P156 PRE-RELEASE DETERMINATION OF ENDOTOXIN IN SHORT-LIVED RADIOPHARMACEUTICALS USING AN ENDOSAFE-PTS

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Objectives: Pre-release QC methods for carbon-11 labelled PET products must be fast to ensure as little loss in activity and specific activity as possible. The Endosafe-PTS is a handheld spectrophotometer that utilizes FDA-approved disposable cartridges for accurate and fast endotoxin testing. Here we describe the validation process of Endotoxin testing for several radiotracers formulated in a physiological saline solution containing approximately 10% ethanol (v/v).

Methods: Inhibition/Enhancement cartridges were used to determine the optimum dilution that gives recovery close to 100% and does not exceed the Maximum Valid Dilution (MVD), where: MVD= (EndotoxinLimit)(ConcentrationOfSampleSolution)/λ With Endotoxin Limit = 175EU/V; dose volume V = 11.1mL(10mL saline + 1.1mL ethanol formulation); the concentration of the sample solution is 1mL/mL when the endotoxin limit is in EU/mL; λ is the confirmed label claim sensitivity of the gel clot lysate or lowest point on the reference standard curve. For 10-0.1EU/mL cartridge sensitivity, the MVD is 158 and for 5-0.05 EU/mL cartridge sensitivity, the MVD is 315. Dilutions were prepared of ^{11}C-labelled radiopharmaceuticals for human use to determine the optimal dilution to avoid interferance with the test.

Results: Resulting optimal dilutions are shown in table 1 for four ^{11}C-labelled tracers in use for clinical scanning at the GSK CIC.

Table1. Summary data for optimum dilution

TRACER	OPTIMUM DILUTION	MINIMUM CARTRIDGE SENSITIVITY
[11C]DASB	1:100	10-0.1 EU/mL
[11C]PHNO	1:200	5-0.05 EU/mL
[11C]Raclopride	1:200	5-0.05 EU/mL
[11C]GR205171	1:200	5-0.05 EU/mL

Conclusions: The Endosafe-PTS allows fast and reliable determination of endotoxin and may be used as a pre-release test in the release process of PET-labelled products.The optimum dilution does not depend on the radiopharmaceutical as it is present in tracer amounts but on the ethanol contained in the formulation which is known to inhibit the test. Although the percentage of ethanol in the final dose it is not a constant factor in radiopharmaceutical productions, the validated dilution for each tracer shows consistent results with recoveries close to 100% (acceptance criteria: 50-200%).

P157 UTILITY OF COMMERCIAL RADIOSYNTHETIC MODULES IN CAPTIVE SOLVENT [11C]-METHYLATION REACTIONS

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Objectives: Captive solvent [^{11}C]-methylation reactions have proved efficacious for the radiosynthesis of [^{11}C]-radiotracers from either [^{11}C]-iodomethane or [^{11}C]-methyl triflate. The attractiveness of the technique lies in its simplicity (no heating, no cooling), its ease of automation, its reliability, and its efficiency (no transfer losses). The original description of the apparatus required in-house assembly of commercially available components and subsequently a commercial dedicated apparatus has become available (AutoLoop™). The advantages of [^{18}F]-radiotracers (principally their ability to be shipped off-site) over [^{11}C]-radiotracers has manifest in the widespread use of versatile modules capable of producing a variety of [^{18}F]-radiotracers over and above [^{18}F]-FDG. We demonstrate here that said modules can easily be adapted to produce [^{11}C]-radiotracers by the captive solvent [^{11}C]-methylation technique.

Methods: A commercial module for the preparation and HPLC purification/formulation of [^{18}F]-radiotracers was prepared for use as a captive solvent module by the following steps. 1. The inlet nut on the HPLC valve was replaced by an injection port (Valco #VISF-2) 2. With the HPLC valve in the "Load" position, the precursor solution (80 μl, Wilson 2000) was loaded onto the clean and dry injection loop. 3. The Valco injection port was replaced by the line which carried the [^{11}C]-methylation synthon. With the above modifications either [^{11}C]-iodomethane or [11C]-methyltriflate was trapped in the coated loop, reacted at ambient temperature, and injected onto the HPLC column by changing the valve position to "Inject".

Results: A variety of [11C]-radiotracers in general use were successfully synthesized using the commercial module from either [^{11}C]-iodomethane or [^{11}C]-methyl triflate (Table). In general, outcomes were no different whether our in-house "LOOP" apparatus was used or the commercial box. Splitting of the steam to allow delivery of the [11C]-methylation synthon to both our in-house "LOOP" apparatus and the commercial module allowed the simultaneous production of two different [^{11}C]-radiotracers (Koeppe, 2001; Quincoces, 2006). The stream splitting had no effect on the outcome of either process, apart form the reduced overall quantities produced by the reduction in starting radioactivity in each module.

Radiosynthesis results

Radiotracer	Time (min)	Yield% (uncorr from 11CO2)
PIB	1	7-9
PE2I	1.5	15-20
Raclopride	3	9-14
DASB	5	15-20
Harmine	1	15-16
DTBZ	1	12-15
SKF 82957	3.5	12-16%

Conclusions: Many commercial modules for the production of short-lived radiotracers (including those designed for either [^{18}F] or [^{11}C]) are equipped with HPLC purification capabilities, including the ability to load crude material onto an injection loop, monitor the chromatogram, collect the appropriate fraction, and formulate the purified radiotracer into an appropriate form for animal or human studies. All that is required to adapt the modules to [^{11}C]-captive solvent methylations is to plumb into a clean, dry HPLC injection loop line carrying the stream of [^{11}C]-iodomethane or [^{11}C]methyl triflate. An ability to detect radioactivity build-up in the injection loop is advantageous, but not critical. The built in capabilities of the module essentially takes care of the rest.

P158 FULLY AUTOMATED SYNTHESES OF [11C]FALLYPRIDE AND [18F]FALLYPRIDE

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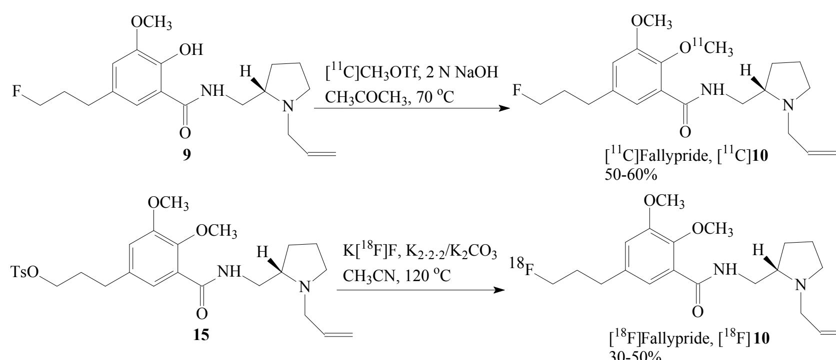
Objectives: Fallypride [5-(3-fluoropropyl)-2,3-dimethoxy-N-[(2S)-1-(2-propenyl)-2-pyrrolidinyl]methyl-benzamide] is a well-known dopamine D_2/D_3 antagonist with high affinity (Ki 30 pM for D_2 receptor sites). Fallypride radiolabeled with fluorine-18 and carbon-11 as [^{18}F]Fallypride and [^{11}C]Fallypride is originally developed by Mukherjee group. [^{18}F]Fallypride has become a commonly used PET tracer for D_2/D_3 receptors, and [^{11}C]Fallypride has a potential advantage in back-to-back same-day PET studies. Wishing to study this compound in this laboratory, we investigated fully automated syntheses of [^{11}C]Fallypride and [^{18}F] Fallypride.

Methods: Phenolic precursor 9 for carbon-11 labeling and Fallypride 10 reference standard were synthesized from the starting material 2-hydroxy-3-methoxy-5-(2-propenyl)benzoic acid methyl ester (1) in 7 and 8 steps, respectively. Tosylated precursor 15 for fluorine-18 labeling was synthesized from compound 1 in 5 steps. An alternate synthetic approach for Fallypride has been developed using compound 1 in 5 steps. [^{11}C]Fallypride ([^{11}C]10) was prepared by O-[^{11}C]methylation of phenolic precursor 9 with [^{11}C]CH_3OTf and purification with a semi-preparative HPLC method. The radiosynthesis was performed in a home-built automated multi-purpose ^{11}C-radiosynthesis module, allowing measurement of specific activity during synthesis. [^{18}F]Fallypride ([^{18}F]10) was prepared by nucleophilic substitution of tosylated precursor 15 with K[^{18}F]F/Kryptofix 2.2.2 and dual purification using semi-preparative HPLC (C-18 column) combined with solid-phase extraction (SPE) (C-18 Plus Sep-Pak cartridge) method. The radiosynthesis was performed in a home-built automated multi-purpose ^{18}F-radiosynthesis module.

Results: The overall chemical yields for phenolic precursor 9 and standard 10 were 16% and 5%, respectively. The overall chemical yield for tosylated precursor 15 was 32%. The overall chemical yield for alternate synthesis of 10 was 26%. The decay corrected radiochemical yields for [^{11}C]10 were 50-60%, and the specific activity was 10 ± 5 Ci/mmol at EOB. The overall synthesis, purification and formulation time was 25-30 min from EOB. The decay corrected radiochemical yields for [^{18}F]10 were 30-50%, and the specific activity was ~1.0 Ci/mmol at EOS. The overall synthesis, purification and formulation time was 60-70 min from EOB.

Conclusions: Efficient and convenient automated syntheses of [^{11}C]Fallypride and [^{18}F]Fallypride have been developed, and the tracers [^{11}C]Fallypride and [^{18}F]Fallypride prepared are suitable for preclinical and clinical studies in animals and humans using PET.

Research Support: Supported by Indiana Genomics Initiative (INGEN) of Indiana University.



Synthesis of [^{11}C]Fallypride and [^{18}F]Fallypride

P159 AUTOMATED PRODUCTION OF [18F]FDDNP USING A TRACERLAB MXFDG

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Objectives: To get an automated method for GMP production of [^{18}F]FDDNP using a commercial [^{18}F]FDG unit for clinical applications.

Methods: Radiolabeling with fluorine-18 was carried out by a [^{18}F]fluoro-de-tosylation reaction on the precursor 2-(1-{6-[(2-tosyloxyoethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile. The reaction conditions were adpated from the UCLA group [1]. The reaction was performed in acetonitrile for 15 minutes at 90°C, and then the reaction mixture was injected into a semi-preparative HPLC system. The desired [^{18}F]FDDNP fraction was collected after 21 min, and a solid-phase extraction was performed.The [^{18}F]FDDNP was formulated in a sodium chloride/ ethanol (9/1:v/v) solution and then passed through a 0.22 μm filter to get an injectable solution. Quality controls were performed on batches such as radiochemical purity, pH, stability, K_{222} test, specific activity and biological tests.

Results: The overall decay-corrected radiochemical yield was 12 ± 3 % (n=8) which is lower compared to the yield obtained by Klock et al. Radiochemical purity was > 98 % and the specific activity was 82 ± 25 GBq/μmol at the end of synthesis. Stability of [^{18}F] FDDNP was studied after 4h and radiochemical purity of [^{18}F]FDDNP remained > 98%. pH of the injectable solution was between 5.5 and 6.1. Krytofix color spot test demonstrated that the concentration of the cryptand was below the authorized limit. The sterility, endotoxin and bioburden tests demonstrated the fiability of our process to get a safe injectable solution of [^{18}F]FDDNP.

Conclusions: We developed a method for [^{18}F]FDDNP production on a tracer lab MX module. The radiosyntheses showed that the process allows a preparation in a moderate yield but with a good fiability and reliability . Moreover, the quality controls and biological tests warrant the safety of the production for clinical application.

Research Support: 1) Shoghi-Jadid K., Small G. W., Agdeppa E. D., Kepe V., Ercoli L. M., Siddarth P., et al. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. Am J Geriatr Psychiatry. 2002;10:24-35. 2) Klok R. P., Klein P. J., van Berckel B. N., Tolboom N., Lammertsma A. A. and Windhorst A. D. Synthesis of 2-(1,1-dicyanopropen-2-yl)-6-(2-[18F]-fluoroethyl)-methylamino-naphthalene ([18F]FDDNP). Appl Radiat Isot. 2008;66:203-7. 3) Liu J., Kepe V., Zabjek A., Petric A., Padgett H. C., Satyamurthy N., et al. High-yield, automated radiosynthesis of 2-(1-{6-[(2-[18F] fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononi trile ([18F]FDDNP) ready for animal or human administration. Mol Imaging Biol. 2007;9:6-16. This study was funded in part by the "EC - FP6-project DiMI, LSHB-CT-2005-512146".

P160 FULLY AUTOMATED SYNTHESIS AND INITIAL PET EVALUATION OF [11C]PBR28

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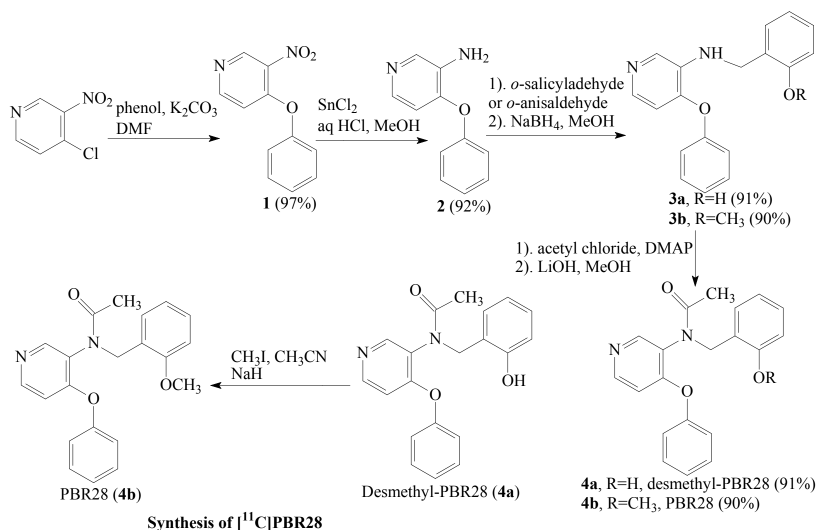
Objectives: The peripheral benzodiazepine receptor (PBR) is an attractive target for molecular imaging of neuroinflammation and tumor progression. [^{11}C]PBR28 (N-(2-[^{11}C]methoxybenzyl)-N-4-phenoxypyridin-3-yl)acetamide) was originally developed by Innis and Pike et al. at the NIMH as a promising PET brain PBR radioligand. Wishing to study this compound in our laboratory, we investigated a fully automated synthesis of [^{11}C]PBR28 and performed initial PET imaging in an animal model of traumatic brain injury (TBI).

Methods: The precursor desmethyl-PBR28 and the authentic standard PBR28 were synthesized from 4-chloro-3-nitropyridine and o-salicylaldehyde or o-anisaldehyde in 4 steps, respectively. The target tracer [^{11}C]PBR28 was prepared by O-[^{11}C]methylation of desmethyl-PBR28 with [^{11}C]CH_3OTf and isolated by HPLC method in an in-house automated multi-purpose ^{11}C-radiosynthesis module, allowing measurement of specific activity during synthesis. Three female Sprague-Dawley rats were scanned on the IndyPET-III small animal PET scanner (1.1 mm FWHM transaxial resolution and 1.5 mm FWHM axial resolution). Two animals had received a TBI to the left parietal cortex; the third animal received a sham surgery and no TBI.

Results: The overall chemical yields for desmethyl-PBR28 and PBR28 were 68% and 63%, respectively. The radiochemical yields for [^{11}C]PBR28 were 70-80%, decay corrected to EOB, based on [^{11}C]CO_2. The specific activity was 6.0-16.0 Ci/μmol at EOB. Injected activity for PET scanning was (mean ± sd) 0.31 ± 0.07 mCi, and mass dose was 0.58 ± 0.35 nmol/kg. Overall brain uptake in the sham animal and in the unlesioned hemispheres of the TBI animals was very low. SUV values in the lesioned region in TBI animals were 2-3 times higher than SUV from the unlesioned side. The sham animal had no evidence of significant [^{11}C] PBR28 binding in the brain, consistent with low constitutive expression of the PBR in brain.

Conclusions: An efficient and convenient automated synthesis of [^{11}C]PBR28 was developed, and PET evaluation of the [^{11}C] PBR28 product was performed in a rat model of TBI. These results suggest that the tracer [^{11}C]PBR28 is suitable for preclinical and clinical studies in animals and humans using PET.

Research Support: Supported by Indiana Genomics Initiative (INGEN) of Indiana University and NIH 5P50NS052606.



Synthesis of [^{11}C]PBR28

P161 LC-MS EVALUATED THE PET TRACERS OF 5-HT1A LIGANDS [BR]-WAY

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Objectives: The value of LC/MS as a complementary research tool to evaluate the primary biodistribution of PET radiotracer had been described recently. This technique could provide the following information on a newly developed chemical entity without the need to prepare a radioactive analogue: 1) quantitative biodistribution of the molecule in target tissue using injected doses similar to the radiotracer level; 2) evaluation of input function via temporal sampling; 3) binding specificity through displacement and/or blocking with a similar chemical entity; and 4) quantitation of the biodistribution of metabolites. We have applied this method to the evaluation of 3 novel brominated analogs of WAY100635.

Methods: High sensitivity LC/MS instrumentation (API 4000 QTRAP MS coupled with an Agilent HPLC 1200) was applied to evaluate ex vivo biodistribution and metabolites of novel bromine-containing 5-HT_{1A} ligands (Br-WAY) in rats. The compounds were injected (i.v.) at mass doses similar to those expected for radiolabeled compounds. At designated times, tissues were dissected from the animals and extracted using a barocycler extractor which cycles hydrostatic pressure between ambient and ultra-high levels to provide efficient extraction. The differential uptake ratio (DUR) and the brain tissue specific binding ratio were calculated from the tissue concentrations determined by the LC-MS method. We also propose structures for the metabolites of each Br-WAY observed in vitro (liver hepatocytes) and in vivo (plasma and brain).

Results: We prepared 3 isomeric Br-Way analogs (fig.1) and evaluated the brain biodistribution to evaluate receptor specificity. From previous studies in this class of molecules, a high ratio between hippocampus uptake and cerebellum uptake predicts high affinity. The specific binding ratio of 3 Br-WAY and FPWAY showed in fig.2. Using in vitro methods we proposed structures for the major metabolites of each compound. Analysis of the in vivo metabolites in the rat plasma and brain were conducted. The metabolites observed were consistent with in vitro data. Plasma contained parent, oxidation metabolite, amide hydrolysis metabolites, and demethylation metabolite. In the rat brain, parent predominated; minor amounts of oxidation and demethylation metabolites were also observed. Quantitation of the metabolites would be possible if authentic standards were available.

Conclusions: The high sensitivity LC/MS is an indispensable tool in evaluating the presence of tracer and its metabolites in target tissue in the development of new molecular imaging probes. We found the Br-WAY analogs had significantly lower uptake (DUR) and the specific binding ratio (hippocampus to cerebellum ratio) compared to their fluorine containing analogs (FPWAY) .

Fig. 1

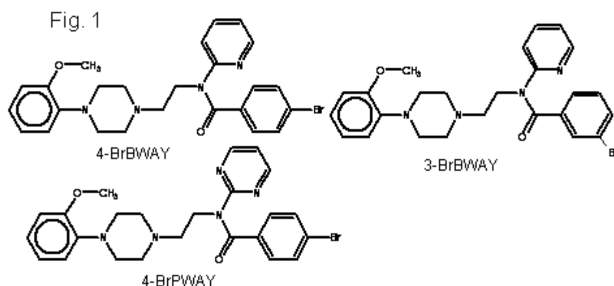
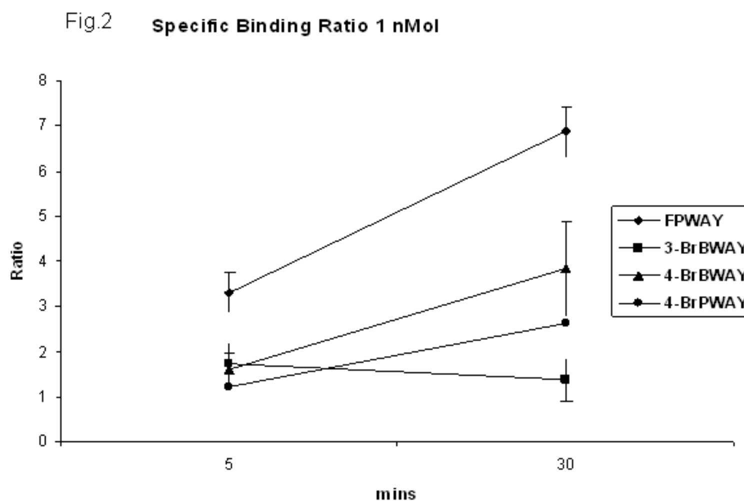


Fig.2



P162 AN AFFORDABLE AND FLEXIBLE ONE STOP SHOP LIMS

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Objectives: To facilitate the daily work and fulfill GMP and Radiation Safety compliance, a commercially available, pre-configured, computerized LIMS has been implemented in our PET laboratories.

Methods: Using a touch screen computer all of the required information for radiopharmaceutical production is readily at hand. The workflow for any tracer is given from starting material to finished product, including quality control. Rather than spending time on finding the latest version of a document such as an SOP, checklist or inventory, users can use a computerized "one stop shop". There is no need to check that a document is valid as only the latest approved version is displayed. Analytical results are entered directly into the system which maintains full version control and auditing for GMP and regulatory compliance. No paper is needed – paper poses both a contamination and microbiological risk. Full traceability allows a user to view results and certificates of analysis for all the raw materials used in production with all actions time/date/user-stamped for a full audit trail.The LIMS conforms to regulatory requirements such as FDA 21 CFR11, current cGMP and European regulations. Double sign-off have been implemented so a scientist is not allowed to validate their own results. System and user actions are stored in the system's event log.

Results: A brief introduction to the system will be given and the pros and cons will be discussed.

Conclusions: A brief introduction to the system will be given and pros and cons discussed.

P163 68Ga-LABELLING OF PEPTIDES USING DIFFERENT STRATEGIES FOR A DISPOSABLE CASSETTE SYSTEM

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Objectives: Generator-based ^{68}Ga is attracting interest especially for labelling of DOTA-derivatised peptides. Here we describe a comparison of two approaches based on preconcentration of ^{68}Ga-eluate on a cation exchanger and on fractionation of the generator eluate on a fully automated modular synthesis system (system 1). Both methods were transferred and validated on a system using a disposable cassette system (system 2).

Methods: Commercially available ^{68}Ge/^{68}Ga generators (IGG, Eckert & Ziegler, 1110 MBq) were eluted with 0.1 M HCl. The ^{68}Ga-eluate was preconcentrated on a re-useable Bio-Rad AG 50W-X4 cartridge, later replaced by a commercially available cartridge (Strata X-C, Phenomenex, USA) and eluted with acetone/HCl solution into water containing DOTA-peptides (method A). Alternatively direct labelling was performed after fractionated collection of the ^{68}Ga-eluate and pH adjustment with acetate buffer (method B). The resulting solutions were heated at 90°C for 7 min and then transferred to a C18 cartridge for purification. Radiochemical yield (RCY) and radiochemical purity (RCP) were determined by ITLC-SG (0.1 M sodium citrate pH 5) and RP-HPLC (ACN/H_2O/0.1% TFA). Overall yields were calculated. Metal contents and ^{68}Ge breakthrough of all products were determined. Acetone content in the final preparation was analyzed by GC. After optimization in system 1 the technique was transferred to system 2.

