OVERLOOKING THE SITUATION OF NUCLEAR MEDICINE IN CENTRAL AND EASTERN EUROPE

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This paper reviews the situation of nuclear medicine in Central and Eastern Europe, i.e., a group of 15 countries lying east of Oder River — Trieste line and west of present/planned EU eastern border. Together they count 106.6 millions of inhabitants, i.e. about a quarter of inhabitants of European Economic Space. Its nuclear medicine, however, represents less than 10% of European nuclear medicine manpower and equipment.

In those countries there are at least 245 nuclear medicine departments with 661 nuclear medicine specialists and 376 gamma cameras. There are 6 PET units operable, 1 manufacturer of gamma cameras, 6 radiopharmaceutical manufacturers, 2 nuclear medicine scientific journals. The biggest and best developed nuclear medicine communities are in Czech Republic and Hungary, in absolute numbers to some extent also Poland.

The scientific input of those countries to European science is moderate, about 10% which measured by CND conference abstracts, 5% when measured by the number of papers in MEDLINE indexed journals. Mean European bibliometric parameters are approached only by Hungary and — to some extent — Czech Republic.

This survey indicates the need of international cooperation to improve the level of nuclear medicine in those countries for reaching the European standards, but also the tremendous potential which could be used for a benefit of European nuclear medicine.

PRESENTATION OF THE PREPARATION METHOD FOR 188Re-LABELLED RADIOPHARMACEUTICALS

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Introduction: Rhenium-188 became one of the more and more frequently used radionuclides from the last decade. The labelled ligands deliver a significant whole body internal dose to different critical organs and the lack of requirement for functional P53, implies the contribution of RIBBE to cell kill from different targeted radiation qualities.


The contribution of RIBBE to cell kill in NAT transfected cells after exposure to the radioactive complex 188ReN-DEDC into this hydrophobic material. In situ administration of labelled radiopharmaceuticals with high and stable labelling could be applied in a safer manner even in high-dose monitoring the critical organ parameters is essential to prevent the side effects.

Changes in the hematological, biochemical parameters, in thyroidal function and in micromolecular frequency in dogs after different Re-188 radiopharmaceutical application

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Introduction: Radiotheraphy is the selective irradiation of tumour cells by radionuclides conjugated to tumour seeking molecules. Gene therapy can expand the tumour types accessible to this type of therapy. We recently introduced the noradrenaline transporter gene (NAT) into tumour cells endowing them with the capacity for uptake of radiolabelled MBG. Current gene therapy strategies are however limited by low gene transfer efficiencies so cancer gene therapy strategies must have a component of collateral cell kill to neighbouring cells. Utilising the radiation-induced biological bystander effect (RIBBE) to its full potential could increase therapeutic efficacy. We adapted media transfer methodology to quantify the contribution of RIBBE to cell kill in NAT transfected cells after exposure to the emitter [131I]MBG, the CI-emitter [211At]MBG or the Auger emitter [123I]MBG. The role of p53 in mediating RIBBE was investigated.

Material and methods: NAT transfected human cancer cells and their p53 null variants were irradiated using a 60Co source or by incubation with radiopharmaceuticals. An amended media transfer protocol was employed to assess the magnitude of RIBBE contributing to cell kill from different targeted radiation qualities.

Results: Dose-dependent RIBBE were identified in human cancer cell lines following X-ray external beam radiation. RIBBE were p53 independent. Treatment with [131I]MBG, [123I]MBG and [211At]MBG showed a substantial impact of RIBBE on cell clonogenic survival. Cell kill due to RIBBE in cells never exposed to radiation was equal to that afforded by radiopharmaceutical treatment. The level of RIBBE correlated with dose of radiopharmaceuticals.

Discussion: The large RIBBE observed with radiopharmaceutical treatment of NAT transfected cancer cells and the lack of requirement for functional p53 implies the feasibility of utilising this strategy to enhance the efficacy of combined gene therapy and targeted radiotherapy.

TRACER-LEVEL CHEMISTRY OF THE 188Re N GROUP FIRST CLINICAL APPLICATION TO THE TREATMENT OF HEPATOCELLULAR CARCINOMA

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Introduction: Recently, we proposed a novel procedure for the efficient reduction of generator-produced [188ReO4−]− based on the combined action of oxalate and Sn3+ ions [1]. We describe here the successful application of this method to the production of the first class of complexes containing a terminal 188Re group, and their use for the labeling of the iodinated “lipiodol” employed in the treatment of hepatocellular carcinoma (HCC).

Material and methods: The 188Re N group was obtained from a freeze-dried kit formulation containing 2.0 mg of N-methyl-dihydrothiochelate (DTC), 0.4 mg of SnCl2 2H2O, 28.0 mg of sodium oxalate (Na2C2O4). After addition of 0.1 mL of glacial acetic acid and 1.0 mL of [188ReO4]− solution (activity range 0.1–1.0 GBq), the vial was kept at room temperature for 15 min to yield the [188ReO4]− group with high radiolabeling purity (98.1 ± 0.5%). The [188ReO4]− group produced in this way, was successively reacted with 15.0 mg of sodium diethyldithiocarbamate (NaDDEC), in the presence of a carbonate buffer (0.5 M, pH = 9.0), at 70°C for 15 min to afford the [188ReO4−]− group (yield ≥ 92.2%). Labeling of lipiodol was achieved through selective and quantitative (> 98%) extraction of lipiodol ([188ReN(DDEC)]2− into this hydrophobic material. In situ administration of labelled lipiodol in HCC patients was performed through the hepatic artery using a catheter.

Results: Efficient preparation of [188ReN(DDEC)]2− was obtained through dissolution of the radioactive complex [188ReN(DDEC)] into this hydrophilic material. Administration to HCC patients showed selective localization in tumours immediately following intraportal arterial injection. CT/SPECT imaging confirmed retention of [188ReN(DDEC)] in the hepatoma with minimal gut uptake and no lung activity over 24 hours.

Discussion/Conclusion: [188ReN(DDEC)] prepared using the novel kit formulation is stable in vivo and may provide safe and effective therapy of unresectable hepatocellular carcinoma.

ASTATINE-211: PRODUCTION, AND PROTEIN-LABELLING

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Aim: First experiences with 211At as a α-therapeutic radionuclide [1] encouraged us to improve the production of 211At with a new target, and to develop methods for the labelling of more specific — therapeutic agents, like small peptides and antibodies.

Material and methods: We developed a horizontal target, which is irradiated by a 10° downward γ-beam at our MC-35 cyclotron. It consists of a 2 cm × 4 cm ceramic-holder onto which Bi is deposited at a thickness of ca. 100nm. This allows a quick evaporation of 211At by heating in a quartz oven. 211At can be trapped in 1 ml of cooled aqueous or organic solvents. Reaction of 211At with p-butyln-stannyl-benzoic-acid-succinimidylderivate yielded p-211At-succinimidylbenzoate [2], which after purification and identification was reacted with human IGG. All reactions were verified by analogue reactions with radiodiode, and were analyzed by DC and HPLC.

In-vitro stability of 211At-IGG in serum was analyzed by gel-electrophoreses.

Results: The target tolerates a beam of at least 25NA. 211At production reaches > 80% of the theoretical yield. With a beam energy of 27.5 MeV on target, the production capacity reaches 24 MBq/NAh, leading to > 500 MBq after a 1-hour 20NA irradiation. Recovery from the target by heating (20–90°C) under a 5 ml/min flux of nitrogen takes 30 minutes. The recovery yield in 1 ml of trapping medium is > 90% for H2O, and 90% for CH2O. Preparation of p-211At-succinimidylbenzoate was not yet optimized, and resulted in variable yields of 20–60%. Further reaction of the precursor with human IGG was nearly quantitative with yields > 80%. The in-vitro stability of 211At-IGG in human serum at 37°C was determined by gel-electrophoreses over 14 hrs. The overall stability of the 211At-antibody bond was > 80%.

Conclusions: We developed a new target for 211At-production, which allows production and recovery of 211At in amounts suitable for therapy applications. In order to label antibodies and proteins we prepared p-211At-succinimidylbenzoate, which gave good labelling yields in test-labellings of human IGG. 211At-IGG was proven to be sufficiently stable in serum over a period of 14 hours.

References:

IN VIVO ENHANCEMENT OF ANTICANCER ACTIVITY BY THE COMBINATION OF CHEMICAL AND AUGER ELECTRON EFFECTS OBTAINED WITH FTCL21-IMASTINE COMPLEX

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The in vivo chemotoxicity and radiotoxicity of dichloroplatinum(II)-histamine labelled with iodine-125 was investigated to ascertain the potential of new radioplatinum coordination complexes as antineoplastic agents.

Material and methods: Two murine models of transplantable cancers, i.e. mammary adenocarcinoma (MA) and colon adenocarcinoma (C38) in C3H and C57BL6 mice, respectively, were used for the experiments. The groups of animals were treated every 3-4 days with low doses of Pt(II)C2H5Hist-HYNIC-MASTINE/1-% of MTD, and C57BL6/C28 — 1/3 of MTD, or with the 111I-labelled complex (0.5-1 MBq/animal each time). The solution of 15% DMF in saline was applied for the control groups. Anticancer activity was evaluated based on the variations of the relative tumour volumes of the treated mice and that of the control mice (t-test), and by the comparison of the median survival times (log-rank statistic).

Results: In both tumour models, treatment with PtCl2Hist and PtCl2[125I]Hist preparations revealed inhibiting activity on tumour growth and size in comparison to the control groups. However, significant and enhanced anti-cancer activities were observed for the radiolabelled complexes. The tumour growth delay factors (GDF) observed for C38/HYMA model were 0.29 and 0.68 for PtCl2Hist and PtCl2[125I]Hist, respectively. Relatively higher GDF’s were observed for the colon cancer model (0.84 and 0.90, respectively), which required most probably higher single doses being applied. A significant prolongation of the survival times of treated animals was observed. The median survival time (read from K-M curves) for C57BL6/C38 mice treated with PtCl2Hist complex was 67% longer comparing to the control groups, whereas more than 120% (value undefined) for the group treated with the radiolabelled complex. Conclusion: The significant enhancement of anti-cancer activity by concomitant combination of the therapeutic factors i.e. cytotoxic/cytostatic activity of the platinum(II)-histamine and the Auger electrons effects generated by the attached I-125 radionuclide has been found.
**GA-67 LABELLED DOTA-DERIVATISED PEPTIDE-LIGANDS**


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**Introduction:** Ga-67 labelled peptides may become a new class of therapeutic radiopharmaceuticals, based on the high micro-dosimetric effect of Auger-electrons produced by the electron-capture decay of Ga-67. Since the specifity of peptides can be optimized to a very high degree, the synergistic effects of high target specifity and micro-dosimetric efficacy may lead to an improvement in the therapeutic strategy towards cancers which propagate via micro metastases.

