to the referring physicians of 100 consecutive patients with known or suspected neuroendocrine tumors, who were evaluated with DOTATATE. Questionnaires on 88 patients were returned (response rate, 88%). Referring physicians categorized the DOTATATE findings on the basis of the written PET reports as negative, positive, or equivocal for disease. The likelihood for metastatic disease was scored as low, moderate, or high. Intended management prior to and changes as a consequence of the PET study were indicated. **Results:** The indications for PET/CT were initial and subsequent treatment strategy assessments in 14% and 86% of patients, respectively. Referring physicians reported that DOTATATE led to a change in suspicion for metastatic disease in 21 patients (24%; increased and decreased suspicion in 9 (10%) and 12 (14%) patients, respectively). Intended management changes were reported in 53/88 (60%) patients. Twenty patients (23%) scheduled to undergo chemotherapy were switched to treatments without chemotherapy and six (7%) were switched from watch and wait to other treatment strategies. Conversely, five patients (6%) were switched from their initial treatment strategy to watch and wait. **Conclusions:** This survey of referring physicians demonstrates a substantial impact of ^{68}Ga-DOTATATE PET/CT on the intended management of patients with neuroendocrine tumors.

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Evaluation of ^{18}F- and ^{68}Ga-radiolabeled Cys^{39}-exenatide for insulinoma PET imaging. M. Yang, Y. Xu, D. Pan, L. Wang, Q. Xu, C. Zhu; Jiangsu Institute of Nuclear Medicine, Wuxi, China

Objectives: Glucagon-like peptide-1 receptor (GLP-1R) serves as an attractive target for diagnosis and therapy of insulinoma. Radiolabeled exenatide analogs allow the noninvasive assessment of GLP-1R status in vivo through PET imaging. In this study, a novel exenatide analog, cys^{39}-exendin-4, was labeled with ^{68}Ga,^{18}F-FBEM, or aluminum fluoride (Al^{18}F), respectively, and insulinoma imaging properties of these peptides were also evaluated. **Methods:** ^{18}F-FBEM–Cys^{39}-exenatide was synthesized by coupling Cys^{39}-exenatide with the prosthetic reagent,^{18}F-FBEM, through multiple steps. Malemide-NOTA (MAL-NOTA) were site-specifically conjugated to Cys^{39}-exenatide and labeled with Al^{18}F and ^{68}Ga. The GLP-1R targeting potential and pharmacokinetic profile of these tracers were analyzed in INS-1 insulinoma model, respectively. **Research:** The overall yield of ^{18}F-FBEM–Cys^{39}-exenatide was about 5% (uncorrected) with a total synthesis time of around 2 h. On the contrary, ^{18}FAl-NOTA-MAL-Cys^{39}-exenatide and ^{68}Ga-NOTA-MAL-Cys^{39}-exenatide were obtained nearly 20% and 40% yields (uncorrected), respectively, within 30 minutes. INS-1 insulinoma was clearly visualized with good tumor-to-background contrast after injection of ^{18}F-labeled Cys^{39}-exenatide analogs. ROI analysis showed that the tumor uptake of ^{18}FAl-NOTA-MAL-Cys^{39}-exenatide was slightly lower than that of ^{18}F-FBEM–Cys39-exenatide (7.74 ± 0.87 %ID/g vs. 10.01 ± 1.21 %ID/g at 1 h p.i.). The tumor-to-muscle ratios of both probes was greater than 60 at 1 h postinjection. In addition, the uptake of ^{18}FAl-NOTA-MAL-Cys^{39}-exenatide in liver was significantly lower than that of ^{18}F-FBEM-Cys^{39}-exenatide (1.04 ± 0.37 %ID/g vs. 2.10 ± 0.24 %ID/g at 1 h p.i.). Tumor uptake can be almost blocked by an overdose of exenatide, and unexpected lower radioactivities (<1 %ID/g) were observed in tumors after injection of ^{68}Ga-labeled counterpart. **Conclusion:** Preclinical studies revealed that ^{18}FAl-NOTA-MAL-Cys^{39}-exenatide possessed better performance than ^{18}F-FBEM-Cys^{39}-exenatide for insulinoma PET imaging. Though the preparation of ^{68}Ga-labeled Cys^{39}-exenatide is easy, the value needs further study. **Acknowledgments:** This work was supported, in part, by the National Natural Science Foundation (81171399, 81472749, 81401450, 51473071, 81472749, and 21401084), the Outstanding Professional Fund of the Health Ministry in Jiangsu Province (RC2011095), and the Jiangsu Province Foundation (BL2012031, BE2012622, and BE2014609).