Results: Preconcentration of the eluate on a cation exchange catridge (method A) efficiently removed ^{68}Ge as well as Fe and Zn (<455±0 and 30±0 ppb for Bio-Rad AG 50W-X4, 210±0 and 113±0.2 ppb for Strata X-C, n=3, ^{68}Ge < 0.0001%) and resulted in a high labelling efficiency at high specific activity (SA). Equivalent SA was achieved with method B. Method A resulted in a product with RCY 97.8±1.8 (n=3) and method B with RCY 94.8±1.6 (n=5). ^{68}Ge was efficiently removed by C18-purification and was lower than 11 Bq in all preparations. Overall decay corrected yields were 71.1±9.3% (n=4) for method A and 65.0±1.2% (n=10) for method B on system 1 with synthesis times of 25 min and 10 min, respectively. Using a disposable cartridge (system 2) yields were 74.8±4.3 % (n=7) and 78.7±4.7% (n=4) with synthesis times of 33 min and 22 min for method A and method B, respectively. RCP exceeded 91% by HPLC and 99% by TLC in all cases. Acetone content was < 0.01%.

Conclusions: ^{68}Ga-DOTA-TOC was prepared using different labelling strategies in a fully automated system and using disposable casettes with high yield and pharmaceutical quality. The advantage of preconcentration (method A) with higher activities and removal of ^{68}Ge is impaired by longer synthesis times. Direct use of the eluate (method B) resulted in equivalent quality with the advantage of easier technical implementation for routine use and shorter synthesis times.

P164 TOWARDS THE DEVELOPMENT OF PHARMACEUTICAL KIT FOR GALLIUM-68 LABELLING OF DOTATATE

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Objectives: In the recent yearsthe interest in ^{68}Ga labeled agents useful in diagnostic procedures in PET is increasing rapidly followed by the increasing number of $^{68}Ga/^{68}Ge$ generators users. Currently, two generator types are available commercially: (1) TiO_2 based and eluted with 0.1 M HCl and (2) SnO_2 based, eluted with 0.6 M HCl. Previous studies on the ^{68}Ga labeling of DOTA-chelated peptides revealed that labeling pH at the level of 3.5 – 4.0 has a critical influence on labeling yield. Hence, optimization of labeling procedures is required in order to reduce time necessary for efficient radiopharmaceutical preparation, involving automation of the process [1-5]. The preparation of peptide in a dry kit form would be a step towards that as well, however the same approach of dry kit preparation as it is in case ^{177}Lu labeled kits is not applicable due to the variety in eluate HCl concentration.

Methods: Both the SnO_2 based generator (iThembaLABS) and the TiO_2 based generator (Eckert and Ziegler) were eluted according to the instructions provided by supplier. For labelling of 40 μg DOTATATE (piChem, Austria) the suitable quantity of 1,25 M AcONa was added to provide the final pH of about 3.7. In the second method, a pre-concentration of eluate was carried out as described by Velikyan et al [5]. To 1 ml of 0.1 M AcONa, pH = 3.7, containing 40 μg DOTATATE the water solution of ^{68}Ga (obtained from anion exchange column) was added. In both methods incubation was carried out at 95°C for 15 min using heating oven. Final product was purified using SepPak C-18 columns. The radiochemical purity was assessed by HPLC on C-12 Jupiter/ Phenomenex column.

Results: Both $^{68}Ge/^{68}Ga$ generators performed as declared by their manufacturers. Generally, the labelling yields in the range 60 to 68% were obtained (calculated as percent of ^{68}Ga-DOTATATE fraction radioactivity related to the radioactivity of eluate used for synthesis, no time correction). Slightly higher labeling yields were obtained when the post-elution concentration of eluate was involved, in the range of 65 to 72%, despite the longer time of operations. In both methods the radiochemical purity after SepPak purification was >99%.

Conclusions: The labelling yields in the range of 60-70% are satisfactory. However, the pH of labeling is critical and not easy to maintain when the fixed kit composition is used. The proposed, simplified procedure for ^{68}Ga labeling of DOTATATE is easy and rapid (20-25 min). The eluate concentration step might be an advantage in planning the universal kit composition for both currently available generator systems. It is known that higher labeling yields are obtained when the total reaction volume is not more than 3-4 ml, however in case of insufficient ^{68}Ga eluate radioactivity, the whole elution volume can be used with no need for pre-concentration. The labeling procedure has been validated in the hospital radiopharmacy.

Research Support: COST Actions D38 and BM0607 and the research grant No. 200/N-COST/2008/0 of Polish Ministry of Science and Higher Education

References: 1. Decristoforo C., Knopp R., von Guggenberg E. Rupprich M., Dreger T., Hess A., Virgolini I., Haubner R. [2007] Nucl Med Commun 28 (11): 1-6 2. Breeman W. A. P., de Jong M., de Blois E., Bernard B. F., Konijnenberg M., Krenning E. P. [2005] Eur. J. Nucl. Med. and Mol. Imaging, 32 (4): 478-485 3. Meyer G-J., Macke H., Schuhmacher J., Knapp W. H., Hofmann M. [2004] Eur. J. Nucl. Med. and Mol. Imaging, 31 (8): 1097-1104 4. Zhernnosekov K. P., Filosofov D. V., Baum R. P., Aschoff P., Bihl H., Razbash A. A., Jahn M., Jennewein M., Roesch F. [2007] J Nucl Med. 48 (10): 1741-1748. 5. Velikyan I., Beyer G.J., Langstrom B.[2004] Bioconjugate Chem 15: 554-560

P165 NOVEL ANALOGUES OF 3-(1-METHYL-2(S)-PYRROLIDINYLMETHOXY)PYRIDINE (A-84543) AS HIGHLY SELECTIVE AGENTS FOR NEURONAL NICOTINIC ACETYLCHOLINE RECEPTORS (nAChRs)

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Objectives: Current research efforts on the part of PET radiochemists have focused on development of new, highly specific and highly selective nAChR radioligands with improved brain kinetics that are able to localize high-affinity nAChRs in vivo. The C5 position of the pyridyl moiety of A-84543 tolerated sterically bulky substituents without losing its binding affinity at nAChRs.A serises of nicotinic ligands, different groups into the C5 position of the pyridyl ring of A-84543 have been synthesized and radiolabeled with positron emitting isotopes ^{18}F for PET imaging of neuronal nicotinic acetylcholine receptors (nAChRs) and tested for there affinity for the central nicotinic receptor. This new radioligands, derivatives of A-84543, display better imaging properties than ^{11}C-nicotine and a better toxicity profile than epibatidine analogs. This new PET nAChR radioligands will be examined brain kinetics present.

Methods: PET imaging; receptor binding; brain kinetics

Results: The binding assay demonstrated that all ligands with good Ki values and the experimental lipophilicity values of all ligands were in the optimal range for the cerebral radioligands.

Conclusions: Because of the recent advance in solving the structure of the molluscan AchBP and the resulting homology modeling of the extracellular domains of some nAChRs, strategies for developing new subtype-selective ligands should become more rational.

P166 A CONVENIENT RADIOLABELING OF [C-11](R)-PK11195 USING LOOP METHOD IN AUTOMATIC SYNTHESIS MODULE

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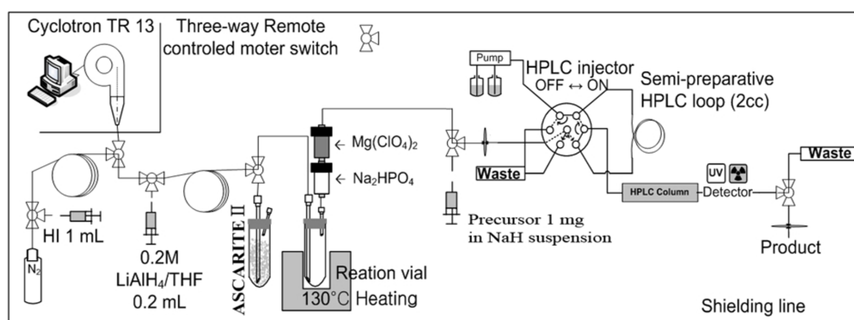
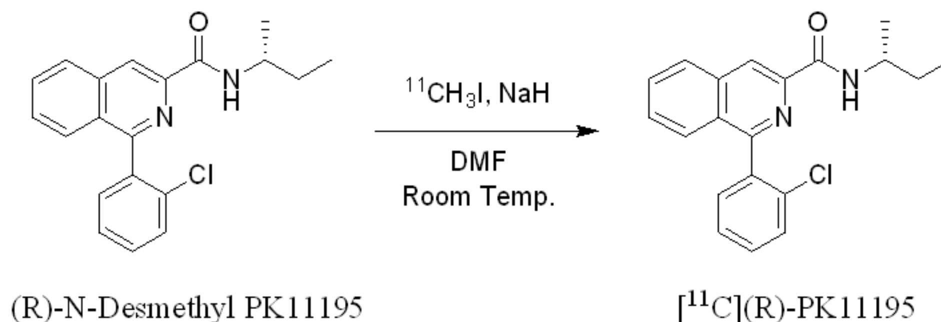
Objectives: The [^{11}C](R)-PK11195 ((R)-1-(2-chlorophenyl)-N-1-[^{11}C]methyl-N-(1-propyl)-3-isoquinoline carboxamide), is a specific ligand for the peripheral type benzodiazepine receptor and a marker of activated microglia, used to measure inflammation in neurologic disorders. We report here that a more direct and simpler radiosynthesis of [^{11}C](R)-PK11195 in mild condition is possible with NaH suspension and an one-steploop method for the automated synthesis module. Direct radiolabeling of the amide nitrogen with NaH suspension results in [^{11}C](R)-PK11195 with good yields.

Methods: In Automated radiosynthesis module, 1 mg of (R)-N-Desmethyl-PK11195 in 0.1 mL DMSO and NaH suspension 0.1 mL injected at radiosynthesis module, [^{11}C]methyl iodide passed through HPLC loop at room temperature (RT). The reaction mixture was separated by semi-preparative HPLC. Aliquots eluted at 11.3 min were collected and analyzed by analytical HPLC and mass spectrometer.

Results: The labeling efficiency of [^{11}C](R)-PK11195 was 71.8±8.5 percent, The specific radioactivity was 11.8±6.4 GBq/μmol, and The chemical and radiochemical purity were higher than 99.2%. The mass spectrum of the product eluted at 11.3 min showed m/z peaks at 353.1 (M+1), indicating the mass and structure of (R)-PK11195.

Conclusions: By the one-step loop method with the [^{11}C]CH_3I automated synthesis module, [^{11}C](R)-PK11195 could be simply prepared in high radiochemical yields with using NaH suspension. Also, the method can be successfully applied for routine clinical application, proved to be a simplified alternative to the bubbling method and offered an easy way to transfer the reaction mixture into an HPLC column.





P167 HIGHLY EFFICIENT AUTOMATED SYNTHESIS OF [18F]FLUOROCHOLINE USING A MULTIPURPOSE CHEMISTRY MODULE

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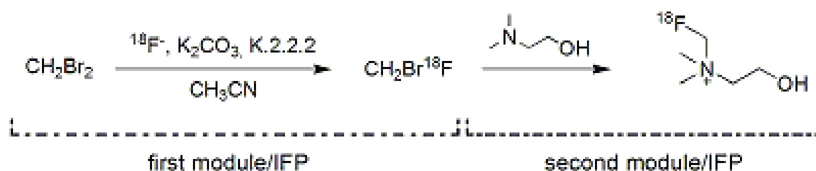
Objectives: To develop a robust and optimized synthesis method for the routine production of [18F]fluorocholine (FCH) on the Synthera®, a fully automated chemistry module employing dedicated auto-ejectable single-use integrated fluidic processor (IFP). In this work, a fully automated two-step synthesis of FCH together with its quality control are reported.

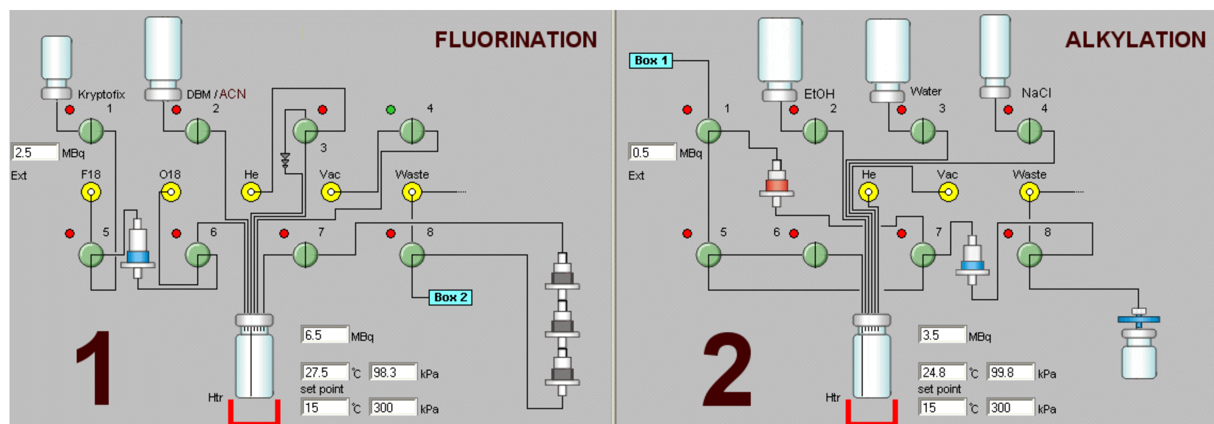
Methods: Synthesis route was based on the two-step methodology (fluorination/alkylation) recently published by Kryza et al. In order to implement this approach, two synthesizers were used without any hardware modifications or adjustments from their standard configurations (multipurpose platform). The system thus operates with two interconnected disposable IFPs which were designed with appropriate pre-defined synthesis hardware and plumbing. The first module/IFP is dedicated to the synthesis of the volatile intermediate [18F]fluorobromomethane (FBM) which is then purified through distillation with a low helium flow to the second module/IFP which supports the alkylation step as well as purification and formulation of the final product. Design and plumbing of the IFP and system ensure the full containment of FBM crucial for the reproducibility of the synthesis.



Results: The fluorination of dibromomethane (DBM) was optimized against reaction time, temperature and concentration. The volatile fluorinated intermediate was effectively and consistently purified by distillation through an array of silica cartridges with controlled heating and helium as a carrier gas (32 ml/min flow achieved by a restrictor built in the IFP) and recovered with a 30 % radiochemical yield. Elution profile has proven to be highly reproducible (n=30) with 90 % of total FBM activity being recovered in less than 20 minutes free of any unreacted DBM. Alkylation was performed on a reversed-phase cartridge connected to the first module/IFP throughout the distillation process and pre-loaded with the N,N-dimethylaminoethanol precursor (DMAE). Choice of an appropriate reversed-phase cartridge has allowed for a maximized and reliable (22+/-2) % FCH yield after a synthesis time less than 50 minutes. The product is effectively purified with inexpensive and commercially available cation exchange cartridge affording FCH in an isotonic saline solution with a radiochemical purity > 95 % and a high chemical purity (residual solvents USP and Eur. Ph. compliant, DMAE < 1500 ppm, DBM below detection limit).

Conclusions: In this work, we have described reliable synthesis for potential clinical applications of a promising PET radiotracer for the detection of prostate cancer on an automated platform. The synthesis employs single-use IFP and pre-loaded reagents, preventing cross-contamination, which is in line with GMP guidelines. The final product is obtained with highly reproducible and stable radiochemical yields and high chemical purity and can be manufactured routinely at large scale in a GMP environment thanks to the robustness and proven consistency (for FDG, FLT and NaF) of the synthesizer platform used.

References: Kryza et al., Nuclear Medicine and Biology 35 (2008), 255 - 260



P168 PREPARATION OF 111In LABELED MORPHOLINO OLIGOMER FOR PRETARGETING OF ABDOMINAL SITES

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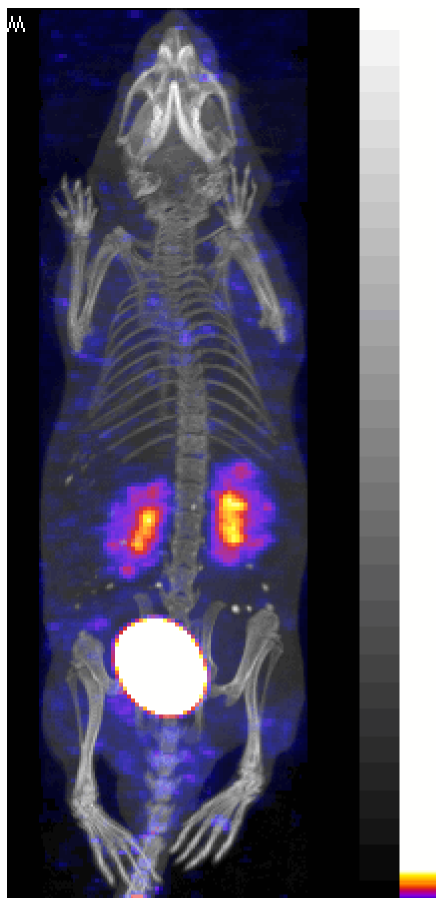
Objectives: Pretargeting of the pancreas requires that the radiolabeled effector shows minimal accumulations in abdominal tissues. We already shown that the phosphorodiamidate morpholino oligomer (cMORF) effector clears from the circulation rapidly and exclusively through the kidney when radiolabeled with ^{111}In via DTPA chelator and therefore is suitable for targeting the MORF-conjugated antibodies in the pretargeted diabetic pancreas. To simplify studies with this effector, we have investigated the conjugation of cMORF with DTPA and the radiolabeling with ^{111}In to provide a product with high specific activity and without the need for post labeling purification.

Methods: Rather than using the conventional cyclic anhydride of DTPA, the cMORF was conjugated with DTPA using the EDC condenser for its versatility and the influences of cMORF and DTPA concentrations on the number of DTPA groups attached was investigated by labeling with ^{111}In followed by SE HPLC analysis. Purification methods for the DTPA-cMORF were then screened.

Results: The number of amine groups in the commercial amine-derivatized cMORF was confirmed as 0.981 by its reaction with trinitrobenzene sulfonic acid and using the native cMORF as control. The number of DTPA groups per cMORF was 0.15-0.20 following conjugation with DTPA over the cMORF/DTPA molar range of 0.5 to 5 and using a cMORF/EDC molar range of 20 to 60. The lower than expected efficiency was probably due to steric hindrance. A 50 cm P4 column was found capable of efficiently separating the DTPA and cMORF. When radiolabeled by transchelation from acetate, the labeling efficiency was greater than 95%, thus avoiding the need for postlabeling purification. Although not more than one-fifth of the cMORF groups were DTPA-derivatized, a specific radioactivity of at least 300 μCi/μg or1.90 Ci/μmol of cMORF was achieved.

Conclusions: A protocol for the preparation of DTPA-cMORF and for the radiolabeling with ^{111}In at high specific activity was developed. Further studies will be required to establish the maximum specific activity achievable by this approach.



P169 DOSIMETRY OF 61CU-BLEOMYCINE: A TUMOR IMAGING AGENT FOR POSITRON EMISSION TOMOGRAPHY (PET)

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Objectives: Radiation dosimetry plays the crucial role for estimating the process of diagnosis as well as for the comparison of various diagnostic methods. ^{61}Cu-bleomycin is a candidate compound, for use in tumor imaging.

Methods: Human absorbed dose estimates extrapolated from rat data were based on the biodistribution of ^{61}Cu BLM in adult normal rats, according to the Medical Internal Radionuclide Dose (MIRD) methodology using the measured residence times and the dose rate S-values. Nineteen tissues were harvested and time–activity curves generated. The cumulative activity (µCi-h or MBq-h) for each organ was determined by integrating the area under the time–activity curves.

Results: kidneys appeared to be the dose-limiting organ in free ^{61}Cu. renal radiation absorb doses for $^{61}Cu^{2+}$, ^{61}Cu-BLM were estimated to be: 0.115 and 0.015 mGy, respectively, per MBq administered. Corresponding radiation absorbed dose in the liver were 0.113 and 0.062 mGy/MBq. Radiation absorb doses in the heart were 0.0243 and 0.033 mGy/MBq for these two radioactive species.the total body dose was 0.10 ,0.065 mGy/MBq for $^{61}Cu^{2+}$, ^{61}Cu-BLM respectively.

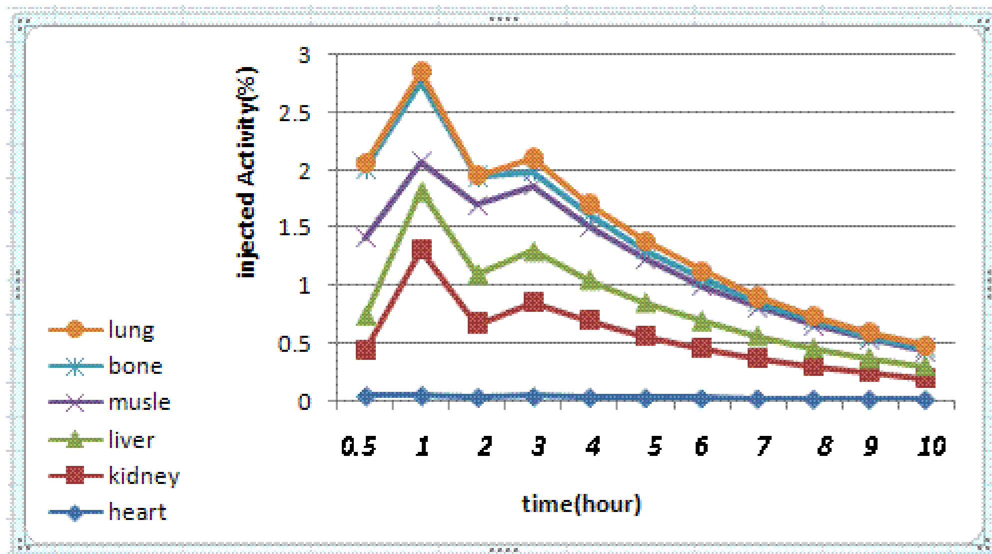

figure: ^{61}Cu-BLM time-activity curve for various organ

Conclusions: Above-mentioned, relatively-small absorbed doses to body organs, make ^{61}Cu-BLM suitable for safe human injection in clinical trials of PET imaging

P170 MAINTAINING RADIOCHEMICAL PURITY OF RADIOPEPTIDES FOR RECEPTOR-TARGETING

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Objectives: A new application of radiopeptides is animal SPECT or animal PET. However, very high activities are required, and, in addition, in a small volume (e.g. 50 MBq of ^{111}In-labeled peptides in a 25 gram mice, which equals 2 GBq per kg). Peptides radiolabeled with ^{111}In or ^{177}Lu are vulnerable for radiolysis and oxidation, e.g. methionine in the pharmacophore of CCK- or GRP-receptor targeting peptides are rapidly oxidized into methionine-sulfoxide, and results in loss of receptor affinity. Quenchers are known to protect peptides, therefore, Radiochemical Purity (RCP) of the radiopeptides in the absence or presence of additives such as quenchers was monitored. In addition, maintaining RCP in time eases logistics and enables production and shipment of these radiopharmaceuticals.