**Material and methods:** For triple loaded cations like Ga³⁺, DOTA (1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraaceticacid) has proven to be a very suitable chelator, which can be attached to peptide-ligands without loss of specificity. Since the concentrations of peptide receptors are usually in the order of nM/mg, higher than µmol amounts of peptide ligands tend to override the specific targeting by unspecific distribution. At these small concentration levels other cations need to be rigorously excluded. This necessitates the prepurification, concentration, and desalination of the Ga-67. Furthermore all handling must be carried out in small volumes in order to maximize the concentration of reactants and to improve the labelling yield. Handling of multi-GBq amounts of Ga-67 furthermore necessitates the use of semi-automated preparation techniques.

**Results:** The DOTA derivatised peptide Tyr-Octreotide (TOC), was labelled at 100 nmol amounts with a concentrated and highly purified solution of Ga-67 (< 200 µCi) at pH 4.5 within 4 min at 90°C. For the adjustment of the pH we used 800 N1 1 m HEPES-solution as a non-ionic buffer. Purification of the end product was achieved with RP18 mini-cartridges within 10 min. Quality control was carried out by DC and HPLC. The overall concentration, labelling-, and purification procedure took less than 50 min and resulted in 50-60% overall radiochemical yield with a radiochemical purity > 97%.

**Conclusion:** Initial experimental screening in guinea pigs ex vivo indicated a high signal/noise ratio in caudate as well as appropriate distribution and pharmacology for this tracer.

**BIO DISTRIBUTION OF THE NK1 RECEPTOR TRACER [¹¹⁸F]SPA-RQ IN GUINEA PIG**

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**Introduction:** The purpose of this study was to evaluate [¹¹⁸F]SPA-RQ (Merck, USA) in a guinea pig (GP) animal model. This tracer is a high affinity, selective ligand for the NK1-receptor.

**Material and methods:** The compound was labelled with fluorine-18 to a high specific radioactivity (¹¹⁸⁰-¹⁸⁰ GBq/mmol) (Selin et al. [2004] Mol Imaging Biol, in press). Atherosclerotic arteries (n = 30) were injected with the tracer i.v. Forty animals were pre-treated with a potent, brain penetrant NK1 receptor antagonist. The animals were sacrificed 15, 60, 180 or 360 min after tracer injection. Animals were then dissected and parts of organs were counted and weighted. The % ID/g tissue of tracer was determined from this data as a function of time. The spatial distribution of ¹¹⁸F-radioactivity from brain slices (20 µm) was determined with digital autoradiography and analyzed for uptake of radioactivity in frontal caudate putamen, cor tex, cerebellum as well as other structures.

**Results:** The tracer shows specific binding in structures of GP brain compatible with the known location of NK1-receptors. In animals pre-treated with the NK1 antagonist the uptake was inhibited to the level of that of cerebellum in all brain structures. The kinetics of the specific uptake in caudate showed promise for the tracer to be useful in human studies. Specific binding was seen in several organs, notably intestine, lung and pancreas. The uptake in bone increased with time, indicating some steliluomination of the tracer.

**Conclusion:** Initial experimental screening in guinea pigs ex vivo indicated a high signal/noise ratio in caudate as well as appropriate distribution and pharmacology for this tracer.

**NOVEL SYNTHESIS OF 4-[¹⁸F]-FLUOROBENZENECARBOHYDRAZIDE-5-ACID-FOLATE AND INITIAL BIOLOGICAL EVALUATION**

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Membrane-folic acid receptors are responsible for cellular accumulation of folate and folate analogs that overexpressed on various cancers, including breast, cervical, ovarian, colorectal and renal cancers. However, these receptors are highly restricted in most normal tissues. in-vivo and in-vivo studies of the Tc-99m, Ga-67 and In-111 radiolabeled folate-conjugates have been revealed to bind folate-receptors with high affinity and were taken up by tumor cells by folate-receptor mediated endocytosis. These have demonstrated their potential as radiopharmaceuticals for tumors detection and visualization. With the increased use of positron emission tomography, there has been great interest in the development of positron emitters radiopharmaceuticals for earlier detection and characterization of cancer; molecular assessment of treatment effects and more fundamental understanding of the disease process. As part of an on-going research effort to develop prosthetic precursors for radiofluorination of peptides, we have synthesized 4-[¹⁸F]-fluorobenzencarboxyhydrazide-folate using two different synthetic approaches. The synthetic approaches for preparation of 4-[¹⁸F]-fluorobenzencarboxyhydrazide-folate (F-Folate, Figure 1) entailed several sequence of reactions. The key precursor 4-((N,N,N-trimethylammonium ethyl)benzoate triflate was treated using catalyzed nucleophilic no-carrier-added radiofluoride produced by the ¹⁸O(p, n)⁴⁺ nuclear reaction on *O*-enriched (90% water and Kryptofix 222 as nucleophilic catalyst) in anodous acetonitrile at 90°C. The resulted ethyl 4-[¹⁸F]-fluorobenzoate in the first approach, was reacted with hydroxime at 90°C followed by reaction with N-hydroxy succinimidyl-acid-folate (NHS-folate) in DMSO at 60°C to give the folate conjugate ¹⁸F-folate in a quantitative yield. However, the resulted ethyl 4-[¹⁸F]-fluorobenzoate was converted to the corresponding acid in the second approach then activated with O-(N-succinimidyl) N, N, N-tetramethyluronium tetrafluoroborate (TSTU) to form the ¹⁸F-N-succinimidyl-4-fluorobenzoate (SBP). This prosthetic intermediate was used to label the hydrazide-folate in DMSO at 60°C to give the folate conjugate ¹⁸F-folate in also quantitative yield. Work up of this product by C-18 Sep-Pak column gave radiochemically and chemically pure ¹⁸F-folate as assessed by HPLC in less than 70 and in 110 minutes for first and second synthetic approaches respectively. The first synthetic approach in comparison with the second appears to be advantageous in the synthesis of ¹⁸F-folate conjugate in less laborious way and shorter time. In-vivo and in-vivo characterization of this radiolabeled folate conjugate is currently in progress.

![Figure 1: Synthetic approaches for preparation of 4-[¹⁸F]-fluorobenzencarboxyhydrazide-folate (¹⁸F-folate).](image-url)
SYNTHESSES OF 18F-LABELLED ACYCLIC PURINE AND PYRIMIDINE NUCLEOSIDES INTENDED FOR MONITORING GENE EXPRESSION

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Introduction: Radiolabeled ganciclovir analogues have shown promise as imaging agents to detect herpes simplex virus 1 thymidine kinase (HSV-1) expression in tumors with positron emission tomography (PET). To search improved PET radiotracers for gene therapy monitoring in addition to 18F-FHBG 1 and 18F-FHPG 2 a series of novel acyclic nucleosides were synthesized (Figure 1).

Figure 1. Synthesized 18F-labelled acyclonucleosides.

Material and methods: The tracers were produced by nucleophilic substitution of the corresponding precursors with a K18F/Kryptofix 2.2.2 complex and subsequent cleavage of methoxyethyl protecting groups under acidic conditions followed by RP-HPLC separation. The radiochemical yield of the 18F-tracers amount to 5–15% (decay corrected) after a synthesis time of 85–95 min, the radiochemical purity was > 98% and the average specific activity was 19 GBq/umol at the end of synthesis.

Results: The labelling procedures of 18F-FHBG 1, 18F-FHPG 2 and of the new tracers 3–8 were studied in detail. The precursors and the reference substances were synthesized in an extensive multistep procedure (1). To evaluate the behavior of the new fluorinated compounds 3–5 and their related hydroxylated analogues against the viral thymidine kinase, screening tests with the isolated enzyme HSV-1 TK were performed. Cell uptake in transfected (HT-29 tk + and MC38 tk +) and non-transfected cell types (HT-29, MC38) depends on the cell types and on the nucleobases used.

Discussion/Conclusion: Discussion/Conclusion: Discussion/Conclusion: Discussion/Conclusion: Discussion/Conclusion: Labelling procedures of all precursors were optimised concerning the reaction time, radiochemical yields and purities. Modification of the lipophilicity of 18F-FHBG 1 by introduction of a methyl group into the N1-position to get N1-Methyl-9-(4-[18F]fluoro-3-hydroxymethyl[buty]yl)-guanine [18F]FMHBG 3 does not cause a decreased cell uptake.

Some kits used in Turkey which are produced by EU countries but do not have the necessary legislation for harmonization to EU which holds for this area also. The status of trials involving radiopharmaceuticals. There is a continuous modification of availability. But still regulations are needed for “in house” preparations and clinical applications. The present status and future plans of radiopharmacy education in Turkey in relation to the standard certification program in EU will be discussed in this presentation. The Turkish Guidelines on Radiochemicals, came into act in 1993 making registration of all radiopharmaceuticals produced in or imported to Turkey compulsory. But still regulations are needed for "in house" preparations and clinical trials involving radiochemicals. There is a continuous modification of availability. But still regulations are needed for “in house” preparations and clinical applications.

Discussion/Conclusion: The complexation rate of this ligand containing the phosphine moiety is higher than 95% and all are stable in saline, PBS and in rat plasma. No exchange with glutathione was observed. One of the complexes has high affinity and selectivity for the 5-HT<sub>1A</sub> receptors (IC<sub>50</sub> for 5-HT<sub>1A</sub> = 2.35 ± 0.02 μM; competitor 5-HT<sub>1A</sub>, 372 ±11 nm). Biodistribution studies indicated a poor brain uptake and high in vivo stability.

Conclusion: H<sup>35S</sup> PNS ligand allows the preparation of stable “3+1” oxetane chelates with high affinity and selectivity for 5-HT<sub>1A</sub> receptors.

Optimization of conditions for complexation of 111<sup>In</sup> with novel bifunctional monophosphinate analog of DOTA

M. Frňšterová<sup>1</sup>, J. Žímová<sup>1</sup>, P. Herrmann<sup>1</sup>, I. Lukeš<sup>1</sup>, F. Melichar<sup>1</sup>

<sup>1</sup>Radiopharmaceutical Department, Nuclear Physics Institute, ASCR, Rez near Prague, Czech Republic, Department of Inorganic Chemistry, Universtita Karlova (Charles University), Prague, Czech Republic, Department of Analytical Chemistry, Institute of Chemical Technology, Prague, Czech Republic.

