DOTA-BI were studied in normal mice. Necrosis avidity was evaluated in a rat model of reperfused partial liver infarction by ex vivo autoradiography in correlation with histochemical staining techniques (TTC and H&E).
Results: bis-DOTA-BI was synthesized with an overall yield of 45% and radiolabelled with ^{68}Ga with a decay-corrected radiochemical yield of 44%. In normal mice, the tracer is cleared rapidly from plasma via the kidneys (41.1% and 87.7% ID in urine at 30 min and 4 h p.i., respectively) and shows a good stability with >78% of intact tracer in plasma at 90 min p.i. On ex vivo autoradiographic slices, ^{68}Ga-bis-DOTA-BI showed a 10–12 times higher uptake in necrotic liver tissue as compared to normal liver tissue, with TTC and H&E staining confirming the presence of necrosis.
Conclusions: ^{68}Ga-bis-DOTA-BI has a favourable biodistribution and is suitable as a tracer for imaging of necrosis.

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In vitro evaluation of ^{68}Ga-Schiff bases for myocardial imaging

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Aims: Coronary artery disease is the most common cause of death world wide. ^{99m}Tc-tetrofosmin and ^{99m}Tc-sestamibi are established single photon emission computed tomography tracers to gain information about heart perfusion and myocardial cell damage. A ^{68}Ga myocardial tracer would be desirable to make it available for positron emission tomography (PET) application. Hexadentate bis(saliylaldimine) ligands are potential ^{68}Ga-tracers to access myocardial perfusion. They are characterized by their high lipophilicity. New monocationic bis(salicylaldimine) derivatives were synthesized and compared by in vitro assay.
Methods: Eight Schiff bases were synthesized by adding different aldehydes on a triamine backbone. The derivatives were labelled with ^{68}Ga (yield ≥70%) and purified by solid phase extraction. The lipophilicity and the uptake of the tracers in HL-1 rat heart cells were determined. The ionophor valinomycin was added to investigate the influence of the cell membrane and mitochondrial potential.
Results: Eight Schiff base derivatives were successfully synthesized and labelled with ^{68}Ga. The lipophilicity of the ^{68}Ga-Schiff base complexes was in the range of 1.3–2.7. Valinomycin increased the uptake of the ^{68}Ga-tracer. For comparison, uncharged tracers did not show this behaviour.
Conclusions: New ^{68}Ga-Schiff base derivatives were synthesized and evaluated. The ^{68}Ga tracers showed varying uptake with or without the ionophor. Future μ-PET imaging will reveal their qualification for myocardial imaging.

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Radiolabeling of neurotensin agonist and antagonist with ^{177}Lu: bioafinity of ^{177}Lu-DOTA-NT and ^{177}Lu-DOTA-SR48692 to neurotensin receptors

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The representative biomolecules chosen as the tumor targeting agents for radiolabeling with ^{177}Lu are neurotensin agonist and antagonist, early documented as potent tumor-avid substrates. As direct incorporation of the ^{177}Lu in either molecule is not feasible, indirect incorporation of ^{177}Lu through a suitable bifunctional chelating agents is envisaged. For the present study, DOTA- Neurotensin agonist (DOTA-NT) was purchased and DOTA-neurotensin antagonist (DOTA-SR48692) was synthesised in our laboratory by performing of the specific reaction conditions as: buffered reaction solvent (DMSO/0.1 M $NaHCO_3$), temperature and time of reaction and 1:1.5 SR48692:DOTA selected molar ratio. The bioconjugates DOTA-NT and DOTA-SR48692 were radiolabeled with ^{177}Lu.
The binding affinity of radiolabeled compounds was determined by evaluation of receptor binding affinity of the cold and radiolabeled conjugates by a competitive (competitive inhibition of ^{177}Lu-DOTA-NT binding by DOTA-SR and competitive inhibition of ^{177}Lu-DOTA-SR binding by DOTA-NT) and specific binding assay. The experimental bioaffinity was performed using newborn rat cortex membrane.
The results for IC_{50} show a comparable high affinity IC_{50}=0.40 nM (^{177}Lu-DOTA-SR) and IC_{50}=0.55 nM (^{177}Lu-DOTA-NT) of both radiolabeled neurotensin agonist and antagonist. The dissociation constant (K_d) suggest that specific binding of ^{177}Lu-DOTA-NT (K_d=1.15637 nM) is higher than the specific binding ^{177}Lu-DOTA-SR (K_d=40.46 nM) to neurotensin receptors. The obtained results in this work constitute a database for the in vivo researches regarding the pharmacokinetic and efficiency of treatment using ^{177}Lu-DOTA-neurotensin in the presence of neurotensin antagonist (SR48692) on pathological animal models, in the hypothesis that targeting neuromodulatory systems, may offer new strategies in the targeted radionuclide therapy of cancer.