Methods: Peptides were labeled with ^{111}In or ^{177}Lu at different specific activities and concentrations. RCP was monitored, while varying t, T and [quencher(s)]. Dose calculations revealed a dose of 200 Gy after 24 h for a solution containing 22 or 110 MBq ^{177}Lu or ^{111}In, resp. in 0.2 mL. The effects of radiolysis were determined by measuring RCP via HPLC reversed phase C_{18} column from t=0 up to 7 days after labeling. Octreotide analogs such as DOTA-TATE (DOTA-DF-C-Y-DW-K-T-C-T), DTPA-octreotide (DTPA-DF-C-F-DW-K-T-C-T(ol)), and methionine-containing peptides, such as DTPA-bombesin (MP2248, DTPA-P-Q-R-Y-G-N-W-A-V-G-H-L-M-NH_2) and DOTA-MG11 (DOTA-DE-A-Y-G-W-M-D-NH_2) were used as models.

Results: Time-dependent formation of different prepeaks on the HPLC chromatogram in the presence or absence of ethanol, ascorbic acid, gentisic acid, amino acids such as methionine, revealed that every quencher seem to have different mechanisms of protection on the radiolabeled peptides and is radionuclide dependent. Combinations of quenchers were more effective than any single quencher. In the absence of quenchers all radiopeptides revealed a drop of ≈ 50 % in RCP at 70-80 Gy, and were radionuclide independent. RCP at t=0 depends on the purity of the peptide, radiolabeling conditions, specific activity, and the combination and concentration of quenchers. Under optimized conditions RCP for ^{111}In-DTPA-octreotide (OctreoScan®) remained high, 97% at t=0 and 96% after 7 days in the presence of gentisic acid, ascorbic acid and ethanol, versus <50% after 1 day without quencher. Under optimised conditions (e.g. 7% ethanol, 3.5 mM ascorbic acid and 3.5 mM gentisic acid), RCP was independent of specific activity and less dependent on the concentration of the radionuclide, e.g. RCP of ^{111}In-DOTA-MG11 could be maintained at ≥ 85% up to 7 days in the presence of 7% ethanol, 3.5 mM ascorbic acid, 3.5 mM gentisic acid and 50 mM methionine. RCP of a solution of 600 MBq ^{177}Lu-DOTA-tate in 1 mL (dose 4 kGy after 4 days) remained 95% at t=0, up to 4 days in the presence of 7 % ethanol, 3.5 mM ascorbate, 3.5 mM gentisic acid.

Conclusions: Combinations of quenchers are essential to maintain RCP of ^{111}In- or ^{177}Lu-labeled radiopeptides.

P171 A RELIABLE AND INEXPENSIVE PLATFORM FOR ASSEMBLING AUTOMATED CHEMISTRY MODULES TO COMPOUND C-11 AND F-18 LABELED RADIOPHARMACEUTICALS

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Objectives: The cost of commercial automated chemistry module can be cost prohibitive in radiopharmaceutical development, justifying the cost of a chemistry module (in excess of a $100,000) to synthesize a radiopharmaceutical perhaps only 50 times is a barrier that prevents tracer development from being accomplished. To address this problem, we have developed an inexpensive, and reliable platform to build chemistry modules that can be customized to synthesize a large array of radiopharmaceuticals. We have used this platform to synthesize C-11 glucose (1-[11C] D-glucose), C-11 PIB (C-11 -6-OH-BTA-1) (PIB), C-11 Palmitate, C-11 Acetate, as well as F-18 Fluorodopa. The cost to build the most capable system that includes HPLC purification is only $10,000.00 US, with $4,000US typically needed to complete quality control testing and validation.

Methods: The chemistry platform we developed is controlled using digitals and analog I/O modules that are operated with a PC. The program was designed to prompt the user through the cleaning and setup of the chemistry module, requiring user acknowledgement after each step. All of the steps are then recorded to a production file. The program proceeds linearly through each step of the synthesis and records the module's action. The chemistry modules are powered with 120Vac, 5Vdc, 12Vdc and 24Vdc. This provides substantial flexibility in choosing components. The first module was construct using stainless steel, but due to cost and poor chemical resistance to strong acids we have constructed subsequent chemistry modules using acetal sheet. Valve choice was based on successful past use and cost. When possible, pinch valves were used to enable the use of disposable tubing sets for reagent pathways. This facilitates setup and cleaning between syntheses. We currently have reactors for 2mL V-vial, 10mL, 15mL and 25mL conical vessels. The temperature range of chemistry platform reactor is 0C to 200C, and is sufficient for numerous reactions.

Results: C-11 acetate, C-11 palmitate, C-11 glucose, C-11 PIB, and F-18 fluorodopa are synthesized using this chemistry platform with batch yields that are practical for clinical applications. For example, F-18 fluorodopa is made with a radiochemical yield (RY) of 20%, radiochemical purity (RP) >95% and specific activity (SA) >1000mCi/mmol. C-11 PIB is synthesized with an uncorrected RY of 7-14%, (RP)>95% and SA 2000-40,000Ci/mmol.

Conclusions: The radiosyntheses performed with these modules meets USP requirements for drug purity. The syntheses performed are fully automated and give the chemist capability to acknowledge and record steps for quality assurance. The module facilitates validation of the automatic process at a significantly reduced cost relative to commercially-available systems. These inexpensive modules greatly enhance the flexibility of PET radiopharmaceutical production, and enhance the clinical supply of numerous tracers on an as-needed basis.

P172 18F-LABELING AND EVALUATION OF NOVEL 18F-LABELED MDL 100907 DERIVATIVES

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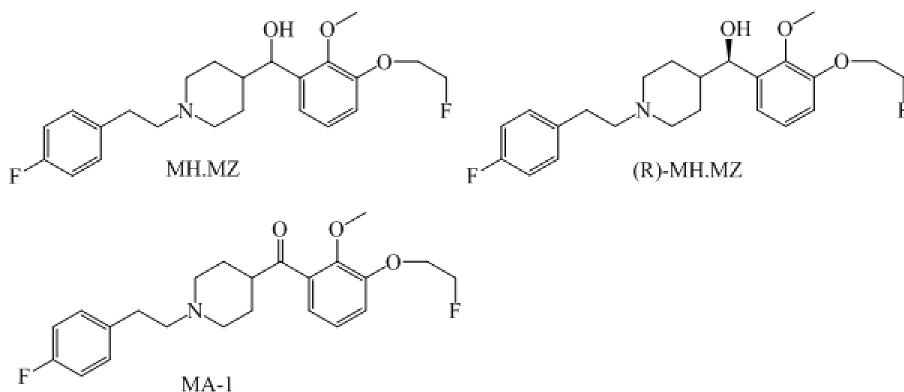
Objectives: [^{11}C]MDL 100907 or [^{18}F]altanserin are the tracers of choice to image the 5-HT$_{2A}$ receptor status. The selectivity of MDL 100907 is preferable, but due to the short half-life of carbon-11 time consuming transportation is not accomplishable. We have recently synthesized analogues of MDL 10007 combining the advantages of the superior selectivity of MDL 100907 over altanserin and the better isotopic properties of ^{18}F. Herein, we report on the radiolabeling and preliminary evaluation studies of various ^{18}F-MDL 100907 derivatives.

Methods: A number of MDL 100907 analogues were labeled by [^{18}F]FETos and optimized regarding time, temperature, solvent and amount of precursor. Purification was carried out via HPLC and cartridge separation. Preliminary evaluation in terms of autoradiography, metabolism-, biodistribution- and μPET-experiments were conducted in male 8 week old Wistar or SD rats.

Results: The optimized labeling procedure provides radiochemical yields of about 80–90% for the fluoroethylation step. An efficient final formulation could be obtained, which took no longer than 100 minutes and provided the labeled compounds with a purity > 96% and a specific activity A_s between 15 – 20 GBq/μmol. Autoradiographic studies for the most promising derivatives MH.MZ (5-HT$_{2A}$ K_i=9.0 nM) and (R)-MH.MZ (K_i=0.7 nM) showed excellent binding, whereas surprisingly MA-1 (K_i=3.1 nM) showed an unfavorable distribution (Figure 1). This is probably due to its increased lipohilicity. μPET experiments including metabolism studies and biodistribution showed a binding potential BP of 1.5 for [^{18}F]MH.MZ and 1.8 for (R)-[^{18}F]MH.MZ, fast metabolism and an approximately brain uptake of 0.6 % ID/g tissue.

Conclusions: [^{18}F]MH.MZ and (R)-[^{18}F]MH.MZ could be obtained as injectable solution in overall radiochemical yields of about 40% within a synthesis time of about 100 minutes in a purity of > 96%. Both tracers showed excellent binding properties in in vitro, ex vivo and in vivo experiments. However, (R)-[^{18}F]MH.MZ is the more valuable tracer due to its selectivity.



P173 A PRACTICAL PREPARATION OF [18F]FEPPA USING A PROTIC SOLVENT SYSTEM

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Objectives: Aliphatic nucleophilic fluorination with [^{18}F]fluoride displacing sulfonyloxyl or halogen gropus is one of the most important methods of PET radiopharmaceutical preparation. However, in some cases this method requires large amounts of precursor and careful optimization of reaction conditions due mailny to side reactions accompanying the fluorination. Chi et al. extensively reported utilization of a protic solvent system for fluorination (1-3). We report herein a practical preparation of a potent radioligand for the peripheral benzodiazepine receptor (PBR), [^{18}F]N-(2-(2-fluoroethoxy)benzyl)-N-(4-phenoxypyridin-3-yl) acetamide (FEPPA) (4) using a protic solvent system.

Methods: Syntheses were carried out using a CUPID F1 radiosynthesis system (Sumitomo Heavy Industries) which was originally designed for FDG preparation. An aqueous solution of [^{18}F]fluoride was passed through a Sep-Pak QMA column (Waters) and trapped radioactivity was eluted with 0.3mL of aqueous 33mM tetrabutylammonium hydroxide. After drying in vacuo a solution of a precursor (2mg) in 1mL of t-BuOH:CH_3CN (9:1) was added to the dried [^{18}F-fluoride. The mixture was heated at 110°C for 30min and purified by HPLC after cooling. The collected fraction containing [^{18}F]FEPPA was diluted with water and further applied to solid-phase extraction column (Sep-Pak -tC18, Waters). Retained radioactivity was eluted with 0.5mL of ethanol.

Results: The desired compound was obtained in radiochemical yields of 39 ±7% (decay corrected) and specific activities of 73 ±30 GBq/μmol at EOS (n=19). Radiochemical purity exceeded 95%. This method allowed us to use less amount of precursor but the yield was lower than the originally reported procedure (4). HPLC purification was accompanied with radiolytic decomposition resulting in an elevation of the baseline of the radiochromatogram. This decomposition was lessened by addition of ethanol to the mobile phase; however, complete suppression could not be achieved. The concomitant byproduct was removed by solid-phase extraction formulaton of the eluate.

Conclusions: In summary, a practical preparation method of [^{18}F]FEPPA was established using smaller amounts of precursor with the aid of a protic solvent system.

References: (1) Kim DW, Ahn DS, Oh YH, Lee S, Kil HS, Oh SJ, Lee SJ, Kim JS, Ryu JS, Moon DH, Chi DY. A new class of SN2 reactions catalyzed by protic solvents: Facile fluorination for isotopic labeling of diagnostic molecules. J Am Chem Soc. 2006;128:16394-7. (2) Lee SJ, Oh SJ, Chi DY, Kang SH, Kil HS, Kim JS, Moon DH. One-step high-radiochemical-yield synthesis of [18F]FP-CIT using a protic solvent system. Nucl Med Biol. 2007;34:345-51. (3) Lee SJ, Oh SJ, Chi DY, Kil HS, Kim EN, Ryu JS, Moon DH. Simple and highly efficient synthesis of 3'-deoxy-3'-[18F]fluorothymidine using nucleophilic fluorination catalyzed by protic solvent. Eur J Nucl Med Mol Imaging. 2007;34:1406-9. (4) Wilson AA, Garcia A, Parkes J, McCormick P, Stephenson KA, Houle S, Vasdev N. Radiosynthesis and initial evaluation of [18F]-FEPPA for PET imaging of peripheral benzodiazepine receptors Nucl Med Biol 2008;35:305–314.

P174 AUTOMATED RADIOSYNTHESIS OF [F-18]EF-5 FOR IMAGING HYPOXIA IN HUMAN

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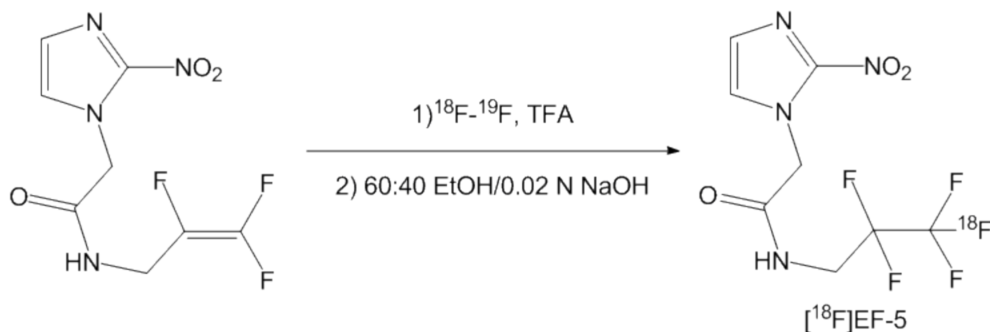
Objectives: Hypoxia is a common phenomenon in human tumors, with most tumors possessing lower oxygenation than their corresponding tissue of origin. 2-(2-Nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)-acetamide(EF-5) is known to measure tumor hypoxia in animals and humans via immunohistochemical methods. More recently, EF-5 has been labeled with fluorine-18 and preliminary imaging results obtained with [^{18}F]EF-5 in rats and humans suggest that it has more homogeneous biodistribution and bioavailability as well as improved stability relative to other hypoxia PET probes. Since the current radiosynthetic procedure is not optimal for providing [^{18}F]EF-5 for the clinic, a safe and automated radiosynthesis for preparing [^{18}F]EF-5 routinely, with a comercially-available automated radiosynthesis module, needed to be developed for future PET studies imaging hypoxia in humans.

Methods: Optimized radiochemistry was performed in a commercial synthesis module with a quaternary HPLC pump. The cyclotron target and delivery lines were preconditioned three times with neon and fluorine gas. 2-(2-Nitro-1H-imidazol-1-yl)-N-(2,3,3-trifluoroallyl)acetamide (22 mg) and trifluoroacetic acid (7 mL) was loaded into the reactor prior to delivery of radioactivity. [^{18}F]fluorine gas was bubbled at RT into the preloaded reactor and stirred (1 min) before the solution was evaporated with MeOH (2 x 1 mL). The remaining residue was neutralized and reconstituted with 60:40 ethanol/0.02 N NaOH (4.0 mL) and injected onto HPLC to afford pure [^{18}F]EF-5 which was processed by C-18 solid-phase extraction, filtered through a sterile Millex-GS filter (25 mm) into a sterile vial, and analyzed for quality control. Formulated [^{18}F]EF-5 (~150 uCi) was injected into mice to evaluate tracer biodistribution with microPET.

Results: All radiochemical yields (RCYs) are decay-corrected and reported as means ± SD. Recent validation runs for preparing [^{18}F]EF-5 gave consistent RCYs (6.1 ± 1.4%; n = 4) and good specific radioactivity, 1004±130 mCi/mmol (37±5 MBq/umol). High radiochemical and chemical purities exceeded 99% and the formulated batch passed the normal battery of quality control tests. Since the entire synthesis is completed with a module and without rotoevaporation, the overall automated process took a total of 80 minutes and reduced radiation exposure to the radiochemist. Tracer uptake (%ID/g) was observed primarily in the gall bladder (12.7 ± 8.1) and intestine (12.0 ± 3.9) but also in liver (3.6 ± 0.8), tumor (2.8 ± 1.5), and muscle (1.1 ± 0.3) with a tumor to muscle ratio of 2.43.

Conclusions: We have developed a method to safely provide clinical-grade [^{18}F]EF-5 with a commercial automated synthesis module for future PET studies imaging hypoxia in humans.

Research Support: Financial support from Varian Medical Systems.



Scheme 1. Radiosynthesis of [^{18}F]EF-5

P175 OPTIMIZATION OF LUTETIUM-177 PROCESSING TO MEET ICH Q7A QUALITY STANDARDS

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Objectives: Lutetium-177 (Lu-177) attached to small molecules, peptides and antibodies has seen increased use for both therapeutic and diagnostic applications due to its favorable nuclear properties, seven day half-life, moderate energy beta particle(~ 0.5 MeV) and a 208 keV (11%) imagable gamma emission. Lutetium-177 made from direct irradiation of Lu-176 has a relatively high specific activity 25 Ci/mg and is easily incorporated into the DOTA and DTPA type chelates that are used most prevalently. The relatively long half-life allows for distribution to remote regions. There is an increasing demand for supply of a cGMP grade Lu-177 for clinical trials, and the aim of this effort was to upgrade production of Lu-177 at the University of Missouri Research Reactor Center from a radiochemical to an active pharmaceutical ingredient (API) compliant with cGMP guidelines established by the FDA. The end goal is to provide an API which meets FDA ICH Q7A quality standards for clinical trial applications.

Methods: A number of modifications to the processing facilities, procedures, and quality control testing were undertaken to ensure a robust process was established to produce a quality final product. This included creating production areas and facilities to meet the stringent environmental controls required for API production. A clean room was built with restricted entry, gowning area, and HEPA filtration to improve the environment of the area containing the processing hot cell. A new dedicated clean facility for the preparation of the Lu-176 targets and non-radioactive solutions was also fitted with a biological safety cabinet and HEPA filtration. Procedures were put in place for routine cleaning and environmental monitoring to maintain a class 10,000 (ISO 7) clean room for processing and class 100,000 (ISO 8) for target preparation. A hot cell was refitted with additional air handling and resurfacing to enable regular cleaning and to maintain the low particulate required for API dispensing. A new product vial was selected and qualified. A filtration step was added to the process and significant testing and validation were performed to confirm no impurities were added to the final product. Evaluation of the commercially available cGMP grade of water was identified and validated. Additionally a risk assessment was performed on every part of the production process. Other enhancements include: qualifying all the equipment, clarifying the product label and improving the required documentation in the form of batch records, and SOP's. Quality control testing of raw materials with material specification sheets.

Results: Modifications will result in a cGMP grade Lu-177 material for clinical trial use.

Conclusions: Significant work to elevate the processing of Lu-177 from radiochemical grade to API has been performed.

P176 FORMULATION OF A Ga-68 LABELING KIT FOR MYOCARDIAL PET

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Objectives: A bis(4,6-dimethoxysalicylaldimine)-N,N'-bis(3-aminopropyl)-N,N'-ethylenediamine (DOSAPEN) is one of the tris(salicylaldimine) derivatives which has been reported to show high heart uptake because of lipophilic cationic characteristics. We produced a kit of DOSAPEN for convenient ^{68}Ga labeling.

Methods: The kits were prepared by dispensing 0.25 mg of DOSAPEN (10 μL) with 490 μL of 1 M sodium acetate buffer solution per vial and lyophilized. Labeling was done by addition of 1 mL of $^{68}GaCl_3$ solution (~740 MBq/0.1 M HCl) eluted from ^{68}Ge/^{68}Ga-generator. Labeling efficiency and radiochemical purity were checked by radioTLC. Biodistribution study was performed by administering ^{68}Ga-DOSAPEN (37 KBq/0.1 mL) into balb/c mouse (male, 20±5 g, n = 4). Stability tests were performed in 1 mL human serum at 37˚C and in the prepared solution at room temperature. Acceleration test was performed with DOSAPEN kits were at 40±2˚C with 75±5 % humidity conditions according to the FDA regulations, and expiry date was calculated by Arrhenius equation.

Results: DOSAPEN kit was labeled with ^{68}Ga at room temperature within 10 min with ≥99 % efficiency. Heart uptake increased from 9.8% ID/g at 10 min to 11.4% ID/g at 2 hr. Decreasing uptake of liver (27.2 % ID/g at 10 min to 9.8% ID/g at 2 hr) and intestine (9.1% ID/g at 10 min to 21.6% ID/g at 2 hr) could be an evidence of hepatobiliary excretion. ^{68}Ga-DOSAPEN were stable at both room temperature and in human serum at 37˚C at least 1 hr. Activation energy of DOSAPEN kit was calculated as 23.28 kcal/mol by Arrhenius equation. Thus, the prepared kits showed longer than 98 days of shelf life and ≥95 % radiolabeling efficiency at 25˚C.

Conclusions: We successfully prepared a DOSAPEN kit which was convenient for labeling, showed high labeling efficiency, showed high myocardial uptake, and showed high stability.

P177 PEDANT 99mTc TRICARBONIL OR BISOXO DIAMINE COMPLEXES OF CARBOHYDRATES AS POTENTIAL TUMOR SPECT IMAGING AGENT

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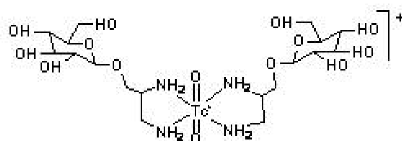
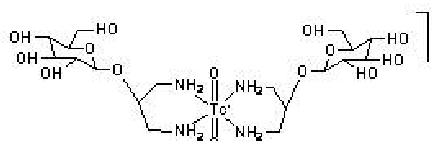
Objectives: The importance of the ^{18}FDG in nuclear medicine tumour imaging has stimulated the investigation for new technetium-glucose pendant complexes, as a way to permit the more popular SPECT imaging. Here we report the preparation and evaluation in tumour bearing mice of four technetium glucose diamine complexes.

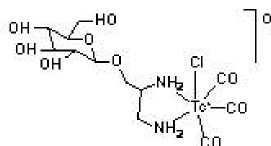
Methods: Bisoxocomplexes $[^{99m}Tc(O)_2(GlucEN)_2]^+$ and $[^{99m}Tc(O)_2(GlucPEN)_2]^+$ were prepared by addition of ligand to a solution containing $^{99m}TcO_4^-$ and Sn^{2+}, and allowing the reaction to stand at room temperature for 15 minutes. The tricarbonyl complexes $[^{99m}Tc(CO)_3(GlucEN)Cl]^o$ and $[^{99m}Tc(CO)_3(GlucPEN)Cl]^o$ were prepared by standard procedure using the IsoLink kit. Animal and tumor model were performed in agreement with ethic procedures using C57BL/6 mice and B16F10 murine melanona cell. "



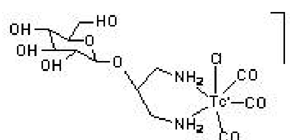
(I) $[^{99m}Tc(O)_2(GlucEN)_2]^+$



(II) $[^{99m}Tc(O)_2(GlucPEN)_2]^+$



(III) $[^{99m}Tc(CO)_3(GlucEN)Cl]^o$



(IV) $[^{99m}Tc(CO)_3(GlucPEN)Cl]^o$

Results: Complexes were obtained with radiochemical purity > 95 % and injection of those compounds in mice gave the following tumor:blood and tumor:muscle ratio (I) 1±0.2 and 2.2±1.3; (II) 1.5±0.6 and 6±1.6; (III) 1.7±0.8 and 1.7±0.7; (IV) 0.6±0.1 and 1.7±0.3, at 120 min post injection. Compounds have fast renal elimination and relative low uptake in the gastrointestinal system.