Introduction: The bifunctional polycarboxylates such as DTPA or DOTA are used in radiomunotherapy and radiomunodiagnosis. A key parameter for these applications is a fast and efficient complexation of a suitable radionuclode. Acyclic DTPA forms complexes immediately, complexation with macro cyclic DOTA is much slower. However, the macrocycles are better from all other aspects (e.g. kinetic and thermodynamic stability). In general, the most suitable central ions for DOTA-like ligands are tetravalent lanthanides and indium. The <sup>111</sup>In isotope was chosen for this study, because it has convenient radio-properties. Our DOTA derivative contains a DTPA ligand with a view to investigating the feasibility of using DTPA with a trivalent lanthanide.

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ASYMMETRICAL NITRIDO TECHNETIUM-99M HETEROCOMPLEXES FOR THE STUDY OF HEART METABOLISM

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Introduction: Under physiological conditions long chain fatty acids (Fa) serve as a major energy source for the normoxic myocardium. During ischemia, however, the extraction of Fa is reduced and glycolysis is enhanced [1]. Thus, an alteration of fatty acids oxidation is considered to be a sensitive marker of ischemia and myocardial damage. Because fatty acids are a major energy source in the myocardium, fatty acids oxidation is considered to be a sensitive marker of ischemia and myocardial damage.

Results: Each compound [99mTc(N)(PNP3)FaDtn] (n = 10, 11) and [99mTc(N)(PNP3)FaDtc] (n = 10, 11) was labelled according to the method shown before and the radiochemical yield determined by TLC was > 90%. After purification for the removal of free Fa, the compounds were studied by isolated working heart experiment in guinea pig have been performed according to literature [6].

Discussion/Conclusion: First results showed the presence of a correlation between the length of the carbon atoms chain and the heart uptake. With the [99mTc(N)PNP3SDFhDtn] the heart uptake value is 4.6%, while with the complex [99mTc(N)PNP3SDFhDtn] we have an heart uptake of 7.6%. The complexes studies with FaDtn are in progress.

References:
SYNTHESIS AND BIOLOGICAL EVALUATION OF A NEW TYPE OF TECHNETIUM-LABELLED FATTY ACIDS FOR MYOCARDIAL METABOLISM IMAGING


Introduction: In an effort to develop technetium-labeled fatty acid analogues for myocardial metabolism imaging, we synthesized a novel fatty acid with a technetium chelate. The compound was evaluated using a perfused heart model to assess its potential for myocardial imaging.

Material and methods: The novel fatty acid was synthesized using published methods with minor modifications. The pyridine-activated precursor was radioiodinated by iododestannylation. The resulting radioiodinated fatty acid was characterized by NMR, IR, MS, EA, and the geometrical impact of the chelate unit on the stability of the iodopyridine carboxylate prosthetic group was investigated in vivo.

Results: The radioiodosubstitution reaction yield was excellent, however the conjugation reaction yield was moderate as a result of competing hydrolytic reaction. As expected, the radioiodinated precursor was stable in vivo and displayed excellent radiochemical purity on Radio-TLC.

Conclusion: The radioiodinated fatty acid was evaluated in vivo in a perfluorinated heart model. The compound showed promising potential for myocardial metabolism imaging.

Discussion/Conclusion: The efficiency of concentration procedure is depends of the specific activity of the tracers, which is influenced by the production yield of 177Lu. However, the specific activity may be increased to 5.5 Ci/mg by irradiating liquid Lu(NO3)3 in the reactor for a period of 96 hours.

PURITY AND CONCENTRATION OF THE SRGA-SOLUTIONS FROM COMMERCIAL GENERATOR FOR PEPTIDE LABELLING

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Introduction: The radiolabelled Ga-68 is emerging as a promising radiopharmaceutical for cancer therapy since decays with half-life of 67.13 mins by emission of photons with E0 of 408 keV (78.6%), 384 keV (9.1%) and 176 keV (12.0%) to stable 68Fe. It also emits gamma rays of 208 keV (11%) and 133 keV (4.4%) suitable for imaging. Recently, somatostatin analogues, DOTATAT-tyramine octreotide, have been studied extensively for their potential applications in the treatment of metastatic bone cancer. In this study, we describe the synthesis of the preparation of 177Lu-DOTA-Tyr3-Octreotidem using rats is also described.

POTENTIAL THERAPEUTIC RADIPHARMACEUTICAL PREPARATION AND QUALITY CONTROL OF 177Lu-DOTA-TYR3-OCTREOTIDE COMPLEXES

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Introduction: 177Lu is emerging as an important radiolucide for cancer therapy since it decays with half life of 67.13 mins by emission of photons with E0 of 408 keV (78.6%), 384 keV (9.1%) and 176 keV (12.0%) to stable 68Fe. It also emits gamma rays of 208 keV (11%) and 133 keV (4.4%) suitable for imaging. Recently, somatostatin analogues, DOTATAT-tyramine octreotide, have been studied extensively for their potential applications in the treatment of metastatic bone cancer. In this paper, we describe the synthesis of the preparation of 177Lu-DOTA-Tyr3-Octreotide complex using rats is also described.

Discussion/Conclusion: The efficiency of concentration procedure is depends of the specific activity of the tracers, which is influenced by the production yield of 177Lu. However, the specific activity may be increased to 5.5 Ci/mg by irradiating liquid Lu(NO3)3 in the reactor for a period of 96 hours. The irradiation data indicate that the specific activity of liquids targets is (5.5 Ci/mg) higher than solid targets (4.8 Ci/mg). Studies on the preparation of 177Lu-DOTA-Tyr3-Octreotide and 177Lu-DOTA-Tyr3-Octreotide complexes have been investigated for their potential use in somatostatin analogue PET imaging.

Abstracts
STABILITY AND BIODISTRIBUTION AFTER PERORAL ADMINISTRATION

Mean ± SD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Large volume</th>
<th>Small volume</th>
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</thead>
<tbody>
<tr>
<td>Current</td>
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<td>17.3 ± 5.6</td>
</tr>
<tr>
<td>Time (min)</td>
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<td>16.7 ± 1.6</td>
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<tr>
<td>µA h</td>
<td>45.3 ± 22.9</td>
<td>35.6 ± 2.2</td>
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<tr>
<td>Production (Ci)</td>
<td>2.1 ± 0.8</td>
<td>0.85 ± 0.1</td>
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<tr>
<td>Yield [%]</td>
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<td>17.3 ± 1.6</td>
</tr>
<tr>
<td>Pressure (bar)</td>
<td>7 ± 1.0</td>
<td>3.7 ± 0.4</td>
</tr>
</tbody>
</table>

**Conclusions:** Our first year experience indicates the SV target has a better yield than the LV target. This is in accordance with the different metal used for the target cavity, as the titanium is known to have a lower yield than silver. In our experience, the most important variable for the final yield is the pressure inside the target, which seems to be independent from the ratio (target current/target + collimator current) and from the foils and stripper status.

**FUSION OF MRI AND SPECT WITH 1H-METHYLTYROSINE IMAGES COMPARED WITH 1H-MRS USED FOR EVALUATION OF MALIGNANT BRAIN TUMORS RECURRENTNESS**

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**Purpose:** The most essential modalities for morphological imaging of brain are magnetic resonance imaging (MRI) and, for metabolic imaging, single photon emission tomography (SPECT). By using image fusion of different modalities, the localisation of areas exhibiting functional changes can be more easily identified. In our studies 131I alpha-methyltyrosine, a radiochromapharmaceutical manufactured in Poland, has been used. This 131I-labeled compound is much less expensive than 123I labeled analogue, used in fMRI studies. Although delivering higher dose, it was found justified in patients with already diagnosed malignancy. The study compares the results of 131I alpha-methyltyrosine SPECT (fMRI) with MRI in detection of brain gliomas tumor.

We used fusion images as the method of planning H-Magnetic Resonance Spectroscopy (H-MRS) and verifying the metabolic content of the regions.

**Material and methods:** We investigated 27 patients. SPECT scintigraphy of the brain was performed using a double head gamma camera (ELSCINT), 15 min after intravenous administration of the IMT at activity of 74 MBq. MRI has been performed using a 1.5 T Magnetom Vision Plus (Siemens) unit. Fusion was made in modern technique of three-dimensional superimposing on the PC workstation. For accurate spatial data Pitting of the image sequences we used isotope markers in specific head points during SPECT. Areas of the biggest activity appointed in this way were used as bire data for planning 1H-MRS.

**Results:** In 19 patients the MRI imaging disclosed presence a polyfocal focus suggesting a tumor recurrence, in 11 subjects the result was equivocal due to presence of post surgery and irradiation sequel. In all 19 patients with a positive release in the MRI and in 4 with the equisolcular image there was an enhanced IMT uptake in SPECT images. In 4 patients the scintigraphy yielded a negative result. SPECT/MRI image fusion enabled a topographic localization of the area with a peak activity, in most cases corresponding to the solid tumor visualized in MRI. In patients with positive SPECT results 1H-MRS done in the determined areas revealed spectra typical for malignancy.

**Conclusion:** The study using 131I alpha-methyltyrosine enables confirmation of the presence of neoplastic tissue that may correspond to the site of tumor glioma recurrence. In equivocal MRI the scintigraphy may disclose or exclude recurrence. It seems also important that 131I IMT yields images of good quality. The fused SPECT/MRI images let to determine areas of tumor metabolic activity, being extremely useful data in planning spectroscopy.
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**[66Ga]oxine complex: preparation and stability as a possible PET radiopharmaceutical.**

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Introduction: [66Ga(Tc,Tc) 2] 9.49 h. E: 833, 1039 keV; 56.5%; E.C: 43.5% [1] is an intermediate-lived radionuclide and has been proposed for PET imaging [2–6]. [66Ga] has been used for the radiolabeling of monticalcol antibiotics [1, 7] and blood cells [8]. Tc(II)-quinolinato(Ga)(II) complex (Ga-oxine) has been proved to have suppressive effects on the viability of A549 human malignant lung adenocarcinoma cells [9]. Due to the increasing importance of PET, [66Ga] complex formation conditions with oxine were optimized, in order to develop [66Ga]oxine.