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Automated synthesis of ^{68}Ga-AMBA

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Ga-AMBA (Ga-DO3A-CH_2CO-G-[4-aminobenzoyl]-QWAVGHLM-NH_2) is a bombesin-like agonist with high affinity for gastrin-releasing peptide receptors. We report the automated synthesis of ^{68}Ga-AMBA, a ^{nat}Ga-AMBA standard, and studies performed to demonstrate their correspondence. The radiodetector in the Tracerlab FX-FN synthesizer was used to monitor fractional ^{68}Ge/^{68}Ga generator elution and high-performance liquid chromatography (HPLC) purification. Sep-Pak purified ^{68}Ga-AMBA was prepared using 1 ml of generator eluant, 0.1 ml of a formulation previously developed for the preparation of ^{177}Lu-AMBA (8 nmol, 12 μg of AMBA) and NaOAc buffer. HPLC-purified ^{68}Ga-AMBA was prepared using 400 μl of AMBA formulation (32 nmol, 48 μg of AMBA) and 3 ml of eluant from a 30 mCi ^{68}Ge/^{68}Ga generator (Eckert and Ziegler). Total synthesis time was 20 min for the synthesis with Sep-Pak purification and 40 min for HPLC-purified ^{68}Ga-AMBA. The RCP values after purification were ≥97% and remained >94% at t=2 h. Overall yields were 55.2±5% and 40.7±6.6% for Sep-Pak and HPLC purified compound, respectively (n=7 each, decay-corrected). Acetonitrile (ACN) content in the HPLC-purified samples was found to be below the 4.1 mg/day limit for residual ACN in an injectable product. Germanium levels by ICP were found to be 0.0001 μCi/sample for Sep-Pak purified Ga-AMBA and below the limit of detection for HPLC-purified compound. The procedures described here should prove useful for the evaluation of ^{68}Ga-AMBA in future clinical trials.

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Poster Communications (Oral)

^{177}Lu-DOTATATE: comparative study between ^{177}Lu NRG/ Netherlands and ^{177}Lu ORNL/USA

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Introduction: Although controversial, the literature suggests the importance of the use of high specific activity radiopharmaceuticals for (1) in vitro studies of binding to specific receptor, (2) acquisition of good scintigraphic images and (3) tumors therapy. This work shows a synthesis study of the radiopharmaceutical ^{177}Lu-DOTATATE using ^{177}Lu radioisotope from two

Table 1
Molar ratios ^{177}Lu: DOTATATE for radiochemical purity ≥95%

	NRG/Netherlands	ORNL/EUA
Theoretical[a]	1:8	1:3.5
Experimental[b]	1:16	1:4

[a] Calculated based on the analysis certificate, considering 5 days after the ^{177}Lu production.
[b] n=4.

distinct laboratories: Nuclear Analytical and Medical Services (NRG/Netherlands) and Oak Ridge National Laboratory (ORNL/USA).
Materials and Methods: ^{177}Lu from NRG/Netherlands (852.4 GBq/mg), and ^{177}Lu from ORNL/USA (1961 GBq/mg). The synthesis experiments were performed at different molar ratios (^{177}Lu:DOTATATE), at pH 7.0 95° C for 30 min. The radiochemical purity was checked by chromatography in ITLC-SG eluted with sodium citrate buffer 0.1 M pH 5.0.
Results: See Table 1.
Conclusion: The ORNL/USA radioisotope enables the ^{177}Lu-DOTATATE radiopharmaceutical synthesis with a highest specific activity which has implications for pharmacoeconomics and possibly in clinical therapy.