Conclusions: Glucose-metal conjugates were readily prepared in high radiochemical purity and high tumor:blood and tumor:muscle ratios suggest that these compounds may be useful in tumour imaging, mainly in melanoma.

Research Support: The authors would like to thank the Natural Science and Engineering Council of Canada (NSERC), TRIUMF and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brazil, for financial support.

P178 PREPARATION AND BIOLOGICAL EVALUATION OF β-ELEMENE-99mTc(CO)3 DERIVATIVES AS POTENTIAL RADIOPHARMACEUTICALS

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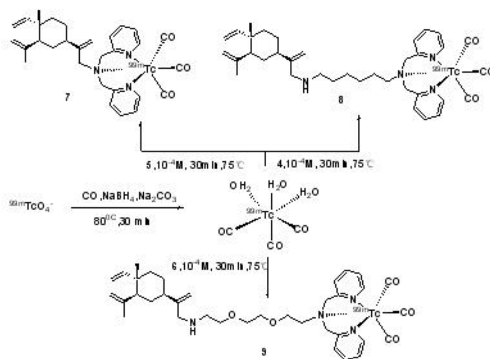
Objectives: β-Elemene, (5S, 7R, 10S) - (-) - (1-methyl - 1 - vinyl - 2,4 - diisopropenyl - cyclohexane) is an anti-cancer agent from the Traditional Chinese Medicinal Herb. Accordingly, we have synthesized three novel $^{99m}Tc(CO)_3$-β-elemene complexes and evaluated it as a potential radiopharmaceuticals

Methods: β-elemene- ^{99m}Tc(CO)3 complexes were prepared by heating $^{99m}Tc(CO)_3(H2O)_3^+$ in an aqueous solution of the previously reported β-elemene-tridentate chain ligands(scheme 1). Log P of β-elemene- $^{99m}Tc(CO)_3$ complexes were calculated in octanol/phosphate-buffered saline (PBS). The radiotracer was intravenously injected to C57BL-6 LLC-bearing mice, and micro-SPECT imaging was performed. Biodistribution of β-elemene- $^{99m}Tc(CO)_3$ complexes were performed on another group of mice at different time points

Results: Results show that the water solubility were improved about 10 times than β-Elemene, their biodistribution and micro-SPECT image study showed there is a visible accumulation in LLC tumor. At 6 h postinjection, the tumor/muscle ratios in LLC-bearing mice were observed to reach 3.38. Micro-SPECT studies of β- elemene-$^{99m}Tc(CO)_3$ in LLC-bearing mouse.Micro-SPECT image shows the summed image during 40–85 min p.i., which has a clear accumulation in theLLC tumor(figure1).

Conclusions: This study indicates that β-elemene-^{99m}Tc $(CO)_3(H_2O)_3^+$ complexes has a certain accumulation in tumor. and after injecting 6 h, thethe tumor/muscle ratios is highter in our research.

References: 1 G. Wang, X. Li, F. Huang, F., Zhao, J., Ding, H., Cunningham, C, Coad, J. E., Flynn, D. C., Reed, E, and Li, Q Q2005Cell. Mol. Life Sci. 62: 881-893 2 X. Li, G. Wang, J. Zhao, H.Ding, C.Cunningham, F.Chen, D.C.Flynn, EReedQQLi(2005) Cell. Mol Life Sci 62: 894-904 3 K. Wang, Z. Li, Y. Chen, C Su (2005) Biopharmaceutica & Drug Disposition 26:301-305 4 S. Zheng, H. Yang, S. Z. Zhang, X Wang, L Yu, J Lu, J Li (1997) J Cell Biochem 27: 106-112 5 L.Y. Xu, S. J. Tao, X. M. Wang, M.W., Chen, D., Jing, Y.K., and Dong, J.H (2006) Bioorg. & Med. Chem 14:5351-5356. 6 Y.F. Ren, Y.H. Sun, K.M. Cheng, G.F. LiuY.M. Shen* Journal of Labelled Compounds and Radiopharmaceuticals. 2009 accepted 7 R. Alberto, R. Schibli, A. Egli, P. A. Schubiger(1998) J Am Chem Soc 120:7987-7988 8 W. J. Babich, W. G. Coco, S. Barrow, A. J. Fischman, F. J. Femia, J. Zubieta(2000) Inorganica. Chimica. Acta. 309:123-136 9 A. Egli, R. Alberto, L. Tannahill, R. Schibli, U. Abram(1999) J Nucl Med 40:1913-1917. 10 A. Hoepping, J. Babich, J. A. Zubieta, K. M. Johnson, S. Machill, A. P. Kozikowski (1999)Bioorg Med Chem Lett 9:3211-3216



Scheme 1. Radiosynthesis of complex 7, 8 and 9.

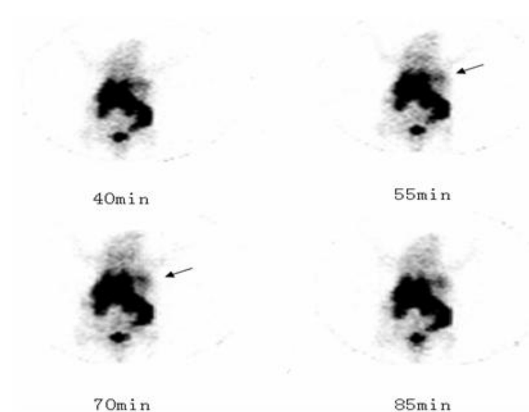


Figure1. SPECT image of LLC-bearing mouse

P179 PRODUCTION OF THE DAT PET-RADIOLIGAND [18F]LBT-999 ON A TRACERLAB FX-FN SYNTHESIZER

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Objectives: LBT-999 (8-((E)-4-fluoro-but-2-enyl)-3-beta-p-tolyl-8-aza-bicyclo[3.2.1]octane-2-beta-carboxylic acid methyl ester) is a recently developed cocaine derivative belonging to a new generation of highly selective the dopamine transporter DAT ligands (K_D : 9 nM for the DAT and IC_{50} > 1000 nM for the serotonin and norepinephrine transporter) [1,2]. Initial fluorine-18 labeling of this ligand was based on the robust and reliable two-step radiochemical pathway often reported for such tropane derivatives, involving first the preparation of (E)-1-[^{18}F]fluoro-4-tosyloxybut-2-ene followed by an N-alkylation reaction with the appropriate nor-tropane moiety [3]. More recently, a simple one-step fluorine-18-labeling of LBT-999 has been reported [4], based on a chlorine-for-fluorine nucleophilic aliphatic substitution, facilitating the final HPLC-purification and now permitting automation of the process on an advanced, commercially available, automated module, such as the TRACERLab™ FX-FN synthesizer.

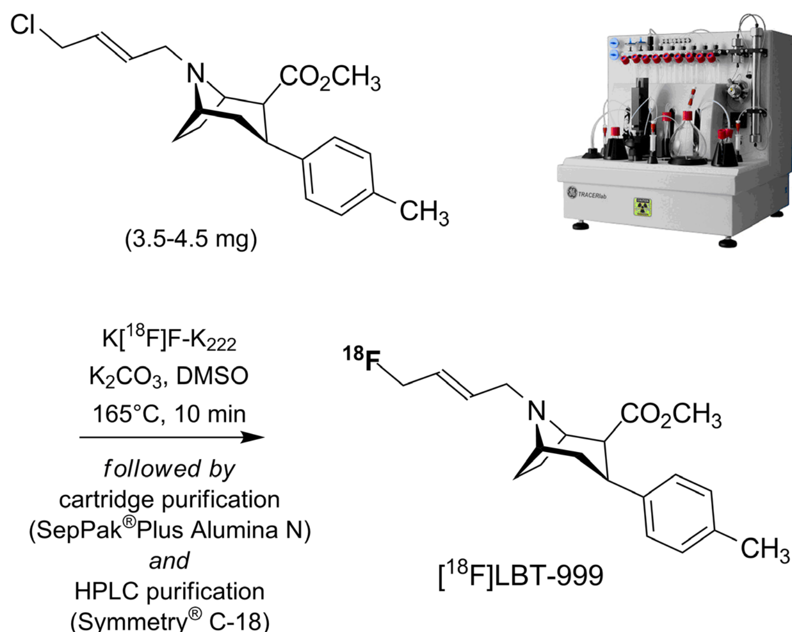
Methods: The automated process implemented on the TRACERLab™ FX-FN synthesizer involves: (A) the preparation of the K[^{18}F]F-Kryptofix®222 complex in two heating steps, first at 60°C for 7 min under a stream of N_2 and then at 120°C under reduced pressure for 5 min, followed by (B) reaction of K[^{18}F]F-Kryptofix®222 with the chlorinated precursor (4 mg, 8.5 μmol) at 165°C for 10 min in DMSO (0.7 mL), then (C) SepPak®Plus Alumina N cartridge pre-purification after dilution of the reaction mixture with HPLC solvent (4 mL) and finally (D) semi-preparative HPLC purification on a Waters Symmetry® C-18 (Solvent : H_2O/MeCN/TFA : 70/30/0.1 (v/v/v), Flow rate : 5 mL/min, Rt = 11-12 min). The HPLC-collected fraction containing pure [^{18}F]LBT-999 was automatically formulated using a SepPak®Plus C-18 cartridge ((i) HPLC-collected fraction dilution and loading on the cartridge, (ii) cartridge washing with 10 mL of water, (iii) cartridge elution with 2 mL of EtOH, and (iv) final dilution with 8 mL of saline). The full process was programmed on the TRACERLab™ FX-FN synthesizer in one single “method” divided in three “time-lists” (preparation of the complex / incorporation of fluorine-18 / HPLC + formulation).

Results: Starting from a 37.0 GBq (1 Ci) cyclotron-produced [^{18}F]fluoride batch, 6.7 to 8.5 GBq (180-230 mCi, 18-23% non decay corrected yields) of [^{18}F]LBT-999, > 99% radiochemically pure and ready-to-inject, were obtained within 50-60 min. The overall decay corrected radiochemical yield reached up to 32%. Specific radioactivities ranged from 111 to 222 GBq/μmol (3-6 Ci/μmol).

Conclusions: Radiosynthesis of [^{18}F]LBT-999 has been successfully implemented on a TRACERLab™ FX-FN synthesizer.

Research Support: Supported by the EC - FP6-project DiMI (LSHB-CT-2005-512146), EMIL (LSH-2004-503569) and the Réseau National de Technologies pour la Santé” program (RNTS 03B243 FLUOPARK).”

References: [1] Dolle et al. Bioorg. Med. Chem. (2006), 14, 1115-1125. [2] Chalon et al. J. Pharm. Exp. Ther. (2006), 317, 147-152. [3] Dolle et al. J. Label. Compds Radiopharm. (2006), 49, 687-698. [4] Dolle et al. J. Label. Compds Radiopharm. (2007), 50, 716-723.



P180 LARGE SCALE SYNTHESIS OF NO-CARRIER-ADDED [123I]mIBG, USING TWO DIFFERENT STANNYLATED PRECURSORS

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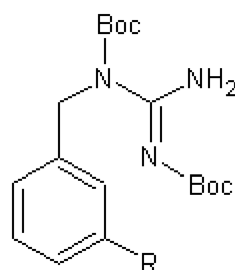
Objectives: Several advantages of no-carrier-added (n.c.a.) meta-radioiodobenzylguanidine ([*I]mIBG) over its carrier-added analogue have been reported in literature. The main objective of this study was to investigate the feasibility of a multi-megabecquerel scale production of n.c.a. [^{123}I]mIBG. The methodology used was based on a published method [1] for small scale radiohalogenations, utilizing a butyloxycarbonyl (Boc)-protected trimethylstannyl precursor. In addition, the performance of a Boc-protected tributylstannyl precursor, as well as a solid phase extraction method for the purification of reaction mixtures, were also investigated.

Methods: N, N'-bis(tert-butyloxycarbonyl)-3-iodobenzylguanidine (bis-Boc-mIBG) was synthesized from 3-iodobenzyl alcohol and N, N'-bis(tert-butyloxycarbonyl)guanidine according to a literature method [2], utilizing the Mitsunobu reaction. The respective stannylated precursors, bis-Boc-mTMSBG and bis-Boc-mTBSBG (see Figure below) were subsequently synthesized, using conventional methods. Radioiodination reaction conditions were optimized, using bis-Boc-mTMSBG. Radioiodinations were carried out at room temperature, using varying amounts of precursor and N-chlorosuccinimide (NCS) as oxidant. Radioactivities ranged between 37 MBq and 5340 Mbq. After quenching reaction mixtures with sodium metabisulphite, Boc groups were removed with trifluoroacetic acid (TFA) at 110°C. After neutralization with NaOH, reaction mixtures were loaded on pre-activated 500 mg Sep-Pak C18 solid phase cartridges. Polar components and product were eluted with water and 0.1% H_3PO_4/ethanol = 75:25 mixture, respectively.



R = trimethylstannyl : Bis-Boc-mTMSBG
R = tributylstannyl : Bis-Boc-mTBSBG

Results: Under optimized conditions, amounts of 200 μg bis-Boc-mTMSBG and 2000 μg NCS gave, after TFA hydrolysis and subsequent work-up, an average [^{123}I]mIBG radiochemical yield of 85% at activities ranging from 1900 to 3280 MBq. A once off double up-scaled reaction at 5340 MBq gave a yield of 86%. Radiochemical purities were in excess of 98%. The specific activity was in the order of 1 TBq.μmol^{-1}. TFA hydrolysis did not only remove Boc groups, but also lead to the formation of the proton-destannylated breakdown product benzylguanidine, which was co-eluted as a relatively polar substance with other polar components. The tributylstannyl precursor initially gave considerably lower yields (43-56%) under the same conditions, due to the presence of m-[^{123}I]iodobenzylamine in hydrolyzed reaction mixtures. The latter impurity was eliminated when using an HPLC-purified precursor, resulting in much improved radiochemical yields (61-81%).

Conclusions: Radiosynthesis of n.c.a. [^{123}I]mIBG up to activity levels of at least 5340 MBq proved to be viable, using the method described in here. A Boc-protected trimethylstannyl precursor gave acceptable and reliable radiochemical yields which were generally superior to those obtained with a similarly protected tributylstannyl precursor. The solid phase purification method provided a radiochemically and chemically pure product with high specific activity which could be suitable for patient study trials.

References: [1] Vaidyanathan G. et al. J. Label. Comp. Radiopharm., 50, 177 (2007). [2] Vaidyanathan G. et al. Appl. Radiat. Isot., 62, 435 (2005).

P181 ASSISTING THE ALKYLATION REACTION IN THE PREPARATION OF (R)-[11C]PK11195 BY SOLVATING KOH IN ADDED WATER

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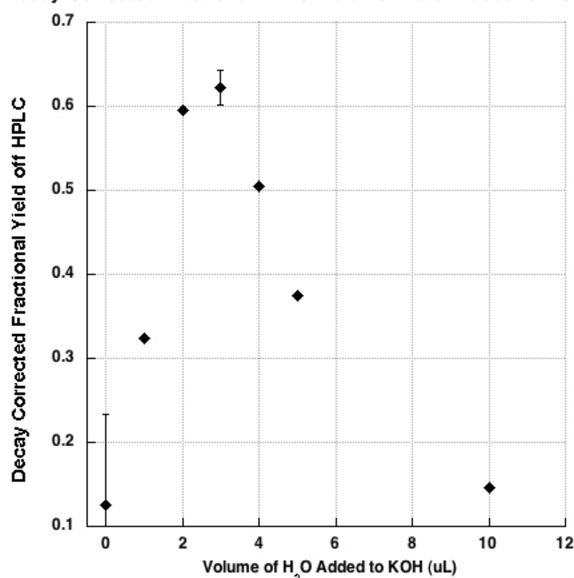
1. University of Wisconsin, Department of Medical Physics, Madison, WI; 2. University of Wisconsin, Waisman Laboratory for Brain Imaging and Behavior, Madison, WI

Objectives: In the preparation of (R)-[^{11}C]PK 11195, a ligand of the peripheral benzodiazepine receptor used in PET imaging of activated macrophages and microglia, we have noted sporadic chemical yields after replacing the ultra-dry DMSO (Baker Scientific) with a fresh vial (Fisher Scientific). We hypothesized that alkylation yields are decreased in the complete absence of water and therefore also that a small amount of water might assist the reaction. We added varying (uL) amounts of water to our basic, organic precursor solution and observed radiochemical yields of the desired product and of a known radioactive side product.

Methods: (R)-[^{11}C]PK 11195 was prepared by bubbling [11C]methyl iodide through a solution containing 1 mg ABX desmethyl precursor in 300 uL DMSO, saturated with 10 mg KOH (Fisher Scientific) to which microliter quantities of water were added. The vial was heated and mixed at 90°C for 2 minutes. The solution was drawn off of residual KOH, mixed with 0.6 ml 1 N HCl and 0.2 ml ethanol, and injected onto an Altec C18 10u Econosil HPLC column running 2:1 MeCN:H2O at 6 ml/min (R_T = 710 ± 20 sec).

Results: The following table summarizes decay corrected HPLC yields of (R)-[^{11}C]PK 11195 and of its known hydro-des-chloro analogue (Cleij et. al. 2003) and suggests a 1% v/v addition of water to the DMSO solution will yield optimal results, or 62 ± 2 % decay corrected yield collected from the HPLC system, normalized to the activity trapped in the precursor solution.



Since this investigation, our syntheses have been uniformly successful. UV chromatography also reveals the suppression of the side reaction that produces the hydro-des-chloro analogue; this dechlorinated species constitutes 12%, 10%, and 4% ± 2% of the radiolabeled fraction when 0, 1, and 2 microliters of water, respectively, are added to the 300 ml precursor solution. When higher volumes of water are added, the decholorinated species is absent from the UV trace.

Conclusions: A decrease in alkylation yield and an increase in dechlorination side products accompany the use of 100% dry DMSO. When a small amount of water is added, the alkylation yields are increased and dechlorination is decreased. We suggest that the addition of polar protic solvent stabilizes the OH^- nucleophile, potentially reducing the likelihood of the substitution reaction that has been suggested as the cause of dechlorination (Cleij et. al. 2003). The nature of the solvent and the suppression of the reaction with larger volumes of water further suggest the S_N2 mechanism with slower kinetics than those of the desired alkylation. Beyond 1% v/v water additions to the DMSO solution, however, the OH^- nucleophile is increasingly unable to deprotonate the desmethyl precursor, decreasing the rate of alkylation from the methyl iodide molecule. The addition of a small amount of water may also increase the solubility of KOH in DMSO.

Research Support: We gratefully acknowledge the support of National Multiple Sclerosis Society grant #TR3761.

References: M. C. Cliej, F. I. Aigbirhio, J-C. Baron, J. C. Clark. (2003) Base-promoted dechlorination of (R)-[^{11}C]PK 11195. J. Label Compd. Radiopharm, 46: S1-S403.

P182 AUTOMATED RADIOSYNTHESIS OF DOPAMINE D2,D3 RECEPTOR AGONIST LIGAND [11C]PHNO FOR HUMAN PET IMAGING STUDIES

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Objectives: The carbon-11 labelled dopamine D2,D3 receptor ligand (+)-4-Propyl-3,4,4a,5,6,10b-hexahydro-2H-naphtho[1,2-b][1,4]oxazin-9-ol ((+)-PHNO) has shown promising properties as an in vivo high-affinity states dopamine receptor imaging agent in monkey & human PET studies. A rapid and fully automated GMP compliant synthesis has been developed to reliably produce [^{11}C]PHNO in good radiochemical yields.

Methods: The automated syntheses of[^{11}C]PHNO were performed using a Modular Lab radiosynthesis module obtained from Eckert & Ziegler-Eurotope (Berlin, Ger). [^{11}C]-(+)-PHNO was synthesized as previously described (Wilson et al. 2005, Hwang et al., 2000) with some modifications. In the first step [^{11}C]carbon dioxide was concentrated on a molecular sieves trap, then released and directed to a reaction vessel containing a Grignard solution of ethylmagnesium bromide. Phthaloyl dichloride and 2,6-di-tert-butylpyridine were successively added and the formed [^{11}C]propionyl chloride was distilled to a receiving vial containing the precursor in THF and triethylamine. The resulting amide was reduced using lithium aluminium hydride to provide [^{11}C]-(+)-PHNO. [^{11}C]-(+)-PHNO was isolated by semi-preparative HPLC using a Gilson binary pump/UV detector system controlled by a Dionex interface, which also acquired data from two Carroll & Ramsey radiodetectors each equipped with 3 pin diodes. Post HPLC purification, [^{11}C]-(+)-PHNO suitable for human use was obtained after a quick solid phase extraction, reformulation and sterile filtration. A semi-automated self-clean cycle was also developed for an effective cleaning of the system. All aspects of the GMP compliant production of [^{11}C]-(+)-PHNO, such as development of a chiral HPLC method to confirm the enantiomeric purity of the precursor, metabolite analysis by HPLC using a double column switching set-up, fast GC and HPLC QC, will be presented.

Results: [^{11}C]-(+)-PHNO was produced in good radiochemical yield: around 30% decay-corrected to EOB; to date: yield = 3707 ± 1590 GBq at EOS (n=22), and high radiochemical purities (> 99%). There was no detectable precursor or other by-products. A reasonable specific activity was also consistently achieved: SA = 83 ± 31 GBq/umol at EOS (n = 21). The average synthesis time was 37.2 ± 2.8 min from EOB.

Conclusions: A rapid and efficient automated radiosynthesis of [^{11}C]-(+)-PHNO has been developed for application in clinical studies.

P183 STUDIES ON THE AUTOMATED PRODUCTION OF [18F]FLUOROBENZOATE SYNTHONS

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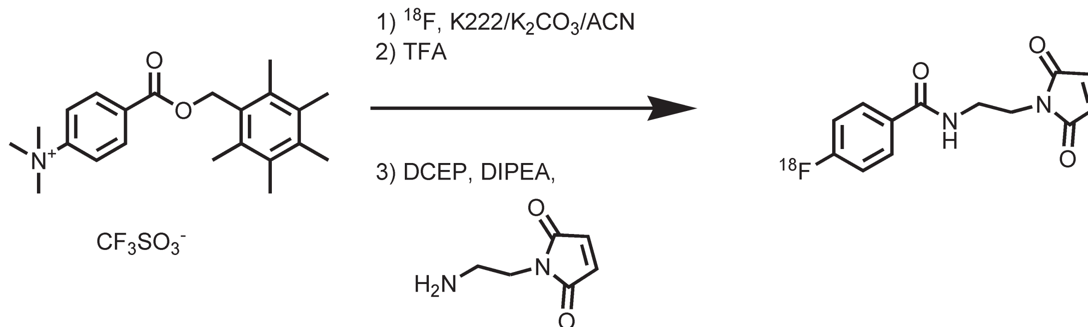
Objectives: As part of our research program on the development of peptide based imaging ligands for oncology, we have utilized two [^{18}F]fluorobenzoic acid derivatives, N-[2-(4-[^{18}F]fluorobenzamide)ethyl]maleimide[^{18}F]FBEM and N-hydroxysuccimidyl-4-[^{18}F]fluorobenzoate. The former has been used for site specific labeling of a C-terminal cysteine in a HER2 selective Affibody ® molecule. The latter we intend to apply to lysine labeling for other peptides of interest to our collaborators. Since the radiochemical syntheses of these two labeling agents are quite similar, we set out to develop an automated synthesis to meet our needs with reduced radiation exposure to our staff.