Material and methods: [66Ga] was prepared via the -Zn(II) n- [66Ga] reaction by 10 MeV proton bombardment of an electroplated enriched 0.04 mg/cm² 66Zn-target. At the optimum temperature and pH, the maximum yield was reached within 15 minutes. Increasing the ratio of oxine to radioactivity increased the yield, presumably due to more available chelate (Figure 3).

Radiochemical purity was checked by polymer-backed silica gel layer chromatography. RTLC showed a major and distinct radio peak at the Rf of 0.8. The radiochemical purity of both iodinated compounds was in the level of 92–98%. The radiochemical purity of both iodinated compounds was employed on the module with the following key modifications of the disposable kit, reagents and synthesis program: [18F]FLT: removal of IC18 cartridges, hydrolysis with 1N HCl, precursor N-(2, 4-Dimethoxybenzyl)-5'-O-dimethoxytrityl-3'-O-nosyl-thymidine, reaction at 130°C for 5 min [19]; [18F]FMISO: hydrolysis with 1N HCl, precursor 1'-2-Nitro-1'-imidazolyl-2-O tetrahydroprop-3-yloxy-propylazol, reaction at 100°C for 6 min. Purification of the radiotracer by radio-HPLC was performed by the transfer of 10ml of the final reaction solution through neutral alumina ([18F]FLT and [18F]FMISO) cartridges on to a preparative HPLC module with external software control for acquisition of radio-detector signal and collection of product fraction. The purity of the radio-tracers ([18F]FLT and [18F]FMISO) was confirmed by thin layer chromatography. At the optimum temperature and pH, the maximum yield of [66Ga]oxine was reached within 15 minutes. Increasing the ratio of oxine to radioactivity increased the yield, presumably due to more available chelate (Figure 3).

Results: The complex formation was optimized for pH, temperature, time, and the amount of oxine. At a random temperature, the best pH for the labeling was 5 (Figure 2).

Figure 2. Effect of pH on radiochemical yield of [66Ga]oxine at 25°C, n = 5, SE < 3%.

At the optimum temperature and pH, the maximum yield was reached within 15 minutes. Increasing the ratio of oxine to radioactivity increased the yield, presumably due to more available chelate (Figure 3).

Figure 3. Effect of the amount of oxine used in the reaction on radiochemical yield of [66Ga]oxine at 25°C, n = 5, SE < 3%.

Heating the reaction mixture to 50°C did not increase the yield. Further heating reduced the radiochemical yield due to the decomposition of oxine and/or the product. The thermal stability of [66Ga]oxine was so excellent, that autoclaving made no change in the amount of free gallium present.

Conclusion: Total labeling and formulation of [66Ga]oxine took about 15 minutes, with a yield of 97%. A suitable specific activity was achieved via insertion of [66Ga]oxine cation. No unchelated and/or labeled by-products were observed upon TLC of HPLC analysis of the final preparations. The radio-labeled complex was stable in aqueous solutions at least for 24 hours. No significant amount of other radioactive species was detected by HPLC 24 hours after labeling. HPLC and TLC showed that radiochemical purity of the [66Ga]oxine component was higher than 95% with a specific activity of 896 mCi/mmol.

Figure 1. Gamma spectroscopy scheme of final product. The presence of copper specific activity of 896 mCi/ml.

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**Radioisynthesis of fluorine-18 fluorodeoxyglucose (FDG) on PET synthesizers.**

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Introduction: The GE TRACERlab MX-FDG Synthesizer (previously the Coincidence FDG Synthesizer) is a high yielding, rapid and reliable system for the preparation of [18F]FDG from cyclotron produced [18F]fluoride. Implementation towards GMP is enhanced with the radioisynthesis being performed on disposable one-use kits. With it’s use of the generic [18F]fluoride radiofluorination method based on the generation of the nuclophile: [18F]fluoride+K+-aminopolyether-2,2,2-s system and with programmable hardware it was considered feasible to use this module for the synthesis of other fluorine-18 tracers.

Material and methods: Additional fluorine-18 tracers preparations were then implemented on the module with the following key modifications of the disposable kit, reagents and synthesis program: [18F]FLT: removal of IC18 cartridges, hydrolysis with 1N HCl, precursor N-(2, 4-Dimethoxybenzyl)-5'-O-dimethoxytrityl-3'-O-nosyl-thymidine, reaction at 130°C for 5 min [19]; [18F]FMISO: hydrolysis with 1N HCl, precursor 1'-2-Nitro-1'-imidazolyl-2-O tetrahydroprop-3-yloxy-propylazol, reaction at 100°C for 6 min. Purification of the radiotracer by radio-HPLC was performed by the transfer of 10ml of the final reaction solution through neutral alumina ([18F]FLT and [18F]FMISO) cartridges on to a preparative HPLC module with external software control for acquisition of radio-detector signal and collection of product fraction. HPLC Method: Phenomenex Luna 5 C-18 100A 250 × 10 mm, water/ethanol, 90/10 v/v, 3 ml/min RT = [18F]FLT, 22 mins; [18F]FMISO, 15 min.

Results and Conclusion: With little modifications to the disposable kit we have implemented the preparation of the radio-tracers ([18F]FLT and [18F]FMISO) on the TRACERlab MX-FDG Synthesizer with good radiochemical yields (FLT, 25%; FMISO 44%, decay corrected) and high radiochemical purities (> 95%). Products, which have been confirmed to be sterile and pyrogen free, are now been used for human and animal PET studies.

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**Pre-clinical investigations of e-Methyltyrosine labeled with iodine-131 or iodine-123 (IMT-[131I], IMT-[123I]).**

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Introduction: The aminosuccinic acid methyltyrosine (IMT) radiolabeled with the iodine-131 or iodine-123 has been used in the diagnostics of recurrent brain tumours, in the planning of re-operation and/or external radiotherapy. The aim of our work was to indicate that both radiopharmaceuticals IMT-[131I] and IMT-[123I] can be prepared in a reproducible manner, retaining high in vitro and in vivo stability and thus can be a subject of preliminary clinical investigation. Although the iodine-123 is more suitable for imaging, due to its very high cost it is not often used for economical reasons while cheaper iodine-131 may be an alternative.

Material and methods: For radiolabeling of IMT-[131I] the electrochemical substitution reaction has been applied in the absence of iodogen. The wall of the reaction vial were covered with a film of iodogen and then 300 µg of L-tyrosine dissolved in the boric buffer (pH = 8.0) was added followed by iodine-131 or iodine-123 (111–3700 MBq) in carbonate buffer (pH =8.5). After 10 min the reaction mixture was transferred on the Sephadex DAEAE A-25 column and the eluted with water. For quality control of the labeling yield and radiochemical purity of the iodinated compounds the methods of HPLC and electrophoresis were employed. The investigations of biological distribution were carried out on Swiss mice.

Results: Altogether 18 batches of IMT-[131I] and 6 batches of IMT-[123I] were prepared. The radioisotope concentrations of IMT-[131I] were at the level of 85–92%, and for IMT-[123I] at the level of 92–98%. The radiochemical purity of both iodinated compounds was in the range of 95-97%. The preparation is not harmful in the dose of 4000 MBq/70 kg.

Conclusions: The final parameters of IMT-[131I] were as follows — solution in 0.9% NaCl for injection, specific activity — 10–36.6 mCi/mg (370–1357 MBq/mg), radioactive concentration 95%, radioinertic purity 98%. Both radiopharmaceuticals IMT-[131I] and IMT-[123I] were pre-clinically tested and their usability confirmed.
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USE OF THE 99mTc-LABELED MONOCLONAL ANTI-SETA3 ANTIBODY FOR DIAGNOSIS OF TUMOR NEOANGIOGENESIS


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Introduction: Anti-angiogenesis treatment is recently drawing more and more attention. In conclusion, some diagnostic methods enabling the estimation of the progress of anti-angiogenic therapy should be developed. Among potential candidates, which could serve as a specific tracer for diagnostic purposes, is a monoclonal antibody (MoAb) directed against subunit \( \alpha_\text{IIb} \) of integrin \( \alpha_{\text{IIb}}\beta_{\text{3}} \) (CD61, CD29.G2 produced by BD Bioscience). Conjugating this MoAb with shortliving isotopes emitting gamma radiation enables the imaging of radiopharmacological disposition using detectors such as a gamma-camera.

Material and methods: For estimation of the applicability of the anti-CD61 MoAb (CD29.G2) to visualization of tumor blind vessels in vivo, the antibody was conjugated with iodine \( ^{131}\text{I} \). For this purpose standard chloramine T method was used. The radiophysical purity of MoAb \( ^{131}\text{I}-\text{CD61} \) measured at 1 hour after the iodination was completed exceeded 99%. Imaging of the distribution of the conjugates in the transplanted syngenic tumors as murine models of angiogenesis was carried out implementing visualization techniques used in nuclear medicine. The biodistribution of the conjugates in the body of mice was evaluated using the same model of angiogenesis as in imaging studies. Results are expressed as the percent of injectate dose in one gram of tissue (%ID/g), each value represents the mean and SD of three animals.

Results: The results of preliminary studies showed that conjugate MoAb antry \( ^{131}\text{I}-\text{CD61} \) given intravenously, accumulates in engrafted subcutaneously Lewis lung carcinoma, keeps steady for 144 hours, and demonstrates high tumor/background ratio (1611 for tumor/muscle). Additionally, the biodistribution reveals predominantly uterine excretion. This data was confirmed in scintigraphic studies, which show a good visualization of neogangiogenesis in tumor bearing mice.

Conclusion: In conclusion, we anticipate that using MoAb anti-CD61 as a radiotracer could be the basis for elaboration of a non-invasive diagnostic method allowing to display tumor neovascularization in vivo, to monitor tumor growth and to estimate the anti-angiogenic therapy progression in early and late stages of disease.

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LABELING OF AMPICILLIN SODIUM WITH 99mTc FOR IMAGING INFECTION

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1Ege University, Faculty of Pharmacy, Department of Radiopharmacy, Izmir, Turkey, 2Ege University, Faculty of Medicine, Department of Nuclear Medicine, Izmir, Turkey

Introduction: There are several radiolabeled antibiotics for diagnosis of infection. \(^{99m}\text{Tc}-\text{ABPC} \) is a suitable agent for scintigraphic detection of infection in the animals infected with Staphylococcus aureus and Escherichia coli and further studies are in progress.

Material and methods: Ampicillin sodium was labeled by a direct method. Stannous chloride was used as reducing agent. Quality controls were performed by thin-layer chromatography by silica gel plates and three different developing media: 1) acetone, 2) butanol:ethanol:water, (35:35:30), 3) butanol:pyridine: water (35:35:30). \(^{99m}\text{Tc}-\text{Ampicillin} \) was given intravenously to rats and rabbits which are infected with Staphylococcus aureus and Escherichia coli. 1 hour later scintigraphic images were obtained by gamma camera.