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A highly stable functionalizable chelator for ^{67}Ga/^{68}Ga

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Many research groups have investigated bifunctional chelators for the isotope ^{68}Ga as potential alternatives to NOTA or DOTA. However, these chelators have established themselves as the "gold standard".
Herein we report our findings about the chelator H_2dedpa. At standard labelling conditions, dedpa^{2-} coordinates ^{67}Ga quantitatively after 10 minutes reaction time at room temperature. Concentration dependent labelling with H_2dedpa of both ^{68}Ga and ^{67}Ga shows quantitative conversion to the desired product with ligand concentrations as low as 10^{-7} M. With ^{68}Ga, we are able to obtain specific activities as high as 9.8 mCi/nmol without purification. To investigate the stability of the radiochemical complex, we use a 2-h competition experiment against human *apo*-transferrin. [^{67}Ga(dedpa)]$^+$ shows no decomposition. In a direct competition for chelation of ^{67}Ga with equal concentrations of NOTA and H_2dedpa, over 96% was coordinated by H_2dedpa.
Additionally, we have investigated the coordination chemistry of a variety of bifunctional versions of H_2dedpa. They all label at room temperature within 10 min. The stability of these derivatives is comparable to DOTA or higher. We are currently investigating their individual biodistributional profile.

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Evaluation of radioisotope quality aspects for preparation of high specific activity [Ga-68]-NOTA-AnnexinA1

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The bi-functional chelator NOTA-(p-Bn)-NCS permits radio-labelling heat sensitive proteins with Ga-68 ($t_{1/2}$=68 min) for positron emission tomography. Complexation at room temperature (RT) completes within minutes and in vivo transmetalation is negligible. Here, influences of trace metal cations, on radiochemical yield (RCY) and specific radioactivity (SRA) are assessed.
Conjugation of NOTA-(p-Bn)-NCS to AnnexinA1 was performed at varying stoichiometries and conjugates purified by size exclusion high-performance liquid chromatography. Available complexation sites per protein were identified by colorimetric assay and titration with carrier added Ga-67. The complexation of Ga-68 by NOTA-AnnexinA1 at RT and 37°C was systematically studied with and without addition of competing trace metal cations. Ga-67 was used for confirmation of observed trends. Integrity of the radio-conjugate was assessed by addition of up to 10^4 fold excess of metal cations or apo-transferin and exposure to human serum at 37°C.
Gallium-68 gave RCY of >99% within minutes at RT whereas, Ga-67 yielded max 85% dropping as the stock decayed. Presence of Fe(III) showed significant influence on RCY. Once formed, the radio-conjugate showed negligible loss of radioactivity under even the most extreme conditions investigated. SRA and RCY of the radio-conjugate depend significantly on absence of particularly Fe(III) during complexation.

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New Chelator for $^{67/68}$Ga with excellent radiolabelling properties and in vitro stability

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Introduction: Radiolabelling of bioconjugates with the short lived ^{68}Ga radioisotope is most commonly achieved using DOTA as a bifunctional chelator. Ga-DOTA has high kinetic stability but harsh and prolonged radiolabelling conditions (95°C, pH ~ 4.6, 30 min) are needed, limiting the targeting vectors to robust molecules and excluding proteins. Here we report the evaluation of a new tripodal *tris* 3-hydroxy-4-pyridinone hexadentate chelator (CP256) for gallium.
Methods: A 100-μM solution of CP256 was labelled with 2 MBq ^{67}Ga-citrate (25°C, pH 7.4.) DOTA was radiolabelled for 30 min (95°C pH 4.6). Both were incubated in 32 μM (physiological concentration) apotransferrin at ligand concentrations of 2.5 μM. ^{67}Ga-citrate was used as a control. Protein binding was determined by gel filtration and centrifugation on 30-kDa size exclusion filters over 4 h.
Results: Radiolabelling of CP256 was complete within 1 minute. Both ^{67}Ga-CP256 and ^{67}Ga-DOTA were ≥99% stable over 4 hours, whereas 74% of the radioactivity from ^{67}Ga-citrate was associated with apotransferrin.
Conclusion: CP256 shows great potential as a new "instant" ^{68}Ga chelator able to label rapidly and efficiently under mild conditions to very high specific activity. Bifunctional derivatives are being synthesised for conjugation to biomolecules.

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Novel ^{64}Cu-labeled bombesins capable of GRP receptor-targeted tumor imaging

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One attractive approach to the development of radiocopper-labeled radiopharmaceuticals has focused on bifunctional agents that couple a tumor targeting molecule with a ligand that binds radiocopper, forming a very stable and kinetically inert complex. Recently, we have reported that a TACN derivative, 2-[4,7-bis(2-pyridylmethyl)-1,4,7-triazacyclononan-1-yl] acetic acid (DMPTACN-COOH), binds copper strongly and the resulting