Methods: Our manual synthetic scheme utilized a two separated heated reaction vessels, one for the incorporation of [^{18}F] fluoride into pentamethylbenzyl trimethylammoniumbenzoate triflate and a second for the conversion of [^{18}F]fluorobenzoic acid into either of the two products. Two solvent changes are required as is the use of trifluoroacetic acid for hydrolysis of a protecting group. We acquired the necessary hardware to assemble a two reaction system from Eckert & Ziegler (Berlin, Germany) and with the assistance of the company developed the program to adapt our manual synthesis. Initially semipreparative HPLC was conducted on an external HPLC system. Analysis of products was conducted on a separate HPLC system.

Results: The focus thus far has been [^{18}F]FBEM The synthetic procedure was based on the two step radiosynthesis of [^{18}F] fluoropaclitaxel ([^{18}F]FPAC). In the second step of the [^{18}F]FPAC synthesis, we could combine paclitaxel primary amine and iPr_2NEt amine in the same vial prior to addition. We discovered that N-aminoethylmaleimide decomposed upon standing with iPr_2NEt. We lacked sufficient valving to add iPr_2NEt separately, but we discovered that N-aminoethylmaleimide was stable on standing with diethylcyanophosphonate. The learning curve from manual synthesis to automation has been relatively steep. Plumbing and programming the system to perform the many steps of the synthesis was not difficult, however working out the necessary timing for evaporations and volume transfers proved more challenging. We have achieved radiochemical yields for [^{18}F]FBEM of up to17% (uncorrected) after 95 min whereas the manual synthesis has recently provided a yield of 28.3 ± 2.7 % (n=61, uncorrected) after 60 min. The majority of the increased time required is due to our [^{18}F]fluoride drying process. As this is a work-in-progress, we are still working to optimize yield and reproducibility as well as to incorporate the automation of the HPLC purification. The radiosynthesis of N-hydroxysuccimidyl [^{18}F]fluorobenzoate will utilize the same apparatus.

Conclusions: The Eckert & Ziegler Modular Laboratory system has been successfully applied to the automated synthesis of [^{18}F]FBEM. We expect that more optimization of process timing will result is yields similar to the manual process, but with great reduction in personnel radiation exposure.

Research Support: This research was supported by the intramural research program of the NIBIB/NIH.



Radiochemical Synthesis of [^{18}F]FBEM

P184 AUTOMATED RADIOSYNTHESIS AND SPECIFIC ACTIVITIES OF MULTIPLE C-11 LABELLED PET TRACERS USING SIEMENS GPC AND CH3 CHEMISTRY MODULES

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Objectives: C-11 labelled tracers such as DASB, PK11195 and Raclopride, are widely used radiopharmaceuticals for neuroimaging and as a result, there is a steady & increasing interest in the automated synthesis of these labelled compounds. Many modules have been developed to meet the demand, and although radiochemists have several choices with regards to automated chemistry equipment, specific activity and yield data are rarely supplied. Herein we present, specific activity and yield data collected from specific radiosyntheses using the new automated system Explora GPC, a [C-11] methyl iodide/triflate synthesis module, in tandem with Siemens Explora CH_3, a standalone methylation system.

Methods: All reagents were purchased from Aldrich or Fisher, with the exception of DASB, PK11195 and Raclopride precursors, which were purchased from ABX. $^{11}CO_2$ was produced in target using a Siemens Eclipse RDS. In the synthesis,^{11}C-CO_2 is reduced to ^{11}C-CH_4 and then via radical mechanism, ^{11}C-CH_4 is iodinated to ^{11}C-CH_3I in our novel reversible Sublimator/Condenser. Taking advantage of it's boiling point & vapor pressure, iodine is sublimed at the entry of the iodination oven & then collected via condensation upon exit. This technique enables the direction of flow to be reversed & the unused portion of iodine salvaged for subsequent runs. ^{11}C-CH_3OTf , from^{11}C-CH_3I in a single step, was used in the methylations due to higher reactivity. Routed to the Explora CH_3, it underwent an S_N2 reaction with the respective precursor under appropriate conditions. A stand-alone methylation system allows for precursors such as [^{11}C] cyanide or acetate to also be utilized, in addition to others. After neutralization, HPLC workup on a reverse phase C-18 column was done with mobile phases 60% acetic acetate/40% CH_3CN for DASB and 60% 0.1M ammonium formate (w/ 0.5% acetic acid)/40% CH_3CN for Raclopride and PK1195.

Results: MeI decay corrected yields from CH_4 of 45% (Ave. 29.1%, n=37, std 6.82%) were not uncommon using a high yield method. To allow for user flexibility, more stable yields were achieved by adjusting parameters (Ave.18.2%, n=121, std 2.68%). DASB was produced in good DCYs from MeI (23-71%) and radiochemical purities (43-89%). Purities proved to be dependant on allowed reaction time, with higher yields obtained when reaction with precursor exceeded five minutes. Specific activities at EOS of DASB ranged from 1.03-3.14 Ci/μmole (n=12, ave 2.23, std 0.64). Synthesis times ranged from 4-8 minutes (post MeI). Raclopride, methyl tyrosine, and PK11195 DCY from Explora CH_3 were 6.2%, (n=6, std 1.68%), 22% (n=2, std 2.56%), and 22.5% (n=3, std 3.53%), respectively. For either module, little to no clean up needed, as proven by back-to-back runs of same or different tracers and observing no cross-contamination or loss of reactivity.

Decay Corrected Radiochemical Yields and Conversion Efficiencies

C-11 Labelled Compound	Radiochemical Decay Corrected Yield (EOS)	Radiochemical Conversion *(average)*
PK11195	22.5%, n=3 std 3.5%	56%
DASB	33.4%, n=5 std 1.14%	92%
Methyl Tyrosine	22%, n=2 std 2.56%	45%
Raclopride	6.2%, n=6 std 1.68%	68%

Conclusions: A simple, efficient and automated radiosynthesis of routine radiotracers for preclinical and clinical use has been achieved with the Explora GPC and CH_3 radiochemistry modules.

P185 PRODUCTION OF [F18]ISO-1 USING THE ECKERT AND ZIEGLER MODULAR - LAB

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Objectives: Washington University purchased an Eckert and Ziegler Modular- Lab in the fall of2007. The Modular-Lab is a fully automated synthesis platform used for the production of radiopharmaceuticals. The system can be purchased as a pre validated system developed by Eckert and Ziegler engineers or as a radiopharmaceutical developmental tool. We purchased the Modular-Lab as a radiopharmaceutical development tool to develop several syntheses on one platform. ^{18}F ISO-1 has been developed on the Modular-Lab and is approved to be administered into patients.

Methods: We purchased two Peltier reaction modules, one HPLC module, one 3-way module, three 2-way modules, two 1-way modules, a stopcock module, a pneumatic lift arm, a vial holder module and a multi-position valve. ^{18}FISO-1 is a straight forward one pot synthesis which utilizes most modules. The ^{18}FISO-1 program was developed using the drag and drop user interface of the Modular-Lab. Setup includes following a software prompted step by step procedure that is checked off by the chemist upon completion. Target activity is delivered directly to the module via peek tubing from the cyclotron vault. The vial holder module, which incorporates two radioactivity detectors, is utilized for monitoring activity trapped on solid phase extraction cartridges. Reagents are delivered using a combination of vacuum and pneumatic systems. The pneumatic system is simply an Argon gas line connected to the stopcock module for distribution. The vacuum system was built "in house" and consists of a 24V vacuum pump, power supply and a liquid trap. This is connected to the reaction module via a 2-way valve which also serves as a vent. The reaction module is equipped with an internal camera and radioactivity detector, which serves as a vital monitoring tool during production and development. Heating is done using 8 double thermoelectric Peltier elements and cooling is achieved through a liquid heat exchanger. The HPLC system consists of a Knauer pump, Knauer UV monitor, and an injection module supplied by Eckert and Ziegler. The radioactivity detector is external and shielded with lead bricks.

Results:

Yield(%) @ EOB	SA(Ci/mmol)	Radiochemical Purity(%)	Synthesis Time(hrs)
58.4	2221	99.4	1.3

All results, except synthesis time, calculated as average The Modular-Lab software has the capability to produce post synthesis reports. Reports can include data from all of the sensors and detectors. This data can be displayed graphically on report printouts or viewed and saved in the report and database file. Valve actuation with time stamps can also be printed out to show if there was any deviation or manual override that needs to be addressed.

Conclusions: The Eckert and Ziegler Modular-Lab has shown to be a versatile and reliable radiopharmaceutical production device. The inclusion of a camera in the reaction vessel is a unique property that not only shortens development and troubleshooting time, but also allows complete monitoring of the production. We are currently moving human targeted syntheses from the robot to the Modular-Lab.

P186 PRODUCTION OF [18F]FALLYPRIDE ON A TRACERLAB FX-FN SYNTHESIZER

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Objectives: [18F]Fallypride is a radiotracer suitable for D_2 receptor imaging with PET in both striatal and extrastriatal regions. The high signal to noise ratio of [18F]fallypride has been attributed to its high affinity for D_2 receptors (K_D = 0.03 nM). Therefore, [18F]fallypride is more and more often favorably proposed in clinical studies as an alternative to the well-established, carbon-11 labeled, D_2-receptor raclopride, justifying the development and set-up of highly reproducible production processes on automated, GMP-compatible and commercially available synthesizers. We report herein the preparation of [18F]fallypride using a TRACERLab™ FX-FN synthesizer.

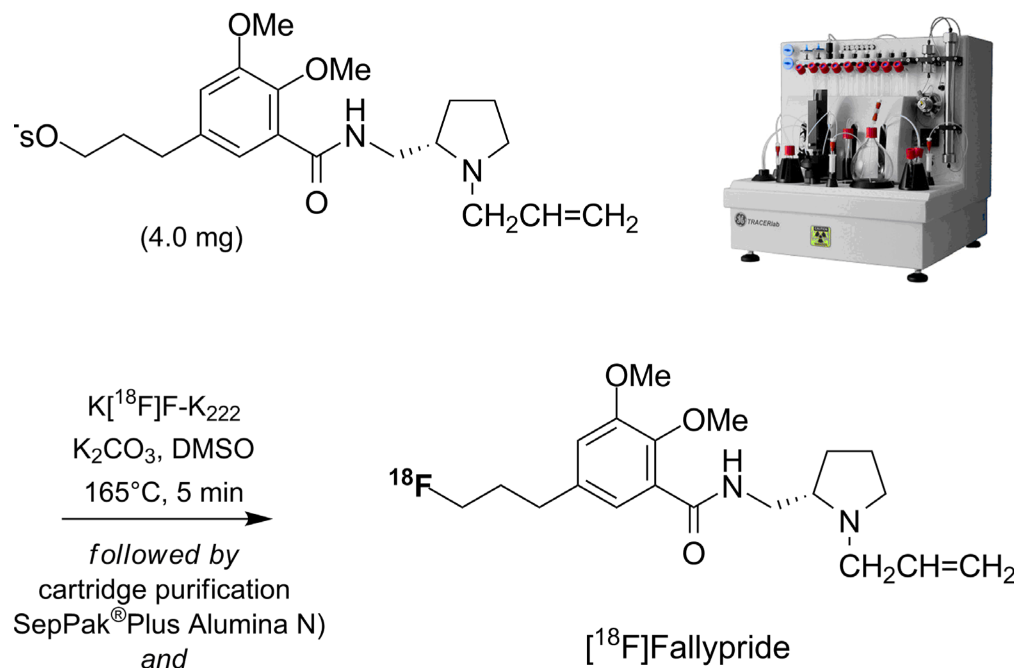
Methods: The radiofluorination process using a TRACERLab™ FX-FN synthesizer involves: (A) preparation of the K[18F]F-Kryptofix®222 in two heating steps, first at 60°C for 7 min under a stream of N_2 and then at 120°C under reduced pressure for 5 min, followed by (B) reaction with the commercially available tosyl precursor (ABX, Germany) (4.0 mg) at 165°C for 5 min in DMSO (0.7 mL), then (C) SepPak®Plus Alumina N cartridge pre-purification after dilution of the crude with HPLC solvent and finally (D) semi-preparative HPLC purification (Waters SunFire™ C-18 column, elution : H_2O/MeCN/TFA 70/30/0.1 (v/v/v), flow rate : 5 mL/min). The collected HPLC fraction containing radiochemically pure [18F]fallypride was automatically formulated using a SepPak®Plus C-18 cartridge. The process programmed on the TRACERLab™ FX-FN consists in one single "method" divided in three "time-lists". Chemical and radiochemical purities were determined by radioHPLC using a Waters Alliance 2690 system equipped with a UV spectrophotometer (Photodiode Array Detector, Waters 996) and a Berthold LB509 radioactivity detector (column: analytical Symmetry-M® C-18, Waters; conditions: isocratic elution with solvA / solvB: 50 / 50 (v/v) [solvent A: H_2O containing Low-UV PIC® B7 reagent (20 mL for 1000 mL); solvent B: H_2O / CH_3CN: 30:70 (v/v) containing Low-UV PIC® B7 reagent (20 mL for 1000 mL)]; flow rate: 2.0 mL/min; temperature: RT; absorbance detection at λ = 254 nm).

Results: Typically, starting from a 37.0 GBq cyclotron-produced [18F]fluoride batch, 12 GBq (30 % n.d.c yield) of [18F]fallypride were on average obtained in 45 min. Quality control demonstrates that the tracer ready to inject is > 99% radiochemically and > 95% chemically pure. The decay corrected radiochemical yield reached up to 40 %. Specific radioactivities ranged from 222 to 333 GBq/μmol.

Conclusions: Radiosynthesis of [18F]fallypride is implemented and routinely produced at our laboratory on a TRACERLab™ FX-FN synthesizer.

Research Support: Supported by the EC - FP6-project RATstream™ STREP (LSHM-CT-2007-037846) and NeuroNE (LSHM-CT-2004-512039).

References: [1] Mukherjee et al. Nucl. Med. Biol. (1995), 22, 283-296.



P187 INVESTIGATION ON THE SYNTHESIS AND WORKUP OF [18F]FLUMAZENIL FOR HUMAN PET STUDIES

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Objectives: The central benzodiazepine receptors (BZR) plays an important role in various neuro-pathologies such as epilepsy and alcohol-dependency. With the advent of high-resolution scanners such as the HRRT (Siemens), which can only live up to its full potential when the radioisotope ^{18}F is applied, an ^{18}F-labeled Flumazenil ([^{18}F]FZ) is a valuable addition to the portfolio of clinically used radio-tracers for PET imaging. Applied in our laboratory, the synthesis and especially the workup of [^{18}F]FZ according to Halldin and co-workers [1] was proven to be feasible but purification was found to be difficult. We therefore endeavored to find an easier method of purification to take full advantage of this highly important tracer.

Methods: [^{18}F]FZ was synthesized from its nitro-precursor Ro 15-2334 in DMF at high temperatures between 130-160°C. Other solvents like acetonitrile and DMSO were also investigated. Two HPLC systems for the final purification of [^{18}F]FZ were compared: 1) a Waters μ-Bondapak C18-column as described by Halldin et al. which was eluted with 0.01 M H_3PO_4 and CH_3CN and 2) a Waters Symmetry Prep C18 which was eluted with 0.05 M NaOAc pH 5/THF/MeOH (80/10/10; flow 3 mL/min). The synthesized [^{18}F]FZ was applied in human PET studies using the HRRT high resolution scanner (Siemens).

Results: The synthesis of [^{18}F]FZ in our laboratory was initially performed according to Halldin et al. yielding the radiotracer in 1-2% RCY (EOB) after 80 min. The tracer could be produced in RCYs sufficient for human PET imaging using the HRRT high resolution scanner in the context of our ongoing stroke imaging program. Halldin et al.'s described HPLC-system for final purification elutes the [^{18}F]FZ shortly before the labeling precursor Ro 15-2344 which in some cases led to an accidental contamination of the final product rendering a human application impossible. It was also observed that up to 80% of the injected radioactivity remained on the described HPLC column (Waters μ-Bondapak) which significantly decreased preparative overall RCY. In order to obtain higher RCYs and to make the purification more reliable we developed a new HPLC purification method perfectly separating the [^{18}F]FZ (R_f = 14.5 min) from the Ro 15-2344 (R_f = 21 min) precursor. A trapping of radioactivity was not observed. Applying these new conditions the final product was obtained in reproducible RCYs of 15-20% EOB within 70-80 min and was used for human PET imaging.

Conclusions: A new HPLC workup method for [^{18}F]FZ was developed yielding [^{18}F]FZ in an overall RCY of 15-20% after 70-80 min (EOB). This HPLC method is characterized by the fact that [^{18}F]FZ and the precursor molecule Ro 15-2344 are perfectly separated. The synthesis time could be slightly reduced and the [^{18}F]FZ was used in human PET studies in stroke patients and healthy volunteers taking advantage of our HRRT PET camera. Our novel workup procedure bears a clear advantage and might facilitate the dissemination of this important tracer.

References: [1] Ryzhikov, N. N. et al. Nucl. Med. Biol. 32 (2005) 109-116

P188 PREPARATION OF 6-[^{18}F]FLUORO-L-DOPA USING CARRIER ADDED [^{18}F]F_2 PRODUCED BY A COMMERCIALLY AVAILABLE PROTON TARGET

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Objectives: To commission a [^{18}F]F_2 proton target system and assess its efficacy in the production of 6-[^{18}F]fluoro-L-DOPA ([^{18}F]FDOPA).

Methods: Radioactive carrier-added fluorine was produced via the ^{18}O(p,n)^{18}F reaction using the [^{18}F]F_2 Proton Target System and the PETtrace cyclotron (GE Healthcare). This production system differs greatly from its predecessor that employed the ^{20}Ne(d,α)^{18}F reaction and 1% F_2 carrier combined with ^{20}Ne target gas. The [^{18}F]F_2 Proton Target System is a two step process (two shot), requiring (1) irradiation of $^{18}O_2$ followed by cryo-recovery of the unused target gas and; (2) a second irradiation following the addition of F_2 carrier in Ar to liberate ^{18}F. Different irradiation conditions/carrier gas concentrations were applied and the [^{18}F]F_2 measured on soda-lime traps. Specific activity of [^{18}F]F_2 was determined by High Performance Liquid Chromatography (HPLC) with conductivity and radiation detection. Batches of [^{18}F]FDOPA were prepared and tested for chemical purity, radiochemical purity, and specific activity. The synthesis was based on that described by Füchtner (2007)[i], employing the electrophilic radio-destannylation of the precursor 6-trimethylstannyl-L-DOPA and using the TRACERlab$_{FX-FE}$ (GE Healthcare) automated chemistry module. HPLC with UV and radiation detection was employed to determine the isomeric, chemical and radiochemical purity, and gas chromatography-mass spectrometry to determine the presence of residual solvents.

Results: Results of successful runs are tabulated below:

[^{18}F]F_2 Proton Target Yields for Different Irradiation Conditions

Shot 1		Shot 2			
Current (μA)	Time (mins)	Current (μA)	Time (mins)	F_2 %	Mean Activity EOB (GBq)
40	45	35	20	1.5	60 ± 10 n = 2
40	45	35	20	1.0	40 ± 4 n = 2
40	60	35	20	1.0	50 ± 10 n = 8
40	60	35	20	0.3	35 ± 4 n = 9

These results are favourable when compared to that of the deuteron target: for 40 μA and 21 minutes beam time, mean activity (EOB) = 2.2 ± 0.2 GBq, n = 3. Of the 35 runs attempted, 23 were acceptable, 9 resulted in poor yields, and 3 failed due to leaking valves (66 % success). It is believed that the poor yields were due to contamination of the system with corrosion, and dilution of the enriched $^{18}O_2$ target material with Ar. With carrier F_2 at a concentration of 0.3% the specific activity of ^{18}F trapped in solution was determined to be 861 GBq/mmol at end of bombardment (EOB). It follows that a total of 21 μmol F_2 is extracted from the target. The radiochemical yield of [^{18}F]FDOPA (with 0.3 % carrier F_2 from target) was found to be 11 ± 3 % at end of synthesis. Quality control analyses proved the specific activity and purity of the product met the specifications set by the United States Pharmacopoeia (USP).

Conclusions: The [^{18}F]F_2 Proton Target System proved to give higher yields than the deuteron method used previously. Specific activity of the [^{18}F]F_2 was determined to be favourable. With 34 % of runs having either failed or not delivered sufficient [^{18}F]F_2, reliability and robustness of the system remains a major concern. Batches of [^{18}F]FDOPA were produced and demonstrated reproducible yields when 0.3 % carrier F_2 was used. Quality control analyses demonstrated that the product meets USP specifications.

Research Support: The Authors wish to acknowledge the support given by the Sciences Group – Department of Nuclear Medicine & Queensland PET Service, and by the Director – Queensland PET Service.

References: i) F. Fuchtner, J. Zessin, P. Mading, F. Wust, Aspects of 6-[^{18}F]fluoro-L-DOPA preparation. Deuterochloroform as a substitute solvent for Freon 11, Nuklearmedizin 2007, 46.

P189 AUTOMATED SYNTHESES OF N-SUCCINIMIDYL 4-[18F]FLUOROBENZOATE ([18F]SFB) AND N-[2-(4-18F-FLUOROBENZAMIDO)ETHYL]MALEIMIDE ([18F]-FBEM) USING A CUSTOMISED IBA SYNTHESISER

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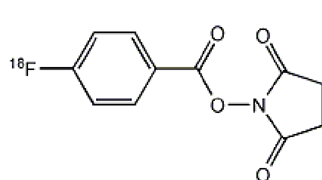
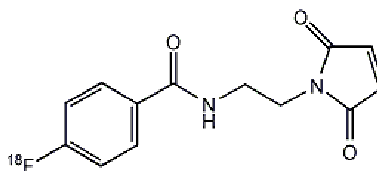
Objectives: The objectives of this project were to make modifications to an IBA synthesis module, to fully automate the [^{18}F]SFB and [^{18}F]-FBEM syntheses, and to improve the synthesis of [^{18}F]SFB in a one-pot reaction.



1 ([^{18}F]SFB)



2 ([^{18}F]FBEM)

Methods: The facile synthesis of [^{18}F]SFB, which consisted of a simplified three steps in a one-pot procedure, was based on a recent publication by Tang and co-workers[1]. The preparation of [^{18}F]SFB involved: 1) [^{18}F]fluorination of an aromatic precursor, ethyl 4-(trimethylammonium triflate)benzoate at 110°C, 2) saponification to generate 4-[^{18}F]fluorobenzoate salt ([^{18}F]FBA), and 3) activation of the salt with N,N,N,N'-tetramethyl-O-(N-succinimidyl)uronium tetrafluoroborate (TSTU) to form [^{18}F]SFB. The crude reaction mixture was trapped on a C18 Sep-Pak cartridge (omitting the use of other cartridges used in the literature) and eluted with acetonitrile, to afford [^{18}F]SFB that can then be used for labeling of free amino groups. The [^{18}F]-FBEM was synthesized by coupling the [^{18}F]SFB with N-(2-amino-ethyl)maleimide in a separate reaction vial. [^{18}F]-FBEM was HPLC purified on a semi-prep column. The product can be employed to react with a thiol containing peptide and hence providing a labeling agent for Positron Emission Tomography (PET) tracers.