Results: The radiochemical purity of the compound was higher than 95%. According to scintigraphic studies the compound was located at infection site. Conclusion: There are several radiolabeled antibiotics for diagnosis of infection.

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LABELING OF ZOLEDRONIC ACID WITH 99mTc FOR IMAGING AND BIODISTRIBUTION STUDIES IN RABBITS

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Introduction: Zoledronic acid is a new generation bisphosphate strongly inhibit bone resorption. Bisphosphonates have high affinity for calcium phosphonates and hydroxyapatite. They have been chosen agents for bone imaging because of their structure: the most commonly used agent for skeletal scintigraphy in nuclear medicine is a radiolabeled bisphosphonate, \(^{99m}\text{Tc}-\text{MDP} \). For this reason it is important to evaluate the new generation bisphosphonates that have better pharmacokinetic parameters as bone scanning agents when they labeled with \(^{99m}\text{Tc} \). Zoledronic acid is a new generation bisphosphate strongly inhibit bone resorption. The aim of the present study is to label zoledronic acid and evaluate its in vitro stability and its biodistribution in rabbit system and ITLC paper chromatography. Preliminary pharmacokinetic studies were performed in healthy Swiss mice and Wistar rats.

Material and methods: Recombinant human thyrotropin (rhTSH, Thyrogen) was labelled with technetium-99m using direct method with the addition of SnCl2 and indirect — using the bifunctional chelating agent HYNIC. Purified HYNIC-rhTSH complex was labelled with technetium-99m in presence of SnCl2 and tricine as co-ligand. Radiochemical purity of the obtained tracers and their in vivo stability in human serum was studied using chromatography on BioSep-SEC-S 2000 column in HPLC system and ITLC paper chromatography. Preliminary pharmacokinetic studies were performed in healthy Swiss mice and Wistar rats.

Results: Obtained tracers \(^{99m}\text{Tc}-\text{rhTSH} \) and \(^{99m}\text{Tc}-\text{HYNIC-rhTSH} \) were almost 100% pure (unbound \(^{99m}\text{Tc} \)-rhTSH-cholesterol was not detected) and specific activity of 125 mCi/mg \(^{99m}\text{Tc} \)-HYNIC-rhTSH was very stable in serum up to 3 hours. The thyroid uptake of the tracers tested in mice and rats was stable and at the even level over the period of 3 hours while in the same time fast blood clearance was observed.

Conclusions: After labelling with technetium-99m the obtained rhTSH complexes presented high radiochemical purity and in vitro stability in serum. The retention of radioactivity in thyroid showed that affinity to specific receptors was not affected by the radiolabelling process. These initial data require confirmation in cell and animal studies.

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RECOMBINANT HTHS RADIOLABELLED WITH TECHNETIUM-99m: A NEW PROMISING RADIOPHARMACEUTICAL FOR THE DIAGNOSIS OF METASTASES IN DIFFERENTIATED THYROID CANCER — PRELIMINARY STUDIES

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Introduction: The imaging of TSH receptors using technetium-99m labelled TSH (mTSH) might be useful to follow-up differentiated thyroid cancer (DTC) (after ablation by iodine-131 therapy) because currently used whole body scan (WBS) technique is very often characterized by poor sensitivity. The aim of our preliminary studies was to prepare tracer — mTSH labelled with technetium-99m with high specific activity, good radiochemical purity and stability in vitro.

Material and methods: Recombinant human thyrotropin (rhTSH, Thyrogen) was labelled with technetium-99m using direct method with the addition of SnCl2 and indirect — using the bifunctional chelating agent HYNIC. Purified HYNIC-rhTSH complex was labelled with technetium-99m in presence of SnCl2 and tricine as co-ligand. Radiochemical purity of the obtained tracers and their in vivo stability in human serum was studied using chromatography on BioSep-SEC-S 2000 column in HPLC system and ITLC paper chromatography. Preliminary pharmacokinetic studies were performed in healthy Swiss mice and Wistar rats.

Results: Obtained tracers \(^{99m}\text{Tc}-\text{mTSH} \) and \(^{99m}\text{Tc}-\text{HYNIC-mTSH} \) were almost 100% pure (unbound \(^{99m}\text{Tc} \)-mTSH-cholesterol was not detected) and specific activity of 125 mCi/mg \(^{99m}\text{Tc} \)-HYNIC-mTSH was very stable in serum up to 3 hours. The thyroid uptake of the tracers tested in mice and rats was stable and at the even level over the period of 3 hours while in the same time fast blood clearance was observed.

Conclusions: After labelling with technetium-99m the obtained rhTSH complexes presented high radiochemical purity and in vitro stability in serum. The retention of radioactivity in thyroid showed that affinity to specific receptors was not affected by the radiolabelling process. These initial data require confirmation in cell and animal studies.
Introduction: The aim of the present study was to investigate how affect four different 99mTc labelling methods in the in vivo and in vivo behaviour of the UBI 24-41 and to select the most appropriate 99mTc-labelled UBI 24-41 for detection of Staphylococcus aureus infected sites in mice.

Material and methods: The UBI 24-41 was labelled with 99mTc by two direct methods: a) using stannous pyrophosphate and BHCl4 and b) using ScI, and NaOH, and by two indirect methods: previous conjugation with BPCs. c) NHS-MAQ, and d) NHS-HYNIC using tricine as coligand. HPLC studies, stability in saline, cysteine challenge and in vitro binding to 107 CFU of S. a. were done. Distribution studies in S. a. infected mice were carried out and injected thigh/intrathaligal thigh ratios (IT/IT) were calculated.

Results: Radiochemical purities were higher than 97%, stability in PBS for 24 h was higher than 95% and the percentage of total activity transchelated to cysteine was lower than 10%. In vitro binding to bacteria showed big differences: the highest value was 41.4% of total activity for 99mTc-UBI 24-41 (method a) and the lowest value was 12.5% for 99mTc-MAQ, UBI 24-41. IT/IT ratios of each compound were: a) 2.56, b) 1.50, c) 1.60 and d) 1.76 respectively.

Discussion and conclusion: Our results showed that the direct labelling approach (method a) applied to UBI 24-41 gave the best complex for S. a. infection detection in mice. Due to its high IT/IT ratio and easy labelling procedure compared with indirect labelling methods.

**MYOCARDIAL EXTRACTION OF A NEW TYPE OF TECHNETIUM-LABELLED FATTY ACID**

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Introduction: Newly developed technetium-labeled fatty acid analogues are promising agents for myocardial metabolism imaging. We tested the myocardial extraction of 99mTc analogues of rhenium model complexes synthesized according to the “4 + 1” mixed-ligand approach (see presentation M. Walther et al.) in a guinea pig heart LANGENDORFF model.

Material and methods: Firstly, 30 min of steady state perfusion with 10 mCi/ml of normaltech kit-1, with technetium-99m, through 99mTc-HMPAO, could be useful. Recently, a new radiopharmaceutical 99mTc-ciprofloxacin has been developed. 99mTc-Sn complex of ciprofloxacin was proposed for skeletal imaging in 1972. Since that time, 99mTc-PYP has been used for visualisation of acute myocardial infarction as well as for in vivo labelling of red blood cells for radionuclide ventriculography and blood pool scintigraphy. In this study the possibilities for use of 99mTc-PYP as potential specific agent for bacterial infection and sterile inflammation-imaging were investigated. In vivo imaging studies of 99mTc-PYP to bacteria, as well as in vivo studies in infected animals and human with known infection or inflammation, were presented.

Results/Discussion: The in vivo binding results have shown that uptake of 99mTc-PYP by S. a. was higher than 30%. The in vivo investigation results on rats have shown some increase of radioactivity in infected muscles (TNT > 2.5) and high bone uptake (5.46.9% ID/g). Scintigraphic study in a patient with pleuropneumonia and chronic rheumatoid arthritis has shown that 99mTc-PYP accumulated in pulmonary and bone lesions. Lesion to non-lesion ratios (L/NL), expressed as a ratio of total counts in infected/inflamed region and regional region in the contralateral normal tissue, for early sequential whole body scintigraphy were 1.48 for lung and 6.03 for bone.
INTRODUCTION OF 99mTc-EDDA/HYNIC-TOC: PRECLINICAL EVALUATION
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Introduction: The use of 99mTc-labeled somatostatin analogues has been a valuable diagnostic tool in nuclear oncology for over a decade. Therefore, our goal was to introduce an in house production of 99mTc-EDDA/HYNIC-TOC, within the project activities supported by the IAEA. Initially, we tried to optimize the labeling protocol concerning our own facilities and perform a basic quality control, before proceeding to the clinical application.

Material and Methods: The conjugated peptide (HYNIC-TOC) was provided by Polatom and wet labeled according a given procedure. The incubation step was performed using two labeling conditions. The radiochemical purity was assessed on ITLC-SG plates (Merck, 5555) in different solvents. The biological distribution was performed on Wistar rats, both with crude and Seppak purified radiopharmaceutical.

Results: The fraction of free pertechnetate in crude RF ranged from 0.5–0.9%. 99mTc-RH were between 1.6 and 3.0%, while for the 99mTc-non peptide bound impurities we found 7.6–23.5%. The biodistribution experiments with crude and purified RF showed certain differences.

Conclusions: According to the results presented, we couldn’t omit the Seppak purification of the wet labeled product. Further activities will be undertaken towards production of a small batch kit.

PREPARATION AND PRELIMINARY EVALUATION OF THE LIPOSOME-ENCAPSULATED 99mTc-DITHIZONE
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Introduction: Research on radioisotope markers for viable pancreatic islets cells resulted in development of conjugate of 2,2'-dicycloxy-dithizone and 131I-H-HYBAmine. Conjugate has properties of binding to 21R(I)on and shows a specific distribution in pancreas in vivo. Nevertheless, cumulated activity was not satisfac-
y to use it in scintigraphic methods. The aim of the research was focused on

Material and Methods: During the study the method of labeling dithizone with Tc-99m has been developed using of NaBH4 as a reducing agent. Liposomes with positive and modified membrane (Caltionc-MPEG) were formed from L-alpha-phos-
"phatidylcholine, stearylamine, cholesterol and DSPE-MEG. The Tc-99m dicyclo-
xy-dithizone was encapsulated by incubation 30 min at 50°C. The yield of the complex

Results: The yield of incorporation 99mTc dithizone into liposomes was 40%. Column separation resulted in pure encapsulated Tc-99m dithizone (ca 100%). Biodistribution studies of entrapped 99mTc-dithizone showed greater accumulation in pancreas (most activity located in spleen 13.1%ID/g) than that of 99mTc-dilution without carrier. Additional biodistribution study of 99mTc-dithizone-cationic-MPEG in C3H tumor bearing mice revealed a great uptake of radioactivity in tumor tissue (93.94ID/g) calculated TMI = 14.