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The prospective study of ^{68}Ga-DOTANOC PET/CT for the evaluation and management of NET: first experience in China. X.C. Yao[1], F. Wang[1], S.Y. Ai[2]; [1]Nanjing First Hospital, Nanjing Medical University, Nanjing, China, [2]No. 81 Hospital of PLA, Nanjing, China

Objectives: The aim of this prospective study was to evaluate the clinical value of ^{68}Ga-DOTANOC PET/CT in the clinical diagnosis and management of neuroendocrine tumors (NET). **Methods:** 41 patients with clinically diagnosed or suspected NET were enrolled in this study. PET/CT was performed in all patents at 1 h after injection of 111–185 MBq (3–5 mCi) of ^{68}Ga-DOTANOC, the CGA level in blood was measured in all patients, and the final diagnosis was confirmed by histopathology and clinical follow-up. **Results:** Twenty-nine patients were finally diagnosed as having GEP NET. Out of 27 patients with suspected NET—2 patients with esophagus neuroendocrine neoplasm, 1 patient with gastrinoma, 1 patient with lung NET, 1 patient with midear NET, 1 patient with small cell lung cancer, and 21 patients with GEP NET—a total of 106 lesions were found in the ^{68}Ga-DOTANOC images. Six patients were false-negative, 1 with malignant pheochromocytoma, 1 with benign pheochromocytoma, 2 patients with the hereditary syndrome of multiple endocrine neoplasia type 2A and who had a RET mutation, 1 with parathyroid cancer, and 1 with malignant adrenal cortical carcinoma. Out of 14 patients with clinically diagnosed NET, 32 lesions were found in 9 patients. The SUVmax of the primary lesion was 44.00, whereas that of the metastatic lesion was 51.4. The CGA level in true-positive patients with GEP NET was 429.1 ± 129.61,whereas that in true-negative patients was 58.10 ± 56.28. **Conclusion:** ^{68}Ga-DOTANOC PET/CT was of great value for the diagnosis of GEP NET, especially in localization of primary lesion and staging, which further guided the clinical management.

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One-step, mild efficient ^{68}Ga "cold" PET kits: performance characteristics and robustness of *tris*(hydroxypyridinone) chelators. J.D. Young[1], M.S. Cooper[1], B.M. Paterson[1], M.T. Ma[1], J.R. Ballinger[1], S. Nawaz[1], D.J. Berry[1],

R.C. Hider[2], G.E.D. Mullen[1], P.J. Blower[1]; [1]Division of Imaging Sciences and Biomedical Engineering, King's College London, St. Thomas' Hospital, London, United Kingdom, [2]Institute of Pharmaceutical Science, King's College London, London, United Kingdom

Background: The $^{68}Ge/^{68}Ga$ generator offers PET molecular imaging to hospitals without a local cyclotron and complex radiochemistry facilities if simple labelling methods can be devised (one step, room temperature, low concentration, moderate pH). No established chelators meet this challenge. However, *tris*(hydroxypyridinone) (THP) ligands such as CP256 show promise of this capability. **Objectives:** To evaluate the comparative efficiency and robustness of ^{68}Ga chelation, by CP256 and other chelators, from different generators as a function of eluate postprocessing, time, ligand concentration, temperature, pH, buffer, and metal ion contamination. **Methods:** CP256 labelling was evaluated by HPLC, TLC, and iTLC with eluates from E&Z IGG100, Obninsk, and iThemba Labs generators and with ^{67}Ga-citrate, at CP256 concentrations from 0.1 to 1,000 mM, pH values of 4–7, buffers, and different trace metal concentrations (Mg^{2+}, Fe^{3+}, and Zn^{2+}). In some cases, CP256 was compared with NOTA, DOTA, and HBED. **Results:** At 10 mM and above, 20°C, and all pH values and times, labelling efficiency of CP256 reached >95% faster (2 min) than other chelators and was unaffected by contaminating Mg^{2+}, Zn^{2+}, and Fe^{3+} at 30, 20, and 0.3 mg/L, respectively. CP256 was more tolerant of different generators, with and without preelution, than NOTA. Addition of unprocessed eluates to vials containing THP conjugates and buffers gave quantitative radiolabelling in <5 min. **Conclusions:** Uniquely, THP conjugates chelate ^{68}Ga in one step from generator eluates rapidly, with high specific activity and low concentration, under mild conditions over a wide pH range, without the need for purification, and likely tolerate trace metal contaminants.