Results: In this study, DMSO replaced acetonitrile as solvent for the [^{18}F]fluorination reaction. The incorporation of fluoride was variable when acetonitrile was used because it was found that in some cases the solvent evaporated too quickly, which consequently led to an unsuccessful synthesis. The experimental failure rate was lower when DMSO was used as a solvent. In addition to this, the radiochemical yield in DMSO was up to 65 + 5%. [^{18}F]-FBEM has been successfully synthesized with [^{18}F]SFB coupled to N-(2-amino-ethyl)maleimide in an individual reaction vial.

Conclusions: The customised IBA synthesis module was successfully modified for the preparation of both the [^{18}F]SFB and [^{18}F]-FBEM tracers. Modification to the synthesis increased the [^{18}F]SFB radiochemical yield from 43.8 + 4.6%[1] to 65 + 5%.

References: [1] G. Tang, Wenbin Zeng, Meixiang Yu and G. Kabalka, J. Label Compd. Radiopharm., 2008, 51, 68-71.

P190 QUALITY CONTROL OF Ga-68, In-111, Y-90 AND Lu-177 LABELED DOTA-DERIVATISED PEPTIDE ANALOGS USING A COMBINATION OF HPLC AND TLC

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Objectives: DOTA-derivatised peptides and especially somatostatin analogs have found increasing clinical application, labeled with Ga-68 for PET, with In-111 for SPECT and with Y-90 and Lu-177 for therapy. In-house production requires compliance with specific acceptance criteria for identity, concentration, quality, purity and sterility. We here present the determination of the radiochemical purity in our laboratory using a combination of HPLC and TLC. Beside determination and identification of all possible impurities, this method allows distinction between commonly used DOTA-peptides, including quantification of the peptide amount. Additionally, we present alternative paper chromatography methods, which can eventually replace methods based on silica gel impregnated glass fiber plates (ITLC-SG, Pall Life Sciences), currently not available.

Methods: Identification and quantification of peptides (DOTA-TOC, DOTA-TATE, DOTA-lanreotide) was optimized using RP-HPLC (ACE3 C18 column ,150 x 3 mm, 5μm; gradient system of solvent A: 0.1% TFA in water and solvent B: 0.1% TFA in acetonitrile; flow rate 0.5 ml/min) with radiometric and UV detection at 220 nm. Different solvents were tested for paper chromatography based on Whatmann 3mm in comparsion to ITLC methods. Radiochemical purity of ^{111}In/^{68}Ga/^{90}Y-DOTA-TOC, ^{111}In/^{68}Ga/^{90}Y-DOTA-lanreotide and ^{177}Lu-DOTA-TATE was determined with the same HPLC and paper chromatography system. Reference solutions of the possible radioactive impurities (free radionuclide, DTPA-complexes, radiocolloid) were analyzed for comparison.

Results: Identification of the starting DOTA-peptide analogs and of the corresponding radioligands was optimized using an initial linear gradient from 20 to 24% solvent B in 9 min followed by 60% solvent B for 2 min and re-equilibration to 20% solvent B for 4 min. Resolution between the different non radiolabeled DOTA-peptides was >3. Retention times allowed to distinguish between ^{111}In/^{90}Y-DOTA-TOC (6.4 min), ^{177}Lu-DOTA-TATE (7.9 min), ^{68}Ga-DOTA-TOC (10.2 min) and ^{111}In/^{68}Ga/^{90}Y-DOTA-lanreotide (>12 min). UV at 220 nm allowed quantification of pepide amount in the final product. ITLC-SG and paper chromatography with Whatmann 3MM showed comparable results.

Conclusions: In-house produced radiolabeled DOTA-peptides have to meet specific acceptance criteria before their release for clinical use. HPLC with radiometric and UV detection allows peptide identification and quantification of free radionuclide or DTPA complexes and peptide degradation products. TLC is additionally required to quantify radiocolloids, which are adsorbed on the HPLC column. With the described combined HPLC and TLC system quality control including identity, concentration, quality and purity can be performed in a convenient and rapid way. The system is applicable to most of the commonly used radiolabeled somatostatin analogs to guarantee their safety and efficacy for clinical applications.

P191 STERILE VIAL FILLING WITH PET RADIOPHARMACEUTICALS

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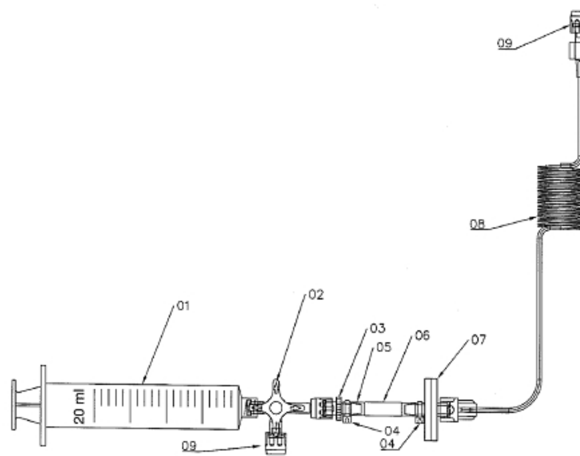
Objectives: Despite their proven track record, traditional approaches for formulation and packaging of PET radiopharmaceuticals are subject to small but finite, risk of contamination (eg. during pre-release product sampling, and removal of vent needles), an issue that has more recently raised concerns by radiopharmaceutical licencing authorities. The objective of the work presented here, was to find and implement alternative methodologies to the traditional vial filling method for PET radiopharmaceuticals that might a) minimise product contamination concerns and, b) minimise procedural and infrastructural requirements to ensure a quality vial filling and QC sample withdraw operation.

Methods: Initial scoping of the vial process led to the development and investigation of two alternative approaches i) a vial-needle clamp to minimise the risk of needle movement through vial septa ii) a syringe set-up which does not require septum penetration for introducing/sampling the sterile product. The vial clamp is made of ABS plastic which is hot injection moulded into its final shape. The clamps are gamma irradiated and individually sealed in plastic bags. The syringe set-up consists of a QC sampling loop in series with a 0.2 micron sterile filter, an aluminium sealing crimp and to a 3-way stopcock attached to a 20mL syringe. Each set-up is irradiated and packed individually.

Results: Vial Clamp: The aim of the vial clamp was to secure the needle connected to the 0.22 micron sterile filter and the 'bleed' needle in position during filling and sampling the vial. When the vial filling is completed, the operator disconnects the delivery line from the filter and the assembly is transferred to the QC lab where the vial clamp is removed. All samples (70 batches) were tested for sterility and endotoxin levels. All samples were sterile and show typically endotoxin level of 10 EU, well below the 175 EU limit. IMG 1 Syringe set-up : Bubbles in product formulation stream from the synthesis unit are removed using a 'vented' filter connected to the set-up. Following that first step, the product is delivered through a QC sample loop of approx 1 ml volume. The product passed over a 0.22 micron filter (sterilising filter, non-vented) and is collected in a sterile syringe. The QC loop and filters are sealed and separated from the syringe using an aluminium sealing crimp in such way that the QC loop containing a product sample and filters are subject to QC testing before the crimped syringe assembly is released to user. IMG 2

Conclusions: The vial clamp can be easily adapted to existing traditional vial assembly operations. Its implementation still requires an isolator and the piercing of the septum to sample the finished product. The syringe set-up can be pre-assembled and pre-sterilised in units packed individually. No septa or needles are required/used in filling or sampling and set-up, and maintenance and daily use of an isolator or LAF unit is avoided



Schematic Representation of the Syringe Set-up

P192 LARGE SCALE PREPARATION OF [18F]FLUOROMETHOXYBENZYL BROMIDES, KEY PRECURSORS FOR 2-[18F]FLUORO-L-TYROSINE AND 6-[18F]FLUORO-L-DOPA SYNTHESES

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Objectives: Automation of radiopharmaceutical syntheses is an important challenge for any PET center. With automated systems, high level of radioactivity can be handled with a maximum of reliability and a minimum of radiation exposure for the radiochemist. Among the commercially available synthesizers present on the market, the new FASTlab module from GE (Loncin, Belgium), presently used for FDG and NaF syntheses appears as a GMP compliant, versatile, user-friendly solution to our automation need for 6-[^{18}F]fluoro-L-dopa and 2-[^{18}F]fluoro-L-tyrosine syntheses.

Methods: In order to realize these syntheses in a commercially available synthesizer, several chemistry improvements have been recently realized. For example, halogenation can now be realized directly on the SPE support with aqueous HBr rather than with the gaseous specie (Lemaire, 2009) and the alkylation step can now be conducted at room temperature (RT) rather than at 0°C (Libert, 2009).

Results: The standard FDG sequences and cassette were modified to meet the amino acid synthesis requirements. The cassette is constituted of a 25-valves stopcock manifold, a reactor vial connected by silicone tubing to the manifold, one 1 ml syringe and two 6 ml syringes. The right part of the FDG cassette has been modified by removing the C18 and Al_2O_3 cartridges. Reagents for the synthesis were placed in five crimped vials containing the QMA eluent (750 μL), acetonitrile (4 ml), trimethylammonium precursor (30 mg) previously solubilized in 1.5 ml of DMSO, $NaBH_4$ (20 mg), 4 ml of HBr (47%) and toluene (4 mL). The system was equipped also with a 100 ml water bag and three SPE cartridges (QMA, C18 and K_2CO_3). The first steps of the synthesis were similar to those used for FDG synthesis up to the end of the labeling step and trapping on the C18. Once the dry $^{18}F/K_{222}$ complex obtained, the quaternary ammonium precursor dissolved in DMSO was transfered in the reactor for labeling. After dilution with water, the [^{18}F]aldehyde was trapped onto the C18 cartridge. The aldehyde was then converted into the corresponding benzyl bromide by passing successively through the support an aqueous solution of $NaBH_4$ (3 mL, 2 min) and HBr (1 mL, 2 min). Finally, the benzyl bromide derivative was eluted from the support with 2.5 ml of toluene through a small K_2CO_3 column. The synthesis time is about 25 minutes and the overall decay corrected radiochemical yield of 2-[^{18}F]fluoro-4-methoxybenzyl bromide and 2-[^{18}F]fluoro-4,5-dimethoxybenzyl bromide are 45 ± 5 % and 60 ± 5 % respectively.

Conclusions: In spite of its complexity, automation of the first synthesis steps (labeling, trapping on a SPE, reduction, bromination) has been realized with success. Starting from 1 Ci of [^{18}F]fluoride, more than 500 mCi of 2-fluoro-4-methoxybenzyl bromide and 385 mCi of 2-fluoro-4,5-dimethoxybenzyl bromide are available at the end of the 25 min of synthesis. Implementation on the same module of the last fluorodopa and fluorotyrosine syntheses steps (enantioselective alkylation at RT and hydrolysis) is currently under progress.

References: Lemaire C. , et al. Fast and reliable method for the preparation of various [^{18}F]fluorobenzyl halides. Abstract, this meeting Libert L., et al. New improvements in the enantioselective synthesis of 2-[^{18}F]fluoro-L-tyrosine and 6-[^{18}F]fluoro-L-dopa. Abstract, this meeting

P193 ELECTRONIC INVENTORY SYSTEM

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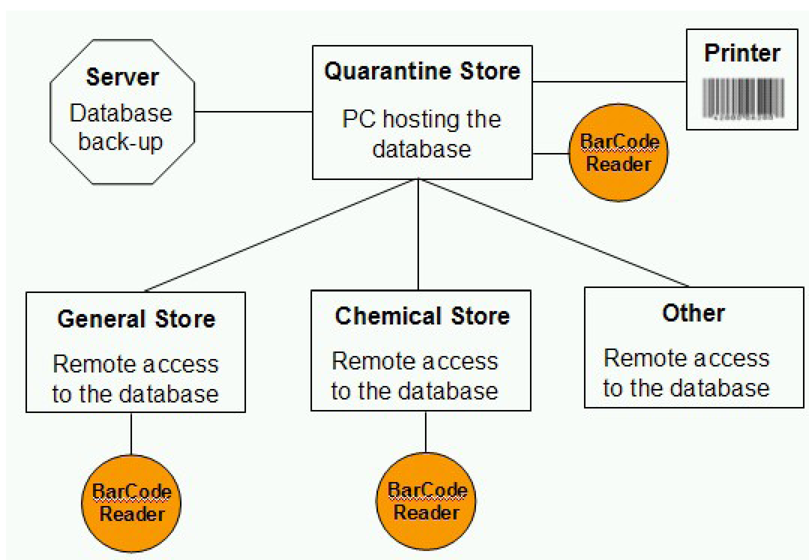
Objectives: Due to the increasing regulatory requirements applicable to PET radiopharmaceutical manufacture, systems need to be implemented to comply with regulations. One aspect of these requirements is the control of raw materials entering the manufacture of PET ligands. Raw materials need to be logged, quarantined, tested, released or rejected and their use in the production area recorded. To comply with these requirements, an Electronic Inventory System has been designed at the Clinical Imaging Centre to track raw materials for the duration of their shelf life. A description of this system is presented herein.

Methods: The Electronic Inventory System consists of a central MS Access database, a bar code generating and printing programme, bar code readers and remote view nodes.

Results: Upon receipt of a new raw material, an entry is made in the database and the material is labelled and quarantined (orange "Quarantined" label). Testing is performed against the raw material specification and recorded in the system. Following approval by Quality Assurance, the raw material is formally released from quarantine, re-labelled with a green "Approved for use" label and transferred to the appropriate area within the chemistry stores. The material can be checked in and out from the stores, according to needs. To do so, operators must log in to the system trough their user accounts, for which different access levels can be defined. Integrated controls also allow the database to automatically email key personnel to: re-order raw materials when stock falls below defined limits, re-test raw materials when approaching their retest date, remove raw materials reaching their expiry date and ensure compliance with the First-In-First-Out principle.

Conclusions: The Electronic Inventory System has been in used at the Clinical Imaging Centre for one year and proved to be a useful tool.



P194 RECONFIGURATION OF A SIEMENS EXPLORA GN+LC SYSTEM TO ALLOW BOTH SYNTHESIS AND REFORMULATION

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Objectives: One of the options available for the automated regular production of fluorine-18 labelled PET radioligands at the Clinical Imaging Centre is the commercially available Siemens Explora GN+LC module. This system consists of a General Nucleophilic (GN) module allowing two sequential syntheses of fluorine-18 labelled tracers without intervention, linked to a second module which consists of a Knauer semi-prep HPLC module with fixed wavelength UV detector and isocratic pump allowing purification of the tracers. In the default configuration, this system does not offer the possibility of reformulating the tracer after isolation from semi-prep HPLC. The aim of this work was to customize the Expora GN+LC module using the existing valves and software to obtain a more versatile system. Implemented modifications were evaluated through the preparation of [^{18}F] AV-45, which is an effective radioligand for imaging brain β-amyloid aggregates.

Methods: In order to enable the collected fraction from the semi-prep HPLC to be reformulated, the following modifications were made: 1) the line between valves MVP3 and MVP7 was removed; 2) MVP7 valve was connected straight onto the HPLC injection valve; 3) the vial containing the semi-prep HPLC collected fraction was defined as one of the reservoirs (within the delivery system of reagents); 4) QMA N°2 was replaced by a SepPak® cartridge; 5) MVP3 valve was used to switch between waste and dose vial while trapping and releasing the radioligands from the SepPak® cartridge. In addition to this, modifications were implemented to improve the loading step of the crude material onto the HPLC sample loop. In the original setup, the crude solution was pushed through the HPLC sample loop with a nitrogen flow for a given time. In the proposed new configuration, a trap & release cartridge (empty analytical column 4.6 x 5 cm, filled with 550 mg of C18 material, 200-400 mesh, 20-22% carbon loading, obtained from Sigma-Aldrich) is used to replace the sample loop.

Results: These changes described above were applied to the preparation of [^{18}F]AV-45. Typical yields were ~500-700 MBq in final dose (RCY: 27-38% decay corrected; Total synthesis time: ~85 minutes). Trapping of crude material onto the trap & release cartridge was 100% efficient and allowed pre-purification of the crude solution before directing onto the semi-prep HPLC.

Conclusions: The modifications described above turn the Explora GN+LC module into a versatile automated synthesis system for clinical production of PET tracers labelled with fluorine-18. These modifications disable the capability of performing two sequential runs without user intervention.

P195 SIMPLE AND RAPID SYNTHESIS OF N-SUCCINIMIDYL-4-[18F]FLUOROBENZOATE AND N-[2-(4-[18F]FLUOROBENZAMIDO)ETHYL]MALEIMIDE FOR PROTEIN AND PEPTIDE LABELING

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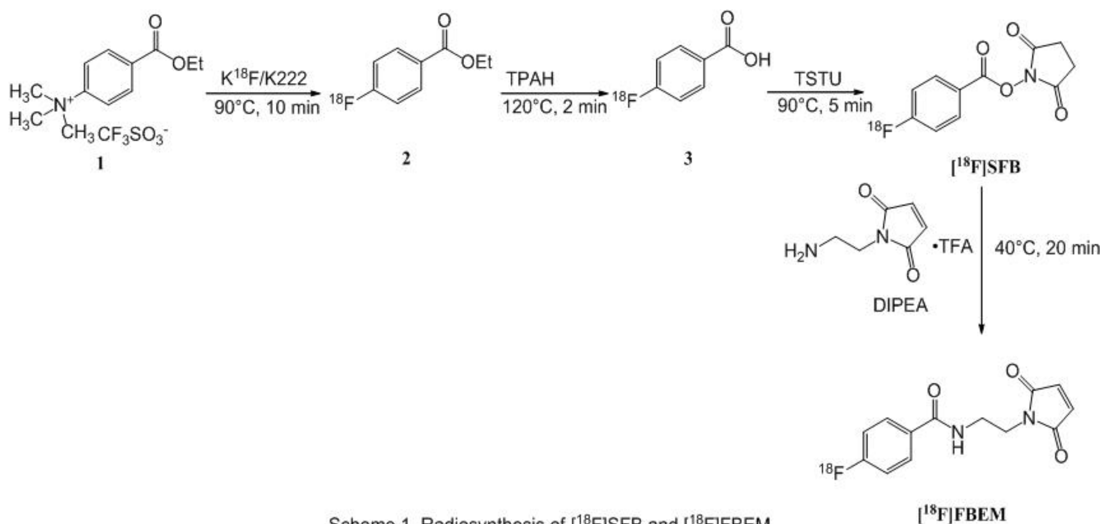
Objectives: Recently, proteins and peptides labeled with positron emitting radioisotopes are widely applied for targeted imaging of in vivo physiological and pathological processes. N-Succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB) is the most commonly used agent for the labeling of lysine residues on proteins and peptides. N-[2-(4-^{18}F-fluorobenzamido)ethyl]maleimide ([^{18}F]FBEM) can be obtained by the one-step synthesis from [^{18}F]SFB, and is used for the specific labeling of thiol-containing proteins and peptides. In this study, we examined a simple and rapid labeling of [^{18}F]SFB and [^{18}F]FBEM.

Methods: In the radiosynthesis of [^{18}F]SFB, 4-(ethoxycarbonyl)-N,N,N-trimethylbenzenaminium triflate (4.3 mg)/MeCN (1 mL) was added to [^{18}F]KF/K_{222} and heated at 90°C for 10 min. To this solution, tetrapropylammonium hydroxide (20 μL)/MeCN (50 μL) was added and heated at 120°C for 2 min, and the solvent was evaporated under N_2 stream at 100°C. Then O-(N-succinimidyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (15 mg)/MeCN (1 mL) was added and heated at 90°C for 5 min (Scheme 1). The mixture was transferred to a vial which contained 2% AcOH (24 ml). The mixture was passed through a SepPak tC18 cartridge. After washing with 10% MeCN-H_2O (15 mL) and purging with N_2, the product ([^{18}F]SFB) was eluted with MeCN (2 mL). In the radiosynthesis of [^{18}F]FBEM, the produced [^{18}F]SFB in MeCN (0.4 mL) was added to N-(2-aminoethyl)maleimide (2 mg)/MeCN (1 mL) and N,N-diisopropylethylamine (20 mL) was added. The reaction mixture was heated at 40°C for 20 min (Scheme 1). The radiochemical yields and purity of [^{18}F]SFB and [^{18}F]FBEM were determined with HPLC.

Results: [^{18}F]SFB was synthesized using 1 as a precursor via a three-step, one-pot synthesis. The mean synthesis time, including a solid-phase extraction (SPE) purification, was 52 min after EOB. The radiochemical yields of [^{18}F]SFB was 37 ± 6% (n=3, not decay corrected) on the basis of [^{18}F]fluoride, and the radiochemical purities were > 95%. Thus, we successfully obtained [^{18}F]SFB without purification of 3, which contributed simple and rapid synthesis of [^{18}F]SFB. [^{18}F]FBEM was obtained by a reaction with [^{18}F]SFBin the radiochemical yields of 39 ± 6% (n=5) on the basis of [^{18}F]SFB. The total synthesis time of [^{18}F]FBEM was about 80 min after EOB. In this study, the produced [^{18}F]SFB in MeCN was used without evaporating MeCN for the subsequent reaction with N-(2-aminoethyl)maleimide to rapidly obtain [^{18}F]FBEM. The intensive purging with N_2 in the SPE purification step of [^{18}F]SFB might contribute to remove impurities and successful synthesis of [^{18}F]FBEM. These results indicate that [^{18}F]SFB and [^{18}F]FBEM can be prepared in shorter synthesis time, compared with the previous report (150 ± 20 min) [1].

Conclusions: We succeeded to shorten the synthesis times of [^{18}F]SFB and [^{18}F]FBEM. The present work provides a simple and rapid labeling methods of [^{18}F]SFB and [^{18}F]FBEM, which are potentially applicable to the subsequent labeling of proteins and peptides.

References: [1] Cai W. et. al., J. Nucl. Med., 2006, 47, 1172-1180.



Scheme 1. Radiosynthesis of [^{18}F]SFB and [^{18}F]FBEM

P196 FULLY AUTOMATED PREPARATION OF [18F]FPyBrA IN A MODULAR SYNTHESIS SYSTEM

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Objectives: Alkylating agents are very promising for the radiolabelling of oligonucleotides with fluorine-18. For the automation of the multiple reaction steps involved modular systems are very useful tools. We here describe the fully automated synthesis of 2-bromo-N-[3-(2-[^{18}F]-fluoropyridin-3-yloxy)propyl]acetamide ([^{18}F]FPyBrA) utilizing such a modular system. Reaction conditions for the coupling of this pyridine-based alkylating agent at the 5'-end of a fully phosphorothioated random 20-mer DNA sequence (PS-ODN) were optimized to achieve very high radiochemical yields (RCY).

Methods: A modular system (Eckert & Ziegler, Berlin, Germany) was used for the fully automated three step radiosynthesis and remote-controlled semi-preparative HPLC purification of [^{18}F]FPyBrA according to (1). Minor modifications of the synthesis allowed improvements of the RCY in each reaction step. Coupling of [^{18}F]FPyBrA at the 5'-end of a model 20-mer PS-ODN was optimized by adjusting the reaction parameters of solvent concentration, pH, temperature and time. The minimum amount of PS-ODN for quantitative alkylation under optimized reaction conditions was evaluated. The final radiolabeled probe was analyzed by reverse phase HPLC with UV and radiometric detection.