Discussion/Conclusions: Performed study resulted in establishing method of la-
beling dicycloxy-dithizone with Tc-99m as well as its incorporation into modified
Caltionc-MPEG liposomes. Biodistribution in rats has shown improved accumula-
tion of the radioactive dithizone, however still not satisfactory for scintigraphy of
viable pancreatic islets. Therefore, further modifications of a liposome membrane
are needed. Moreover, this study has shown the perspective usefulness of a lipi-
some-encapsulated 99mTc-dithizone for tumor scintigraphy.

PRODUCTION OF 99mTc-ANTIMONY TRISULFIDE COLLOID FOR LYMPHOSCINTIGRAPHY
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The lymphatic system provides one of the main paths for the spread (metastasis) of cancer from one part of body to another. Hodgkin’s diseases, lymphocytic leukemia, various metastatic disease and urinary lymphnode disorders can be assessed by lymphoscintigraphy. Radiocuneilum lymphoscintigraphy has been used for urany

d years to define lymphatic drainage of melanoma. The most common radiopharma-
ceuticals used for lymphoscintigraphy are Tc-99m-S, Tc-99m-antimony sulfide colloid and Tc-99m-HSA-nanocolloid. Preparation of Tc-99m-antimony sulfide col-
loid has been chosen among other colloids.

Material and Methods: For antimony colloid preparation, hydrogen sulfide gas was passed through DW until saturation. Antimony potassium tartrate is then added to the solution to form Sb2S3 colloid. The colloid was stabilized with PVP. Ex-
cess H2S was removed by bubbling with nitrogen. The preparation was filtered through a 0.22 Nm membrane filter and aliquots containing 1.017 mg Sb,54 were dispensed into kit vials. Labelling was accomplished by adding 99mTcO4- and HCl2 to the vial then heating it at 100°C in boiling water bath for 10 min. The pH was adjust-
ed by adding a phosphat buffer.

Results: The radiochemical purity of Tc-99m-antimony trisulfide colloid by ITLC-
SG/normal saline was more than 95%. The amount of Sb in reaction vial was 0.729
mg. Conclusion: The study demonstrated that our formulation of antimony trisulfide
which has 0.036 mg (Sb) in 0.2 ml injection per patient (total volume after labeling
with Tc-99m was 4 ml).
**EVALUATION OF **\textsuperscript{90}Y-COLLOID RADIOPHARMACEUTICALS FOR RADIOSYNOVERSITY IN HEALTHY RABBITS**


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**Introduction:** Leakage and biodistribution of radioactivity after intra-articular injection into the knee joint has been studied in healthy rabbit knee joints. Two colloidal systems for \textsuperscript{90}Y have been studied: \textsuperscript{90}Y citrate and \textsuperscript{90}Y silicate.

**Material and methods:** Leakage studies have been performed at 6, 24, 48 and 120 hours post injection with 6 male animals per time point for both preparations. Knee joint injection was done with 100% NCI of activity in 100 NCI volume. Correctness of injection was checked in all animals by gamma camera. The remaining activity was measured in the knees that were prepared by removing the knee joints from the rabbit. The counts per minute in the knees was measured in a gamma counter. For biodistribution studies, biodistribution studies were performed with \textsuperscript{90}Y citrate colloids, at 6 h, 24 h, 5 days, 8 days and 13 days post injection, in 6 male rabbits for each time point. Activity present in the skeleton, liver, spleen, inguinal lymph node, blood, kidney, testes, and injected knee was measured. Residence times and dose metrics were calculated.

**Results:** Results of the leakage studies are summarized in Table 1 for \textsuperscript{90}Y-citrate and in Table 2 for \textsuperscript{90}Y-silicate.

**Discussion:** This extensive study has shown that both preparations reside mostly in the knee, the citrate colloids showing better retention. The estimated radiation burden to other organs is negligible after intra-articular injection of \textsuperscript{90}Y-citrate colloids.

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**RHENIUM-188 SOLUTION OBTAINED FROM THE STATIONARY \textsuperscript{188}Re/\textsuperscript{188}W GENERATOR**

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**Introduction:** Rhenium-188 is a generator produced radiopharmaceutical emitting both beta ($\beta^-$) ($E_\beta^-$ = 2.1 MeV) and gamma ($\gamma$) ($E_\gamma$ = 155 keV, 15%) radiation with physical half-life of 16.98 h. Beta particles provide radiation suitable for destroying tumour cells with little or no damage to adjacent organs. During last decade the interest in using \textsuperscript{188}Re for radiotherapy as well as for brachytherapy in the treatment of coronary vessels was growing rapidly. The technology of manufacturing the rhenium phosphate (\textsuperscript{188}RePO$_4$) solution has been developed at the Radioisotope Centre POLATOM.

**Material and methods:** \textsuperscript{188}Re is the product of tungsten-188 decay. The \textsuperscript{188}Re was adsorbed on the alumina column which was conditioned with 0.9% NaCl and 32% HCl. The daughter radionuclide, \textsuperscript{188}W was eluted from the column using 0.5 M acetic acid. The obtained solution was purified and concentrated in the chromatographic system consisting of cation exchanger AG-50WX12, on which the sodium ions were adsorbed and anionic column Sep-Pak QMA Light, on which the phosphate ions were concentrated. Sodium phosphate (\textsuperscript{188}RePO$_4$) was eluted in 1-3 ml of saline.

**Results:** The developed method enabled preparation of the carrier-free solution of rhenium phosphate (\textsuperscript{188}RePO$_4$) up to 180 GBq in 1 to 3 ml volume. Radiochemical purity of \textsuperscript{188}Re solution was > 99.9%. The highest activity of \textsuperscript{188}Re was obtained 3 days after the previous elution. It was shown that \textsuperscript{188}Re could be efficiently used for labeling of HEDP radiopharmaceutical applied for palliative treatment of bone metastases.

**Conclusion:** The developed method for preparation of \textsuperscript{188}Re in the form of phosphate solution using the stationary \textsuperscript{188}Re/\textsuperscript{188}W generator approach allows obtaining portions of \textsuperscript{188}Re solution with required activity and radioactive concentration, which can be further transported to the clinics and used for patient treatment.

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**COMPARATIVE IN VITRO EVALUATION OF DOTATATE LABELLED WITH \textsuperscript{111}In OR \textsuperscript{90}Y, RADIOPHARMACEUTICAL FOR RECEPTOR MEDIATED RADIOTHERAPY**

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**Introduction:** Rapid growth of clinical applications of peptide receptor radiomunotherapy (PRRT) using somatostatin analogues labelled with beta/gamma-radiation emitters prompted us to establish the laboratory conditions for cell lines studies and to investigate in vitro the peptide DOTATATE (DOTA-Phe1,Tyr3-octreotate) labelling with \textsuperscript{111}In and \textsuperscript{90}Y, both produced at Radioisotope Centre POLATOM.

**Material and methods:** DOTATATE (Pichem, Austria), the radionuclides \textsuperscript{111}In (carri-

er-free) and \textsuperscript{90}Y \textsuperscript{90}Y and \textsuperscript{111}In (about 8 Ci/mg Lu) obtained as chloride solutions (POLATOM) were used for labelling carried out in acetic buffer with addition of ascorbic acid at pH = 4.5–5.3 followed by 30 min incubation at 90°C. The radiochemical purity of radiolabelled peptides was determined by TLC, HPLC and Sep-Pak separation. Serum stability was tested at 37°C for 24 hours after labelling. The internalisation and receptor affinity studies (non specific binding using Sandostatin or cold pep-

ide) were carried out on live AR42J.

**Results:** The complexes of DOTATATE with \textsuperscript{111}In or \textsuperscript{90}Y were obtained with high radiochemical purity exceeding 98%. No significant differences between the stability of \textsuperscript{111}In or \textsuperscript{90}Y labelled peptide were observed (RCP values were: after 4 hours 99.91% and 99.40%, after 24 hours 99.98% and 98.62% respectively). Both comple-

xes were stable in human serum. The tracers were rapidly internalizing to the AR42J cells (about 80% for \textsuperscript{111}In-DOTATATE and \textsuperscript{90}Y-DOTATATE during 60–90 minutes, while the binding to the receptors on cell surface is about 20%). The non-specific binding was low and equal to about 1%. The somatostatin receptor affinity, (IC50, was found 40 nM.

**Conclusions:** The results of in vitro evaluation of \textsuperscript{111}In-DOTATATE and \textsuperscript{90}Y-DOTATATE did not show any significant differences in their in vitro behavior. High labelling yields as well as stability of both radiotracers confirm their suitability for therapeutic appli-

cations. The study was done within the IAEA co-ordinated research project “Comparative Evaluation of Therapeutic Radiopharmaceuticals”.

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**CARRIER-FREE \textsuperscript{90}Y PRECURSOR FOR RADIOLABELLING OF RADIOTHERAPEUTIC RECEPTOR TARGETING AGENTS**

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**Introduction:** The carrier-free \textsuperscript{90}Y manufactured as a precursor for peptides label-

ing should conform to the qualitative and quantitative specification which assure their pharmaceutical usefulness. The parameters having significant influence on the quality is 90Sr content (Sr-90 content) and the content of chemical impurities, such as metallic cations, which may decrease the labelling yield of biological substances.

**Material and methods:** The carrier-free \textsuperscript{90}Y was obtained as chloride solution at the Radioisotope Centre POLATOM. For identification the liquid scintillation methods was used. The content of \textsuperscript{90}Sr was determined by liquid scintillation technique on the Sr-Resin (Eichrom) column followed by LSC measurement. The concentration of chemical impurities was determined by the optical emission spectrometry (ICP-OES). Radioactive concentration of \textsuperscript{90}Y was measured in ionization chamber. Peptide DOTATATE used for verification of labelling yield was prepared in the dry-kit form (1.25 mCi/g, 1800 mCi/ mol). The radiochemical purity of \textsuperscript{90}Y-DOTATATE preparation was determined by HPLC method.