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Finding the cloak-and-dagger tumor in the state of the art via ^{68}Ga-DOTATATE PET/CT. J. Zhang, Z. Zhu, F. Li; Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

Objectives: A novel diagnostic approach, ^{68}Ga-DOTATATE PET/CT, was evaluated for detection of the tumor-induced osteomalacia (TIO) lesions. ^{99m}Tc-HYNIC-TOC scintigraphy and ^{18}F-FDG PET/CT were used for comparison. **Methods:** From December 2011 to October 2014, a total of 113 patients (60 M, 53 F; age, 42.4 ± 12.0 years) with osteomalacia were recruited. All patients had negative finding in prior examinations including CT, MRI, and ultrasonography. The patients underwent PET/CT scans from head to toe using a Siemens Biograph 64 TrueV system 30–45 min after injection of 111–148 MBq (3–4 mCi) ^{68}Ga-DOTATATE. All 113 patients underwent ^{99m}Tc-HYNIC-TOC scintigraphy, and 111 patients accepted ^{18}F-FDG PET/CT for comparison within 2 weeks. **Results:** ^{68}Ga-DOTATATE PET/CT had positive findings in 94 (83.2%) of the 113 osteomalacia patients, while only 24 (21.2%) were positive on ^{18}F-FDG PET/CT and 31 (27.4%) were detected by ^{99m}Tc-HYNIC-TOC scintigraphy. The tumors, sized from 0.7–6.7 (2.4 ± 1.2) cm, were located in the mandible, base of the pelvic cavity, caudal vertebrae, femur, and planta pedis. For the tumors, the SUVmax of ^{68}Ga-DOTATATE (1.6–46.9; mean ± SD, 12.0 ± 8.7) was significantly higher than that of ^{18}F-FDG (1.1–20.0; mean ± SD, 4.5 ± 4.2; $P < 0.05$). Higher ^{18}F-FDG uptake was observed only in three cases with malignant TIO tumor (ki67, >50%) and multiple metastases. Until now, 65 of the 94 positive tumors were surgically removed and among them, 64 were found to be phosphaturic mesenchymal tumors, and 1 was an odontogenic fibrous tumor. So far, all 19 (16.8%) negative patients have been confirmed as true-negative, including those who eventually had diagnoses of other causes of hypophosphatemia such as Fanconi syndrome or responded well to conservative therapy. **Conclusion:** ^{68}Ga-DOTATATE PET/CT is a state-of-the-art approach for detection of the causative tumors in patients with osteomalacia.

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Can ^{68}Ga-DOTATATE replace ^{18}F-FDG PET/CT for detection of bone metastases in small-cell lung cancer? W. Zhang, Z. Zhu; Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

Objective: Small-cell lung cancer (SCLC) had a high expression of somatostatin (SST) receptor that may be used for imaging by ^{68}Ga-DOTATATE. This study aimed to compare ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT in SCLC and to investigate the relation between the two imaging agents. **Methods:** A total of 12 patients diagnosed definitely with SCLC by biopsy underwent both ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT scans. The PET/CT images were evaluated for primary and metastasis lesions with each PET tracer. Other imaging (such as post PET/CT, CT, or MRI) or further information from clinical follow-up results provided the reference standards. **Results:** Both^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT can detect the primary tumors in all of the 12 patients. For the diagnosis of bone metastases, 4 of 12 patients with confirmed bone metastases by other imaging examinations or clinical data were positive in ^{68}Ga-DOTATATE PET/CT imaging while negative in ^{18}F-FDG PET/CT imaging. Statistically significant differences were found in bone metastasis ($P = 0.001$) between the two imaging agents. However, no statistical differences were found in primary lesions ($P = 0.052$) or lymph nodes ($P = 0.387$) for ^{68}Ga-DOTATATE and for ^{18}F-FDG. **Conclusion:** ^{68}Ga-DOTATATE is sensitive for detecting SCLC lesions and may be superior to^{18}F-FDG for judging bone metastases.

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