Results: During the optimization of the automated synthesis a total of 60 batches of [^{18}F]FPyBrA was produced. With an average precursor amount of 5.9 mg (20 μmol), slightly increased reaction temperature of 150°C for fluorination, quantitative deprotection at 75°C under nitrogen stream, an additional drying step with acetonitrile after deprotection and bromoacetylation at 37°C with increased TEA concentration a maximum overall decay-corrected RCY of 24% based on starting [^{18}F]fluoride was achieved with a 65 min synthesis time. Oligonucleotide conjugation using 200 μg PS-ODN (31 nmol) in MeOH/0.1 M PBS (2/8, v/v), pH 7.4, total volume 250 µl, 120°C and 30 min incubation time resulted in RCY >90%. Using 170 MBq [^{18}F]FPyBrA a specific activity of 5-6 GBq/μmol was obtained.

Conclusions: [^{18}F]FPyBrA was produced using a straightforward and reliable synthesis in a remotely controlled synthesis unit. The virtually quantitative yield obtained in the coupling reaction with the PS-ODN raises the possibility of using the labeled ODN product without employing HPLC purification, either directly from the synthesis or by a straightforward solid phase extraction method to remove minor impurities or incompatible solvents.

Research Support: Elisabeth von Guggenberg was funded by an Erwin Schrödinger Fellowship of the Austrian Science Fund (FWF). Research funding from The Alberta Cancer Board and the Alberta Cancer Foundation are gratefully acknowledged.

Reference: (1) Kuhnast B et al. Bioconjug. Chem. 2004, 15: 617-627.

P197 PRE-RELEASE DETERMINATION OF RESIDUAL SOLVENTS IN SHORT-LIVED RADIOPHARMACEUTICALS

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Objectives: Pre-release QC methods for carbon-11 labelled PET products must be fast to ensure minimal losses of product radioactivity and specific activity. The subject of this abstract is the development of generic, rapid and high quality GC methods to allow for the pre-release determination of the level of residual solvents in radiopharmaceutical formulations. Thus, two new fast GC-FID methods were developed to detect and quantify the most frequently used residual solvents in radiopharmaceuticals for human use.

Methods: The methods were developed on an Agilent 6890 GC system equipped with a Gerstel MPS2 (Multipurpose Sampler) and CIS4 (Cooled Injection System) using an Agilent DB-624 column. Low-volatility solvents are tested by a liquid injection of a DCM extract in 6 min (2 uL splitless injection, constant He pressure 22 psi, 6.2 mL/min, calibration range 100 to 5000 ppm). High-volatility solvents are analysed by an optimised headspace injection in 15 min (10 min incubation, 5 min GC runtime, 1 mL headspace injection, constant He pressure 15 psi, 3.6 mL/min, calibration range 100 to 6000 ppm).

Results: Both methods showed good resolution, accuracy, reproducibility and linearity. Representative chromatograms are shown in Figures 1A and 1B.

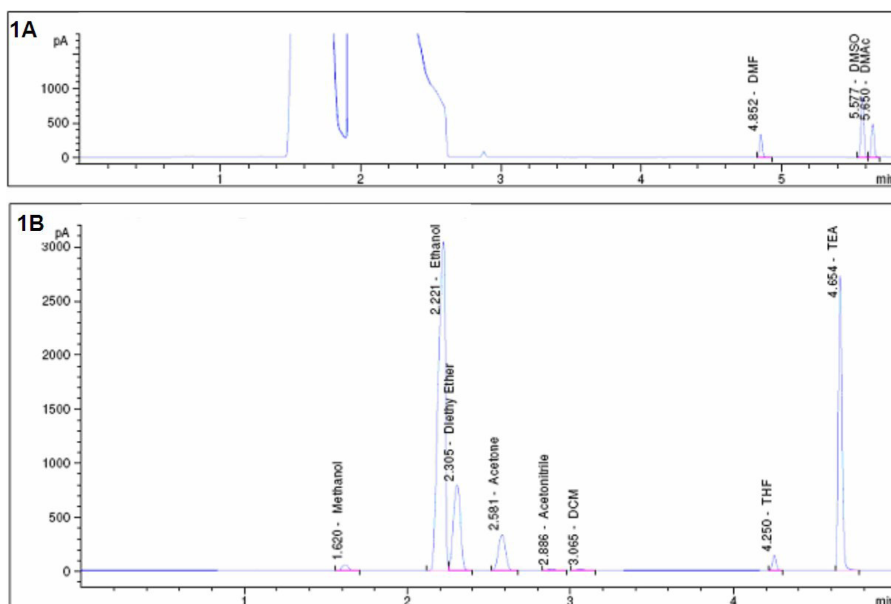

Figure1: representative results for A) low-volatility solvents and B) high-volatility solvents

Conclusions: Both methods proved to be suitable for determination of residual solvents within the appropriate timescale for carbon-11 labelled radiopharmaceuticals. The established limits of detection are in the lower ppm range, easily meeting the limits defined in the ICH guidelines. Full validation data will be presented.

P198 [18F]FALLYPRIDE SYNTHESIS WITH PROTIC SOLVENT MIXTURE

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Objectives: [^{18}F]Fallypride has long been used as a D2 receptor tracer in PET. The required final product purity was difficult to maintain using conditions previously published by others. It has been shown[1] that the use of nonpolar protic tertiary alcohols enhances the nucleophilicity of the fluoride ion and reduces formation of byproducts from side reactions such as elimination and hydrolysis. We report here our currently improved [^{18}F]Fallypride synthesis using t-amyl alcohol as solvent and tetraethylammonium bicarbonate (TEAB) as the base.

Methods: [^{18}F]Fallypride was prepared using a GE TRACERlab FXN. [^{18}F]HF ($\leq$ 0.5mL) was introduced into the reaction vessel containing 1.0 mL acetonitrile (ACN) solution of 1.54mg (8.0 μmoles) TEAB. After azeotropic drying, 2 mg, 3.9 μmoles tosylate precursor was added, in 0.5 mL of the solvent mixture, ACN / t-amyl alcohol 1:9. The reaction proceeded at 105°C for twenty minutes. The solvent was evaporated and the dried reaction mixture was transferred onto the HPLC for purification. Two columns (LUNA C18 (2) 5μ 10 x 50 mm, and a 10 x 250mm) connected in series were eluted at 3.0 mL/min with an eluent[2] containing 55:45 ethanol / 20 mM NaH_2PO_4 pH 6.5. The desired product eluted at about 16 minutes was collected in a receptacle, diluted with 18mL Sterile Water for Inj., USP and sterilized via passage through a 0.22mm Millex into a sterile serum vial as the final product. The entire synthesis took 60 minutes. The product was analyzed using a Zorbax Eclipse XDB C18, 4.6 X 100 mm, 3.5 μm and an eluent containing 100 mM Ammonium Formate pH 3.5 / ACN 70/30 at 1.0 mL/min. Yield and purity were compared with data from previous runs using comparable procedure and the conventional K222/K^+ (Table I).

Results: Chemical purity was found to be consistently > 99%; average Specific Activity (EOS) was 4,600 mCi/mmole (n=13), radiochemical yield averaged 31.7 ± 4.6n = 20) chemical yield 46.2 ± 6.6 which was a 70% increase over averaged yields from previous runs of comparable procedure using the conventional K222/K^+ (Table I).

Conclusions: Use of nonpolar protic tert-alcohol proved advantageous in our [^{18}F]Fallypride synthesis. The use of 55:45 ethanol / 20 mM NaH_2PO_4 pH 6.5 not only offered the advantage of direct collection but it also provided a much cleaner separation.

References: 1. Chi DY, et al., J Am Chem Soc. 2006 Dec 20; 128(50): 16394-7. 2. Baldwin R, personal communication, Feb 2007.

[18F]Fallypride Syntheses: a comparison of procedural differences and results

	Previous (n=3)	Current (n =20)
Catalyst in RV	0.5mL of ACN (K_2CO_3 7.2µmol /K222 14.3µmol)	1mL TEAB reagent (15.4mg /10mL ACN) = 8 µmol
Precursor 2mg (3.9µmol)	0.5mL ACN	50µL ACN + 450µL t-amyl alcohol
Reaction conditions	105°C for 15 min	105°C for 20 min
Transfer to HPLC injection vial	Mixture cooled to 30°C; solvent evaporated. 1.5mL HPLC eluent added	Mixture cooled to 30°C; solvent evaporated. 1.5mL HPLC eluent added stepwise
HPLC LUNA C18(2)	guard cartridge + 10 x 250mm semi-prep column	10 x 50mm pre-column + 10 x 250mm semi-prep column
Retention time/flow rate	12min at 3.6mL/min	16min at 3mL/min
%Product chemical purity	<90	>99
%Radiochemical yield	19.8 ± 1.8	31.7 ± 4.6
%Chemical yield	27.1 ± 2.1	46.2 ± 6.6

P199 SYNTHESIS AND EVALUATION OF RADIOIODINE LABELED 1,5-ANHYDRO-2,3-DIDEOXY-2-(5-IODOURACIL-1-YL)-D-ARABINOHEXITOL FOR HSV-TK IMAGING AGENT

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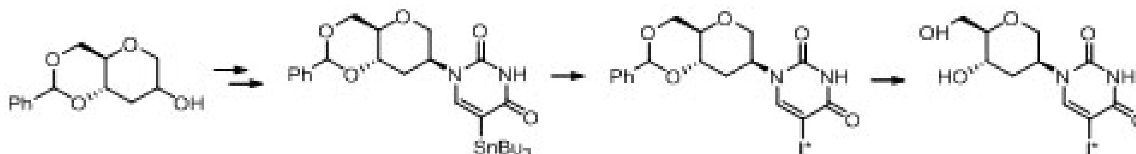
Objectives: The sugar-modified nucleosides have led to develop some nucleoside analogues with antiviral and antitumor properties as previously reported. In general, all these compounds tend that they have to be phosphorylated by cellular or viral enzymes in order to exert their biological activity. For that reason, we tried to develop 1,5-anhydro-2,3-dideoxy-2-([^{125,131}I]5-iodouracil-1-yl)-D-arabinohexitol (ADIDA) based on a six-membered carbohydrate moiety as potential HSV-TK imaging agent.

Methods: ADIDA precursor was synthesized in 5 steps from a commercially available glucose[1-3]. Radioactive ADIDA was prepared by two steps including labeling and hydrolysis as shown in scheme. Briefly, this protocol used general iodine labeling method at room temp, and then passed through C-18 Sep-Pak cartridge. After hydrolysis, it was purified by HPLC using a C-18 reverse-phase column (Waters, detapack, prep-column) with an appropriate solvent (5% EtOH/H_2O) at a flow rate of 3 mL/min. For cytotoxicity analysis of FIAU and ADIDA, MCA rat hepatoma cells and MCA-TK (HSV1-TK positive) cells were treated with various concentration of FIAU, ADIDA and GCV. Cytotoxicity was measured by the MTS methods 5 days later. In vivo imaging was performed on tumor bearing nude mice. Tumors were implanted using MCA, wild type on the left flank and MCA-tk on the right flank. The [^{131}I] ADIDA (300 uCi/ 200 ul) was injected into the tail vein. Planar images were acquired with a γ-camera at 1 h, 4 h after injection."



Results: The radiochemical purity of the product was over 99% in radioTLC scanner. The total elapsed time of synthesis was about 2 hours. In particular, we used C-18 Sep-Pak cartridge to remove impurities having tin before alcohol deprotection. Purified radioactive compound was compared with pure standard analogue using HPLC. Furthermore, FIAU (IC_{50}, 1.11 x 10^{-7} M) and GCV (IC_{50}, 1.17 x 10^{-7} M) in cyotoxicity measurement were shown to be more toxic than ADIDA (IC_{50}, 1.85 x 10^{-5} M) in MCA-TK cells. These compounds exhibited less cytotoxicities to MCA cells, compared with MCA-TK cells. Obtained γ-camera image did not show significant difference between MCA and MCA-tk tumor bearing mice model.

Conclusions: We successfully prepared the radioactive ADIDA with high purity for in vivo test, and also showed the possibility for HSV-TK imaging agent development.

References: 1. Van Aerschot, A.; Verheggen, I.; Herdewijn, P. Bioorg. Med. Chem. Lett. 1993, 3(6), 1013-1018. 2. Verheggen, I.; Van Aerschot, A.; Toppet, A.; Snoeck, R.; Janssen, G.; Balzarrini, J.; De Clercq, E.; Herdewijn, P. J. Med. Chem. 1993, 36, 2033-2040. 3. Verheggen, I.; Van Aerschot, A.; Van Meervelt, L.; Rozenski, J.; Wiebe, L.; Snoeck, R.; Andrei, G.; Balzarrini, J.; Claes, P.; De Clercq, E.; Herdewijn, P. J. Med. Chem. 1995, 38, 826-835.

P200 NON-HPLC METHODS FOR THE PRODUCTION OF F-18 AND C-11 RADIOPHARMACEUTICALS

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1. Bioscan, Inc., Washington, DC; 2. Spectron mrc, South Bend, IN; 3. ABX Advanced Biochemical Compounds, Radeberg, Germany; 4. CERMEP, Lyon, France; 5. Eczacibasi-Monrol, Ankara, Turkey

Objectives: As of today, the most popular PET radionuclides in routine clinical use are C-11 and F-18. This is due to their well established chemistry, their utility for labeling low molecular weight compounds, and their ease of production in modern PET cyclotrons. Their relatively short half-lives have necessitated the development of rapid labeling chemistries and the use of automated radiochemistry systems, which, in turn, has allowed radiosynthesis scale-up and multiple dose preparation. Major impediments to routine production of a number of useful C-11 and F-18 PET tracers, and to new tracer development, remain: 1) the necessity of thorough system clean up in between consecutive runs; and 2) inconsistent yields and prolonged synthesis time when using HPLC methods for final product separation and purification.

Methods: To overcome the logistically difficult but necessary parts of the radiochemical synthesis, we are now offering non-HPLC and disposable kit-based radiochemistry solutions for popular PET tracers and intermediates, such as F-18 FLT, F-18 FMISO, C-11 MeI, C-11 choline, C-11 methionine, and C-11 acetate.

Results: Our FLT-Lite and FMISO-Lite radiochemistry solutions offer F-18 FLT and F-18 F-MISO production based on cartridge isolation and purification only, thereby eliminating the need for HPLC separation. A disposable kit for production of C-11 methyl iodide (C-11 MeI) using the old and well established high yield “wet” method (using $LiAlH_4$ and HI) complements the existing ReFORM-PLUS applications for C-11 choline, C-11 methionine and C-11 acetate synthesis.

Conclusions: Our non-HPLC methods for PET tracer synthesis using disposable kits are fresh departure from the current routine in the radiochemistry lab, and now facilitate the challenging task of reliably supplying multiple doses for every day clinical applications.

P201 A PORTABLE SYSTEM FOR BACTERIAL ENDOTOXIN QUANTIFICATION IN RADIOPHARMACEUTICALS BY THE KINETIC CHROMOGENIC METHOD

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Objectives: Pyrogens include any substance capable of eliciting a febrile response upon injection or infection. Endotoxin is a subset of pyrogens that are strictly of gram-negative origin, a natural complex of lipopolysaccharide ocurring in the outer layer of the bilayered gram-negative bacterial cell. From the circulating blood cells of Limulus polyphemus, called amebocytes, a clear lysate is obtained which forms an opaque gel in the presence of extremely small concentrations of bacterial endotoxins. A quantitative kinetic chromogenic test in an automated Portable Test System (PTS) has been developed for determination of bacterial endotoxins in water, in-process and end-products using the Limulus amebocyte lysate (LAL). The aim of this work was to validate the method for some radiopharmaceuticals with no interfering factors.

Methods: Experiments were performed in three consecutive batches of the radiopharmaceuticals ^{18}F-FDG, ^{99m}Tc, Methylenediphosphonic Acid (MDP) and Pyrophosphate (PYRO) produced at IPEN-CNEN/SP using the PTS from Endosafe, Inc. ™, Charleston, SC. Single polystyrene Endosafe cartridges containing dry LAL-reagents, Control Standard Endotoxin (CSE) and synthetic color substrate were used. The LAL sensitivity was 0.05 EU mL^{-1}. Serial dilutions (1:1; 1:5; 1:10; 1:20; 1:50; 1:100 and 1:200) were carried out. 25 μL samples were pipetted into the cartridge wells and the temperature of the reaction was 37 $\pm$1°C. Results were obtained for the endotoxin concentration in samples by interpolation of an archived standard curve (5.0; 0.5 and 0.05 EU mL^{-1}) at 405 nm OD (Optical Density), after 20 minutes.

Results: The Maximum Valid Dilution (MVD) was calculated to establish the extent of dilution to avoid interfering test conditions (MVD=500). Despite product dilution in this method can be greater than in the gel clot method (MVD=200 for radiopharmaceuticals and 0.125 EU mL^{-1} LAL Reagent sensibility), it is necessary to perform validation experiments to determine the minimum interfering dilution. Experiments showed better results above 1:5 dilution factor for ^{18}F-FDG and ^{99m}Tc, above 1:20 for MDP and 1:100 for PYRO. It was observed that there is a specific dilution for every radiopharmaceutical and the profile for the %RPPC and dilution factor graph was similar in the three analyzed batches of each product. The parameters of coefficient correlation (R) $\leq$ 0.980, recovery of positive product control (RPPC) 50 - 200% and coefficient variation (CV) of the samples less than 25% were satisfied and the endotoxin concentration was lower than the lowest concentration of the standard curve (0.05 EU mL^{-1}), therefore less than the established limit in pharmacopoeias.

Conclusions: The PTS is a rapid, simple and accurate technique using the quantitative kinetic chromogenic method for bacterial endotoxin determination. For this reason, it is very practical in the pharmaceutical area and especially for short-lived radiopharmaceuticals, it trends to be the method of choice for the pyrogen test. For ^{18}F-FDG, ^{99m}Tc, MDP and PYRO, the validation was successfully performed.

P202 RADIOCHEMICAL ANALYSIS OF [F-18]FLUOROTHYMIDINE PRODUCED FROM BOC-PRECURSOR AND PURIFIED WITH A COMBINATION COLUMN OF ANION-EXCHANGER AND ALUMINA

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Objectives: The use of [^{18}F]FLT for PET imaging of cell-proliferation is not popular largely due to the difficult synthesis. This can be simplified by substituting semi-prep HPLC with a disposable column purification step, as reported by us earlier (Ref-1). However, the HPLC analysis of the [^{18}F]FLT produced this way, using the BOC-precursor, showed an anionic radioactive byproduct, probably, 4-[^{18}F]-fluoro-benzenesulphonic acid (4-[^{18}F]FBSA)(Ref-2). The aim of this study was to radiofluorinate nosyl chloride and see if the radiofluorinated byproduct is formed, and examine its bio-distribution in rabbits by PET.

Methods: Substitution of $-NO_2$ in the nosyl chloride by [^{18}F]TBAF (130°C, 6 min) and subsequent acid hydrolysis (1ml of 1M HCl, 5 min) yields 4-[^{18}F]FBSA. The reaction mixture is passed through an anion exchanger and neutral alumina combination-column and then eluted with 10% ethanolic water. HPLC analysis was done using C-18 reverse phase and 92.5:7.5 water:ethanol eluant at 0.5 ml/min. EIMS study of samples of [^{18}F]FLT and 4-[^{18}F]FBSA was carried out using Q-Tofmicro (YA-105). PET-CT imaging was carried out in healthy rabbit at 90 min post injection (~111 MBq/2.5ml).

Results: The HPLC of [^{18}F]FLT product showed two radioactive peaks at 7.85 min (4.13%) and 31.50 min (95.87%) respectively. The latter was confirmed to be FLT by comparing with the R_f of [^{19}F]FLT standard. The chromatogram of the radiofluorinated product of nosyl chloride had a single radioactive peak at 6.85 min matching a UV peak at 7.2 min. Pure nosyl chloride gave a single UV peak at 7.65 min. Further, EIMS study of the radioactivity-decayed samples showed a single peak at 242.3102 mass units confirming that the nosyl moiety of the BOC-precursor is a potential site for radiofluorination, producing 4-[^{18}F]FBSA. As expected, the PET scan showed of [^{18}F]FLT in the rabbit showed distinct accumulation in the highly proliferative tissues like marrow, small intestine, jaws etc, whereas, the PET scan with 4-[^{18}F]FBSA was virtually identical to a [^{18}F]F bone scan. The latter is ruled out in the product but is, apparently, formed from when the former breaks down in circulation. The absence of bone uptake in the [^{18}F]FLT confirms the insignificant quantity of the 4-[^{18}F]FBSA in the injected dose.

Conclusions: We find that the BOC-precursor and combination-column purification produce small amounts of 4-[^{18}F]FBSA in the final [^{18}F]FLT product, but does not appear to impair the image quality. However, its presence in the final preparation of [^{18}F]FLT may be questionable. It is not known if the semi-prep HPLC purification used in commercial synthesis modules takes care of this. If a convenient automated production of [^{18}F]FLT, like that of [^{18}F] FDG, is required, we may have to fall back on the anhydrothymidine precursor, albeit with a somewhat lower yield.

References: J Label Compd. Radiopharm 2007 : 50 : S1-S121 J Label Compd. Radiopharm 2003 : 46 : S1-S403

P203 FULLY AUTOMATED RADIOSYNTHESIS OF [F-18]FLUOROESTRADIOL BY ALKALI HYDROLYSIS AND SIMPLIFIED COLUMN PURIFICATION

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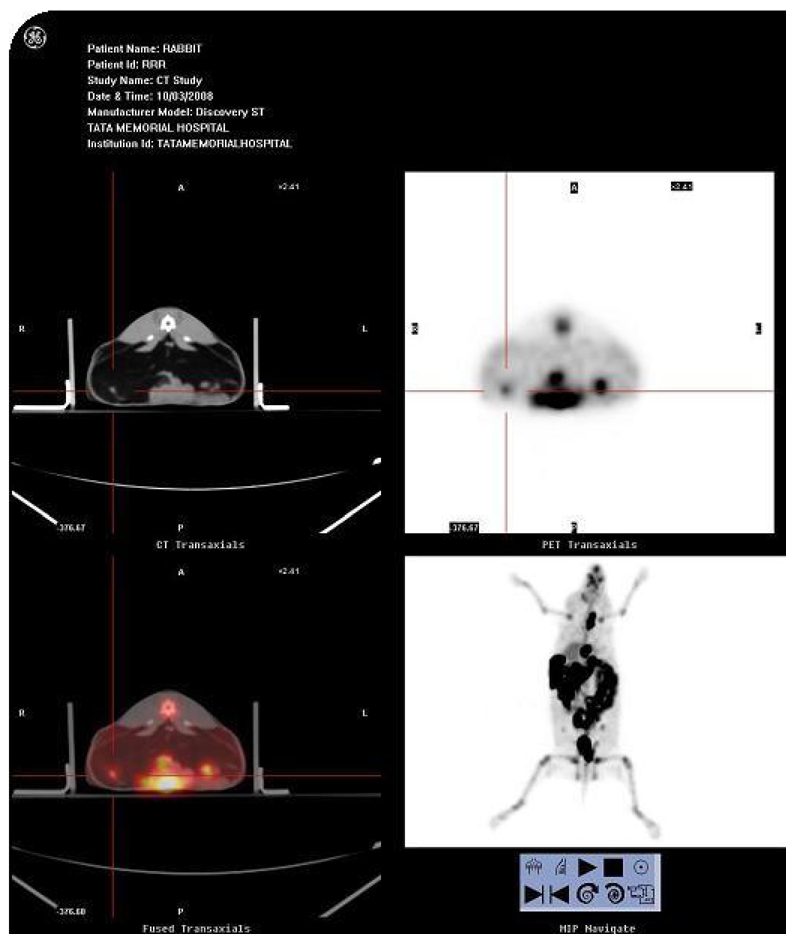
Objectives: ^{18}F-fluoroestradiol ([^{18}F]FES) is a valuable PET tracer to predict the response of recurrent or metastatic breast cancers to anti-estrogen therapy. The aim of this study is to explore the possibility of a fully automated radiosynthesis of [^{18}F]FES by alkali hydrolysis and simplified alumina column purification.