**Results:** In tested batches of \textsuperscript{90}Y the content of \textsuperscript{90}Sr was well below 2.5 \times 10^{-4}%. The radioactivity concentration was about 20 GBq/mL. The content of chemical impurities was below 1.0 g/mL for Ac, Cu and Ni, 5.0 g/mL for Pb and 10.0 g/mL for Fe and Zn. The complex of DOTATATE with \textsuperscript{90}Y was obtained with high radiochemical purity, over 99%. \textsuperscript{90}Y-DOTATATE preparation was stable at temperature 4–10°C over at least 72 hours (RCP > 98%).

**Conclusions:** The methods used for quality control of \textsuperscript{90}Y enable the determination of critical parameters for assessment of \textsuperscript{90}Y purity. The carrier-free \textsuperscript{90}Y manufactured at RC POLATOM conforms to the following specification: content of \textsuperscript{90}Sr < 2.5 \times 10^{-4} g/mL, Pb < 5.0 g/mL, Fe, Zn < 10.0 g/mL. The suitability of \textsuperscript{90}Y precursor to label DOTATATE at patient therapeutic dose level has been proved.
MEASUREMENTS OF COLLOID PARTICLE SIZE IN THERAPEUTICAL RADIOPHARMACEUTICALS

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Introduction: Localization and pharmacokinetics of therapeutic colloidal radiopharmaceuticals mainly depend on their particle sizes. In our experiments we used laser scattering method for determination the sizes of different colloids. Samples tested were 90Y-Clite colloid, 90Y-Silicate colloid, 188Re-(Tin)-Colloid and 166Ho-Fytate colloid. Radiochemical stability was also tested in vitro and ex vivo in synovial fluid.

Material and methods: The analytical instrument used in our experiments named DynaPro is a product of the Proteinsolutions Inc. (USA). The sample is illuminated by a semi-conductor laser of ~830 nm wavelength. The light scattered by the sample is collected and guided via a fiber optic to an actively-quenched, solid state Single Photon Counting Module (SPCM). The photons are then converted to electrical pulses and correlated. The DynaPro analyses the time scale of the scattered light intensity fluctuations by a mathematical process called autocorrelation. The translational diffusion coefficient (D) of the molecules in the sample cell is determined from the decay of the intensity autocorrelation data. The hydrodynamic radius (R) of the sample is then derived from D, using the Stokes-Einstein equation. In our experiments parallelly with the samples calibration standard was measured, it was 160 nm polystyrene standard (Bangs Laboratories Inc., Serial NO: 5692). Radiochemical stability measurements were in different time points by ITLC.

Results: Low sample volume (50 µl) needed for determination, which offers possibility for serial measurements of labelings and incolate colloids. The calibration found more than 95% exactness of the polystyrene standard measurements. Particle fraction of 90Y-Citrte colloid ranged between 1 and 7 µm (mean diameter: 3.5 µm) and particles of 90Y-Silicate colloid particles ranged between 0.1 and 4.5 µm (mean diameter: 1 µm). 188Re-(Tin)-Colloid mean diameter was around 4.5 µm. We also examined the stability of the colloid products. These radiopharmaceuticals showed high particle and radiochemical stability yields (> 99%) in vitro and in synovial fluid. Ideal measurement range of DynaPro is ranged between 1 and 5000 nm. Outside this range particle size measurement needs further evaluation.

Conclusion: Because of pharmacokinetics of therapeutic radioocolloids depends on their particle sizes the measurements by laser scattering method can be a very important element of radiopharmaceutical research.

A KIT-METHOD FOR THE HIGH LEVEL SYNTHESIS OF 211AtMABG


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Introduction: Meta-iodobenzoylguanidine labelled with 211At will be potentially useful in the treatment of metastatic neuroblastomas. Earlier we have developed a method for the synthesis of meta-[211At]astatobenzylguanidine ([211At]MABG) from a silicon precursor by solution-phase chemistry1.

Discussion/Conclusion: The feasibility of [211At]MABG synthesis using a resin-bound tin precursor has been demonstrated. With this method, it was possible to synthesize up to 90% of [211At]MABG from a solid-supported tin precursor by solution-phase chemistry. The yields from the 5 reactions conducted with higher amounts of 211At was 56.4 ± 9.8%; and 50.6 ± 3.7% were obtained during 5, 15 and 30 min, respectively. The radiochemical purity from the 5 reactions conducted with higher amounts of 211At was 56.4 ± 9.8%; and 50.6 ± 3.7% were obtained during 5, 15 and 30 min, respectively. The radiochemical purity was determined from the decay of the intensity autocorrelation data. The hydrodynamic radius (R) of the sample is then derived from D, using the Stokes-Einstein equation. In our experiments parallelly with the samples calibration standard was measured, it was 160 nm polystyrene standard (Bangs Laboratories Inc., Serial NO: 5692). Radiochemical stability was also tested in vitro and ex vivo in synovial fluid.

PREPARATION AND TESTING OF LIPOPROTEIN MACROMOLECULES AND LIPOSOMES FOR SCINTIGRAPHIC DETECTION OF ATHEROSCLEROTIC AND TUMOUR CELLS

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Introduction: Intra-arterial infusion of labeled particles is an effective method for local endoradiotherapy of tumors. In this study, we present data on a efficient radiolabeling of biodegradable human serum albumin (HSA) microspheres with the short-lived beta emitter 188Re by means of a sufficient kit-preparation.

Material and methods: One labeling-kit consists of three vials containing 9.3 mg 2.5 Dihydroxybaryoxenic acid and 11.4 mg Stannous-(II)-chloride dihydrate, and 10 mg HSA-microspheres (1.2-2.0 106 microspheres) to be dissolved in water. The desired quantity of sodium [188Re]perenate in saline available from the aluminia-based 186W/188Re generator system (Oak Ridge National laboratory, USA) should be transferred to the HSA-microspheres. For the labeling reaction the vial is placed on a heat-shaker heated at 95 °C and shaken for one hour. After setting a physiological pH of 5-7 the reaction is ready for injection.

Results: The kit-preparation allows a simple and reliable quantitative labeling (> 97%) within 75 min with minimal handling of high 188Re radioactivity and small radiation risk for laboratory staff. After labeling the microspheres remained in a narrow grayscale distribution (mean diameter = 22 µm). The 188Re bound to the particles was found to be stable in vitro. The biological half life was > 250 h and demonstrated sufficient in vivo stability after i.v. injection in Wistar rats.

Conclusion: A simple and reliable kit preparation of 188Re HSA microspheres is available for intra-arterial infusion of particles for tumor therapy as for possible application in radiolysis in vivo. The quantitative labeling with minimal handling of high 188Re radioactivity and small radiation risk for laboratory staff. After labeling the microspheres remained in a narrow grayscale distribution (mean diameter = 22 µm). The 188Re bound to the particles was found to be stable in vitro. The biological half life was > 250 h and demonstrated sufficient in vivo stability after i.v. injection in Wistar rats.

1. synthesis of [211At]MABG from a solid-supported tin precursor

The goal of this study was to develop a kit method with which high doses of [211At]MABG useful for clinical applications can be prepared.

Material and methods: A solid-supported tin precursor [1] was synthesized as reported [2] (Figure 1). Temporal effect on the [211At]MABG yields was studied by treatment of 5 mg of 1 at room temperature with 60 µl of a solution of 211At in methanol (7.11 MBq) and 10 µl of a 17.10 (v:v) H2O, 30% w/v HOAc. For high level synthesis, 10-12 mg of the resin 1 was treated with 211At at activity ranging from 40 to 300 MBq; Mean 189 MBq in 100 µl of methanol and 20 µl of H2O, HOAc mixture. The reaction mixture was stirred gently for 10 min at room temperature and diluted with 10 ml of water. [211At]MABG was isolated by solid phase extraction and reconstituted in an appropriate buffer for biological applications.

Results: With smaller amounts of 211At, radiochemical yields of 50.8 ± 6.9%, 57.4 ± 6.9% and 50.6 ± 3.7% were obtained during 5, 15 and 30 min, respectively. The radiochemical yield from the shorter reactions conducted with higher amounts of 211At was 56.4 ± 9.8%; a maximum of 185 MBq of [211At]MABG has been synthesized. HPLC indicated just one radioactive peak corresponding to MBG and no UV peaks were detected.

Discussion/Conclusion: The feasibility of [211At]MABG synthesis using a resin-bound tin precursor has been demonstrated. With this method, it was possible to synthesize up to 185 MBq of [211At]MABG in a pure form without the use of HPLC and in a shorter duration than that needed for solution-phase synthesis.


Preparation and testing of lipoprotein macromolecules and liposomes for scintigraphic detection of atherosclerotic and tumor cells

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Introduction: There are strong need for non-invasive techniques in directly imaging atherosclerotic plaques and tumour lesions for early detections. 99mTc(technetium)-labelled lipoproteins and lipoproteins mimic liposomes can be used as radiotrace because it acts as intracellularly trapped lipids providing an scintigraphic measurement of lipoprotein and liposomes uptake by tissues. Liposomes can be prepared with similar features to lipoproteins. The radiolabelling of LDL and liposomes was tested in atherosclerosis and in cancer.

Material and methods: Rabbits fed a diet containing 2% cholesterol for 60 days to develop hyperlipidemia and atheromatous arterial plaques and to detect with 99mTc labelled LDL and liposomes on the basis of scintigraphy. In nude mice developed human tumor cells were also investigated using 99mTc labelled LDL and liposomes. Preparative density gradient centrifugation methods were applied for the isolation of the major lipoprotein density classes i.e. VLDL, IDL, LDL, HDL. Analytical ultracentrifugation methods were developed for the investigation of native and modified lipoproteins. Lipoproteins were manufactured from lipoproteins and from natural phospholipids.

Results: Gamma camera in vivo scintigraphy of rabbits revealed visible signal corresponding to atherosclerotic plaques of aorta and carotid arteries in rabbits with 99mTc labelled LDL and liposomes on the basis of scintigraphy. In nude mice developed human tumor cells were also investigated using 99mTc labelled LDL and liposomes. Preparative density gradient centrifugation methods were applied for the isolation of the major lipoprotein density classes i.e. VLDL, IDL, LDL, HDL. Analytical ultracentrifugation methods were developed for the investigation of native and modified lipoproteins. Lipoproteins were manufactured from lipoproteins and from natural phospholipids.
PROGNOSTIC VALUE OF 99mTc-EDDA-TINCI-HYNIC-TYR-3-OCTREOTIDE IN PATIENTS WITH ADVANCED LIVER CANCER

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Department of Diagnostic Imaging, Unit of Liver Focal Lesions, Unit of Pathologic Anatomy, Regina Apostolorum Hospital, Unit of Nuclear Medicine, Department of Clinical Sciences, University of Rome “La Sapienza”

Aim: To evaluate the potential of 99mTc-EDDA-tincoline-HYNIC-tyrosinamide (99mTc-EDDA-TINCI-Tyr-3-Octreotide) to detect pathologic expression of somatostatin receptor by hepatocarcinomas in order to identify patient who might benefit from the use of long-acting somatostatin analogue (octreotide).

Material and methods: Twenty patients (6 females and 14 females, mean age 68.5±10 years) with advanced hepatocarcinoma were recruited. All patients had a life expectancy greater than 3 months and were previously treated with LTA or somatostatin-approbation and were not amenable to further treatment. All patients underwent confirmatory liver biopsy, abdominal CT, and measurement of alpha-foeto-protein. Somatostatin receptor scintigraphy (SRS) was performed 3 hours after the injection of 99mTc-HYNIC-TOC (370 MBq). Liver scan was performed 20 minutes after the injection of 99mTc-albumin nanocolloids (185 MBq). Tomographic images of the liver were obtained for both scintigraphy using the same acquisition parameters and compared. A SRS was considered positive if uptake of 99mTc-HYNIC-TOC was seen in an area of no colicoids uptake corresponding to a liver detectable on a CT scan. Four patients positive to SRS were treated with long-acting octreotide (30 mg/4 month i.m.).

Results: Fourteen out of twenty patients (70%) showed a significant uptake of 99mTc-HYNIC-TOC. No correlation with -Pheto-protein was found neither with the Edmondson severity score. Patients treated with long-acting octreotide showed stabilization of the disease in a follow up of six months. All patients who were not treated with long-acting octreotide showed progression of the disease. No side effects were observed following SRS.

Conclusion: The 99mTc-HYNIC-TOC showed pathological uptake in most patients with advanced, untreated, liver cancer. In this preliminary study our results suggest that patients positive to 99mTc-HYNIC-TOC scintigraphy benefited from treatment with long-acting somatostatin analogue. The in vivo study of SR on hepatocarcinomas is in progress to correlate the in vivo results.

USEFULNESS OF 99mTc-HYNIC-TOC IN DIFFERENTIAL DIAGNOSIS OF SOLITARY PULMONARY NODULES

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Introduction: Differential of solitary pulmonary nodules (SPN) to malignant and benign tumours is a serious diagnostic problem. The aim of the study was the assessment of clinical usefulness of scintigraphy with 99mTc-EDDA-HYNIC-TOC for purposes of differential diagnosis of SPNs.

Material and methods: 50 consecutive patients with solitary pulmonary nodules (SPN) on chest radiographs were studied scintigraphically, after administration of a somatostatin analogue 99mTc-EDDA-HYNIC-TOC for 3 hours after the injection of 99mTc-HYNIC-TOC (370 MBq). Liver scan was performed 20 minutes after the injection of 99mTc-albumin nanocolloids (185 MBq). Tomographic images of the liver were obtained for both scintigraphy using the same acquisition parameters and compared. A SRS was considered positive if uptake of 99mTc-HYNIC-TOC was seen in an area of no colicoids uptake corresponding to a liver detectable on a CT scan. Four patients positive to SRS were treated with long-acting octreotide (30 mg/4 month i.m.).

Results: Fourteen out of twenty patients (70%) showed a significant uptake of 99mTc-HYNIC-TOC. No correlation with -Pheto-protein was found neither with the Edmondson severity score. Patients treated with long-acting octreotide showed stabilization of the disease in a follow up of six months. All patients who were not treated with long-acting octreotide showed progression of the disease. No side effects were observed following SRS.

Conclusion: The 99mTc-HYNIC-TOC showed pathological uptake in most patients with advanced, untreated, liver cancer. In this preliminary study our results suggest that patients positive to 99mTc-HYNIC-TOC scintigraphy benefited from treatment with long-acting somatostatin analogue. The in vivo study of SR on hepatocarcinomas is in progress to correlate the in vivo results.
**Microbiological monitoring of radiopharmaceuticals preparation**

**Introduction:** Since radiopharmaceuticals are released for use before sterility testing is finished, microbiological monitoring of aseptic conditions should be carried out regularly in order to estimate the risk for microbiological contamination of the final product.

**Materials and methods:** In our department preparation of radiopharmaceuticals from technetium-99m generators and kits is done in a grade A environment/grade B background. Microbiological control of air (two hours exposure of settle plates during preparation), surfaces (24–30 cm² area swabs after preparation), personnel (glove prints), and sterility testing of radiopharmaceuticals is performed regularly from 2001 according to Ph Eur IV. Acceptability limits considering EU GMP recommendations are used.

**Results:**

### Air

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<tr>
<th>Place</th>
<th>Number of exposures</th>
<th>Colony forming unit (CFU/settle plate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>22</td>
<td>1 positive (Staphylococcus haemolyticus)</td>
</tr>
<tr>
<td>Grade B</td>
<td>7</td>
<td>Negative</td>
</tr>
</tbody>
</table>

### Surfaces

<table>
<thead>
<tr>
<th>Place</th>
<th>Number of swabs</th>
<th>CFU/swab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>25</td>
<td>Negative</td>
</tr>
<tr>
<td>Grade B</td>
<td>23</td>
<td>2 positive (Staphylococcus hominis)</td>
</tr>
<tr>
<td>Generator</td>
<td>24</td>
<td>1 positive (Bacillus spp)</td>
</tr>
<tr>
<td>Waste – container 25</td>
<td>22</td>
<td>2 positive (Staphylococcus epidermidis, Bacillus spp.)</td>
</tr>
<tr>
<td>Air lock</td>
<td>20</td>
<td>2 positive (Staphylococcus epidermidis, Bacillus spp.)</td>
</tr>
</tbody>
</table>

### Personnel

<table>
<thead>
<tr>
<th>Right hand</th>
<th>Number of glove prints</th>
<th>CFU/glove print</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>6 positive (Staphylococcus epidermidis, Staphylococcus warner, Staphylococcus haemolyticus, Staphylococcus hominis, Bacillus cereus)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left hand</th>
<th>Number of glove prints</th>
<th>CFU/glove print</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>5 positive (Corynebacterium species, Staphylococcus haemolyticus, Staphylococcus epidermidis, Staphylococcus hominis, Corynebacterium species)</td>
</tr>
</tbody>
</table>

### Sterility testing

<table>
<thead>
<tr>
<th>Number of samples tested</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>397</td>
<td>Negative</td>
</tr>
</tbody>
</table>

**Conclusions:** Hands are the most critical part for microbiological contamination, probably due to handling of unsterile lead containers and shields during preparation. To improve the conditions, repeated decontamination of hands during preparation was introduced. Results of microbiological monitoring during longer time period will be used to set our own acceptability limits, alert and action levels.

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**Studies on the effects of different syringes and personnel applying radiopharmaceuticals in the clinic on the residual activity**

D. Keskintepe 1, 2, A.Y. Ozer 1

1 Hacettepe University, Faculty of Pharmacy, Radiopharmacy Department, Ankara, Turkey, 2 Ankara University, Faculty of Medicine, Nuclear Medicine Department, Ankara, Turkey

**Introduction:** The type of syringes and the volume of the patient doses of radiopharmaceuticals cause high residual radioactivity in the syringes during application to patients. Therefore the investigation of the effects of syringes type and different volumes and personnel on residual activity and adsorption are aimed.

**Material and methods:** Two types of syringes were chosen and the residual activity left in 0.5 and 1.0 mL syringes after the application of different TcO₄⁻ activities was investigated. Commercial radiopharmaceuticals injected to the patients by nurses and technicians. Then, radiopharmacist withdrew these radiopharmaceuticals to the syringes and emptied in-vitro and amounts of residual activity were determined.

The change of residual activity was evaluated depending on the syringe, radiopharmaceutical kit and applicant types.

**Results:** The residual activity reduced by 35–45% in the syringes with flat plungers as the decrease in the amount of radioactivity decreased when the volume was doubled but the radioactivity dose remained the same. The highest values were 15–38% in syringes with an elastomeric lip on the plunger. When the injection of radiopharmaceutical kits were examined the residual activities resulting from personnel application reached up to 10–22% where as the application by radiopharmacist reduced this result.

**Discussion:** The residual radioactivity was decreased in both types of syringes by keeping the radioactivity dose the same and doubling the volume. The residual activity was lower in syringes with elastomeric lip due to smaller dead volume. Radiopharmaceuticals must not be prepared with very small volumes in syringes.

**Conclusion:** Injection of radiopharmaceuticals needs special care. It is concluded that less care during injection or the preparation of radiopharmaceuticals in syringes will cause decrease in the accuracy of the radioactive dose received by the patient and the residual radioactivity in the syringes will cause and increase in the environmental contamination.

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**Abstracts**

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</table>

**Materials and methods:** In our department preparation of radiopharmaceuticals from technetium-99m generators and kits is done in a grade A environment/grade B background. Microbiological control of air (two hours exposure of settle plates during preparation), surfaces (24–30 cm² area swabs after preparation), personnel (glove prints), and sterility testing of radiopharmaceuticals is performed regularly from 2001 according to Ph Eur IV. Acceptability limits considering EU GMP recommendations are used.

**Results:**

| Air Place Number of exposures Colony forming unit (CFU/settle plate) |
|-------------------------------------------------|--------------------------|--------------------------|
| Grade A 22                                       | 1 positive               |
| Grade B 7                                        | 2 positive               |

**Surfaces Place Number of swabs Colony forming unit (CFU/swab) |

| Air Place Number of exposures Colony forming unit (CFU/settle plate) |
|-------------------------------------------------|--------------------------|--------------------------|
| Grade A 22                                       | 1 positive               |
| Grade B 23                                       | 2 positive               |

**Discussion:** The residuel radioactivity was decreased in both types of syringes by keeping the radioactivity dose the same and doubling the volume. The residual activity was lower in syringes with elastomeric lip due to smaller dead volume. Radiopharmaceuticals must not be prepared with very small volumes in syringes.

**Conclusion:** Injection of radiopharmaceuticals needs special care. It is concluded that less care during injection or the preparation of radiopharmaceuticals in syringes will cause decrease in the accuracy of the radioactive dose received by the patient and the residual radioactivity in the syringes will cause and increase in the environmental contamination.

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