Methods: The precursor, MMSE (3-O-methoxymethyl-16α, 17β-epiestriol-O-cyclic sulfone) and all other reagents and chemicals were from ABX, Germany. Chromafix 45-PS-HCO_3 anion exchange column was form Germany. Neutral alumina (Grade I-II) was procured from Merck, India. The synthesis was done in a Nuclear Interface module configured for [^{18}F] FDG synthesis. The dry TBA^{18}F produced following azeotropic distillation was reacted with MMSE in acetonitrile at 115°C for 15 minutes for nucleophilic substitution. After evaporating the acetonitrile, the protecting groups were hydrolyzed by heating with 1 ml 1M NaOH to 110°C for 10 minutes. The reaction mixture was loaded on a neutral alumina purification column and ^{18}F-FES was eluted with 15% ethanolic-water containing suitable volume of 10% NaCl and 1M NaH_2PO_4 to maintain physiologic pH and isotonicity. Radiochemical purity was checked by TLC as well as analytical HPLC using C-18 reverse phase column. PET/CT imaging studies were carried out in three female healthy rabbits, each injected with ~ 100KBq mCi through the ear vein. Images were taken after two hours after suitably anesthetizing the rabbits.

Results: The total synthesis time is 55±1 minutes and the radiochemical yield is 7.0±1.0% (n = 6, without decay correction). The [^{18}F] FES synthesized was clear, colourless. The RCP was >95% by TLC. This was further confirmed by radio-HPLC and comparing with [^{19}F]FES reference standard. Analysis of the probable non-radioactive impurities is under progress. PET/CT imaging studies in normal female rabbit showed very significant uptake in the mammary glands. The absence of bone uptake confirmed the absence of free fluoride in the final product.

Conclusions: [^{18}F]FES can be successfully synthesized in considerable yields by simple neutral alumina column purification method, since the moieties released on hydrolyzing the protecting groups are effectively trapped on the alumina column. Successful de-protection by alkali hydrolysis is feasible at lower temperature which effectively reduces the total synthesis time minimizing the radiation decay. Overall this process can easily be adopted in simple FDG synthesis module. Key words: fluoroestradiol, fluorine-18, PET-imaging



PET-Ct scan of female rabbit adminstered [F-18]FES. The cursor is positioned on one of the mammary glands showing uptake of the radiotracer.

P204 DEVELOPMENT OF 99mTc-NTP 15-5, A NEW TECHNETIUM LABELED RADIOPHARMACEUTICAL FOR FUNCTIONAL IMAGING OF CARTILAGINOUS DISEASES

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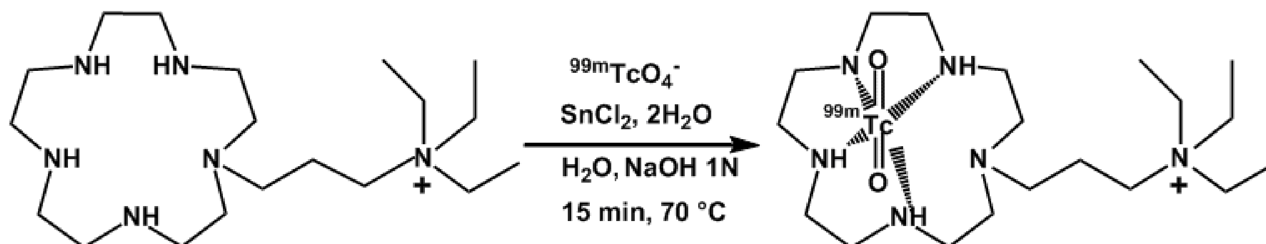
Objectives: The vectorization strategy towards cartilage has been developed by our laboratory after finding out the affinity of the quaternary ammonium function (QA) for negative charges of proteoglycans (PG). The strategy for application to functional imaging of degenerative cartilage pathologies (osteoarthrosis, osteoarthritis and chondrosarcoma) is based on the use of bifunctional agents containing quaternary ammonium moiety able to bind to cartilage PG and a polyazamacrocycle structure able to complex 99m-technetium (^{99m}Tc), the ideal isotope for nuclear medicine. To that end, the N-[3-(triethylammonium)propyl]-1,4,7,10,13-pentaazacyclopentadecane radiolabeled with ^{99m}Tc (^{99m}Tc-NTP 15-5) was selected on the basis of a high stability of the ^{99m}Tc-complex and a high affinity for PG in vivo. The laboratory wishes to initiate a phase I clinical trial in 2009 to assess the potentialities of this radiopharmaceutical for functional imaging of cartilaginous diseases on human. This clinical transfer requests an optimization of the synthesis of NTP 15-5 and his radiolabeling. The objective is to define precise and reproducible radiolabeling conditions for the final formulation, allowing a routine radiopharmaceutical synthesis in nuclear medicine centers.

Methods: The presented work concerns : 1)The optimization of the synthesis and purification of ligand NTP 15-5. 2) The optimization of radiolabeling step in order to set a "^{99m}Tc-radiopharmaceutical kit" for phase I clinical trials.

Results: 1) During the last synthesis step, the QA function is introduced by coupling excess 1,4,7,10,13-pentaazacyclopentadecane (15-5) with (3-bromopropyl)triethylammonium bromide in order to avoid polysubstitution. NTP 15-5 is finally isolated after purification by reverse phase column chromatography. 2) Quantities of reactives (NTP 15-5, $SnCl_2$, NaOH, ^{99m}Tc specific activity) and conditions of reaction (time, temperature) were optimized to set the radiopharmaceutical routine kit. Actually, the radiochemical purity of ^{99m}Tc-NTP 15-5 is over 95 %. Kit formulation is under progress. 3) An HPLC method of analysis usable in routine was validated for the study of the ligand and the technetium-complex.

Conclusions: The optimization of NTP 15-5 synthesis and purification has satisfactorily enabled us to get large quantities of ligand in good purity. The optimization of ^{99m}Tc-radiolabeling was done. Significant progress has to be pointed out which confirms that it is indeed possible to set a "radiopharmaceutical ^{99m}Tc-NTP 15-5 preparation kit".



P205 A MULTIPURPOSE AUTOMATED SYSTEM FOR CLINICAL PRODUCTION OF RADIOPHARMACEUTICALS FOR PET USING DISPOSABLE KITS

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Objectives: We have developed the multipurpose automatic synthesizer system with sterile, disposable kits and a exchangeable micro fluid chip unit to perform a number of critical tasks under cGMP conditions. The principle design goal is to use disposable kits in the most of production processes and to provide a micro fluid chip unit that could transform HPLC purified products in organic mobile phase into saline based injectables which meet regulatory purity requirements. In addition, the unit's flexible programming system makes it an ideal system for the routine production of such useful compounds as [^{11}C]acetate, [^{11}C] methionine and [^{18}F]FLT

Methods: [^{11}C]acetate is produced with [^{11}C]CO_2 release from a molecular sieve into a disposable vial containing 1 ml of 0.1M Grignard reagent in diethyl ether. The product is purified using a series of Sep-Pak cartridges. [^{11}C]methionine is produced with [^{11}C]methyl iodide which is prepared with [^{11}C]CO_2, LAH and HI in this system. [^{11}C]3NMPB is produced with [^{11}C]methyl iodide or [^{11}C]methyl triflate which is prepared in this system. The product is purified with HPLC, and the fraction of the product is collected and transferred into a micro fluid chip unit to remove organic solvents. [^{18}F] FLT is produced with [^{18}F] F, K222/K_2CO_3 and 3-N-boc-5'-O-dimethoxytrityl-3'-O-nosyl-thymidine. Each final product is passed through a sterile 0.22 micro meter filter.

Results: The set up of the synthesis system and disposable kits for [^{18}F] FLT production is shown in Figure 1. The radiochemical yields of these compounds are as follows, [^{11}C]acetate in 80-90 %, [^{11}C]methionine in 60-70 %, [^{11}C]3NMPB in 50-60 %, [^{18}F]FLT in 20-35 %. The radiochemical purity of each compound is above 95 %. The specific activities at EOS are achieved to 40-60 TBq/mmol in ^{11}C and 50-80 TBq/mmol in ^{18}F, respectively.

Fig. 1

Conclusions: The production, purification and formulation procedures result in high yield, high purity products with disposable kits, HPLC and the micro fluid chip unit. The availability of sterilized disposable kits and the exchangeable micro fluid chip unit for these processes allows procedures to readily meet cGMP requirements for clinical use.

P206 PRE-CLEAN-UP OF REACTION MIXTURES IN RADIOPHARMACEUTICAL MANUFACTURING BY ON-LINE SOLID PHASE EXTRACTION USING HPLC

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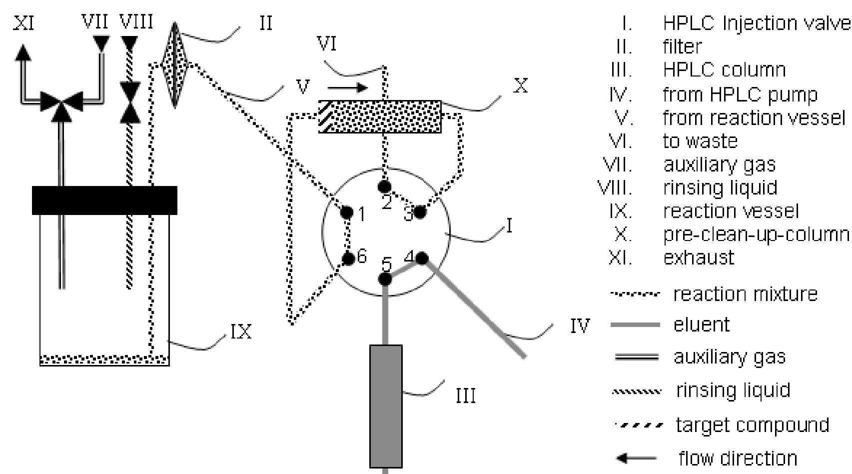
Objectives: Radiopharmaceuticals are usually synthesised by reaction of simple radiolabeled compounds with a non-radioactive precursor. Afterwards the labeled precursor compound undergoes frequently a deprotection reaction. The resulting reaction mixture is often quite complex and needs HPLC purification to isolate the labeled target compound in high chemical and radiochemical purity. In some cases the composition of the reaction mixture is such complex, that an off-line solid phase extraction (SPE) step is carried out before HPLC purification to separate matrix components and/or interfering solvents. This SPE prepurification of the reaction mixture is difficult to automate and needs special hardware and solvents for rinsing and eluting the SPE cartridge. Additionally, remote controlled synthesis modules become more complex.The general aim of the present work is to develop a process, which allows the pre-cleaning of reaction mixtures from disturbing matrix components by online SPE using HPLC. In detail it results from the need to improve the radiochemical purity of [^{18}F]FDOPA and to reduce the solvent content of dimethylformamide (DMF) during manufacturing of the serotonin transporter radioligand [^{18}F]FMeMcN 5652.

Methods:



The figure shows the scheme of the HPLC hardware, whereas a pre- or guard-column is used as pre-clean-up-column (X) instead of an injection loop. The selectivity of the packing material of both columns (III & X) can be selected in accordance with the separation requirements.The process includes following steps:1. Injection valve (I) in “load position”, The reaction mixture is transferred from the reaction vessel (IX) onto the pre-clean-up-column. The diameter of the packing material of the pre-clean-up-column is in the range, which allows the feeding by gas overpressure. The disturbing matrix components are passed to waste and the target compound is retained.2. The rinsing liquid is filled into the reaction vessel and rinse out the dead volume of the pre-clean-up-column. The target compound is cleaned-up and concentrated.3. Injection valve in “inject position”, The target compound is back flushed out of the pre-clean-up-column onto the separation column (III) by the HPLC mobile phase. The finely purification takes place on the separation column. The eluate is fractionated and the target compound is collected in the common way.For the purification of [^{18}F]FDOPA from the critical radiochemical impurity [^{18}F]fluoride a pre-clean-up-column filled with polymer-based reversed phase (RP) material is used. The finely separation was performed on a silica-based RP column.In case of [^{18}F]FMeMcN 5652 production the clean-up from the solvent, needed for the radiolabeling, and the finely separation is carried out on columns filled with silica-based RP materials.

Results:

HPLC purification method	[^{18}F]FDOPA [^{18}F]Fluoride [%]	[^{18}F]FMeMcN DMF [mg/ml]
Injection loop	7.7 (n=93)	1.4 (n=5)
Pre-clean-up-column	1.4 (n=25)	< 0.001 (n=4)

Conclusions: Using the interlinked on-line SPE / HPLC system, reaction mixtures of radiopharmaceutical synthesis can be cleaned up and disturbing matrix components can be separated from the target compound more efficiently.

P207 SYNTHESIS OF NOVEL WAY 100635 DERIVATIVES CONTAINING A NORBORNENE GROUP AND RADIOFLUOROINATION OF [18F]AH1.MZ

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Objectives: 5-HT$_{1A}$ receptors are involved in a variety of psychiatric disorders and in vivo molecular imaging of the 5-HT$_{1A}$ status represents an important approach to analyze and to treat these disorders. Recently, Fiorino et al. synthesized new arylpiperazines containing a norbornene group as 5-HT$_{1A}$ receptor antagonists and reported their outstanding in vitro selectivity for the 5-HT$_{1A}$ receptor. Therefore, we decided to slightly modify promising ligands by replacing a methoxy- by a fluoroethoxy group for labelling purposes, to alter the position of the fluoroethoxy group within the phenylic ring and to determine the affinities of the new compounds towards several 5-HT receptors. Also, we report the optimized labelling and purification procedure of the a promising candidate [^{18}F]AH1.MZ.

Methods: Organic synthesis of WAY 100635 derivatives containing a norbornene group has been described by Fiorino et al. [1]. Due to the necessary structural replacement of a methoxy- by a fluoroethoxy group for labelling purposes, a similar synthesis route was applied, but hydroxyphenylpiperazines were used as starting materials for both precursors and reference compounds. Moreover, the ^{18}F-labelling was carried out similar to the one reported in Herth et al. [2] and the in vitro receptor profile was provided by PDSP.

Results: Three potential 5-HT$_{1A}$ antagonists could be synthesized in total yields of 15%. In vitro affinites of the htree compounds were in a low to moderate nanomolar range for AH1.MZ (1) (K_i = 4.2 nM) and AH2.MZ (2) (K_i = 30 nM), whereas AH3.MZ (3) shows no affinity towards the 5-HT$_{1A}$ receptors. Moreover, AH1.MZ and AH2.MZ showed a reasonable in vitro affinity profile and should enable imagining of the 5-HT$_{1A}$ receptor by PET. The [^{18}F]fluoroalkylation was optimized only due to temperature variation resulting in radiochemical yields of > 70%. Final reaction conditions were 120 °C, 7 mmol precursor and 7 mmol 5 N NaOH dissolved in 1 mL of dry DMSO with a reaction time of 20 minutes.

Conclusions: By replacing the methoxy- by a fluoroethoxy group of the parent compound, three different reference compounds (1)-(3) were obtained enabling a labeling strategy with [^{18}F]FETos. In vitro evaluation of these ligands showed high to moderate affinities to the 5-HT$_{1A}$ receptor of AH1.MZ and of AH2.MZ, but any affinity towards the 5-HT$_{1A}$ receptor of the p-substituted fluoroethylated compound. The receptor profile of AH1.MZ and AH2.MZ demonstrates selectivity within the 5-HT system. However, the outstanding affinity and selectivity of the literature reference compound is mainly lost by introducing a fluoroethyl group. Nevertheless, compounds AH1.MZ and AH2.MZ may provide potential for molecular imaging the 5-HT$_{1A}$ receptor system. ^{18}F-labelling via [^{18}F]FETos was carried out and optimized up to RCY of > 70%.

References: [1] Fiorino F, Perissutti E, Severino B, Santagada V, Cirillo D, Terracciano S,Massarelli P, Bruni G, Collavoli E, Renner C, Caliendo G. J. Med. Chem. 2005; 48: 5495-5503 [2] Herth M M, Debus F, Piel M, Palner M, Knudsen G M, Lddens H, Rsch F. Bioorg. Med.Chem.Letters 2008; 18: 1515-1519

P208 AUTOMATED SYSTEM FOR RADIOPHARMACEUTICAL FORMULATION AND [F-18]SODIUM FLUORIDE PRODUCTION

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Objectives: A radiopharmaceutical formulation system was configured to automate production of [^{18}F]NaF. Yields and production times are compared with current methods for [^{18}F]NaF production.

Methods: The Siemens Explora FM was configured to produce [^{18}F]NaF. Flow paths were set to enable two consecutive productions of [^{18}F]NaF. Nitrogen push gas was used to direct fluid flow through the system. On board radioactivity detectors provide real time feedback on location of product in this flow through reaction process. The final radioactivity and radiochemical purity of the product was measured to determine the yield. The device software was used to create a recipe for automated radiopharmaceutical production. Starting activity of 18F used in this study were 400, 700 and 2200 mCi.

Results: Automated [^{18}F]NaF production using the formulation device gave final product yields of 95-99%. Production time for the automated system took approximately 3-4 minutes. For a two-run configuration, set-up time was reduced.

Conclusions: In this work we demonstrate that automation of this simple flow through synthesis gave the same high yields as with preparing [^{18}F]NaF manually. We were able to utilize a formulation system to automate a flow through reaction for 18F-NaF production. Automation of this process primarily impacts production in: (1) reduction of radiation exposure; (2) repeatability of method across different operators; and, (3) traceability and recordkeeping features of software enables compliance to GMP.

P209 AN INTUITIVE, MODULAR, EASY-TO-MAINTAIN [C-11] ACETATE PRODUCTION SYSTEM WITH TOUCH-SCREEN PANEL INTERFACE

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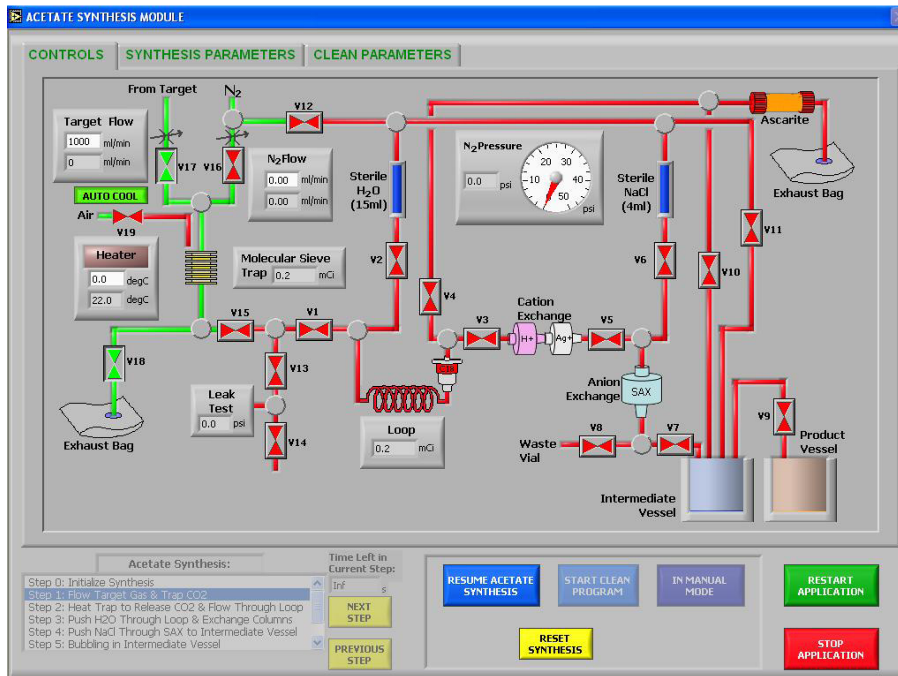
Objectives: To construct an automated user-friendly radiosynthesis module by combining an intuitive graphical control interface with configurable modular chemistry components and industry renowned acquisition and control hardware. We have implemented this method to our optimized synthesis of [^{11}C]acetate (1) based on the “captive solvent” technique and SPE methods (2).

Methods: A touch-screen flat panel PC (Acrosser; Stainless Steel Fanless Ultra Slim Flat Panel PC, Model AR-U150FL-CM1500) was mounted on the hot cell to provide a virtual window (see figure) through which the synthesis can be controlled in a straightforward and intuitive manner. The software was developed using National Instruments Labview 7.1 and Measurement and Automation Explorer 4.0. All of the control and sensor signals are routed through USB data acquisition devices. Due to the lack of a keyboard and mouse, all user-inputs take the form of touch-screen toggle buttons or graphical numerical keypad entry. While in manual mode, the valves themselves become buttons, and all numerical parameters are changed by pressing on them to pull up the on-screen numerical touchpad. The synthesis hardware is mounted on a 2’ by 2’ board which stands vertically in the hot cell. The hardware is modularized onto smaller boards mounted to the main board by quick-release pegs for easier maintenance. There are four separate modules that contain the hardware for the molecular sieve [^{11}C]carbon dioxide trap, the Grignard reaction captive solvent loop, the final product solid phase separation unit, and the electronics.

Results: The stainless steel construction of the flat touch-panel PC and its lack of fan cooling makes it ideal for work in a GMP environment. The synthesis can be automated or controlled manually, and can be paused and resumed at any point. The modular parts of the radiochemistry hardware makes for rapid turnaround of disposable parts (e.g. the loop) and should provide a platform capable of conducting multiple runs in rapid succession or providing different radiopharmaceuticals that can utilize common modules and saving precious hot-cell space.



Conclusions: Using touch-screen hardware and laboratory automation software together with modular radiochemistry units we have demonstrated that we can provide very user friendly radiochemical synthesis. The stainless steel panel can be easily mounted on to hot cells and does not require a keyboard or mouse, making it ideal for GMP environments and conserving valuable laboratory space. Variables such as temperature, pressure, or flow can easily be set from the pop-up keypad. Also, the modular design allows for more rapid chemistry and control hardware maintenance.

References: 1. MK Schultz, GL Watkins, TJ Tewson. “Removal of a [C-11]-carbonic acid impurity arising in the synthesis of 1-[C-11]-acetate using the captive solvent method” J Nucl Med (2008) 49 (Suppl 1): 308P 2. D Soloviev, C Tamburella. “Captive solvent [^{11}C]acetate synthesis in GMP conditions” Appl Rad Isot (2006) 64: 995-1000

P210 AUTOMATED RADIOSYNTHESIS OF [18F]PBR111 AND [18F]PBR102 – SELECTIVE RADIOLIGANDS FOR IMAGING THE PERIPHERAL BENZODIAZEPINE RECEPTOR WITH PET

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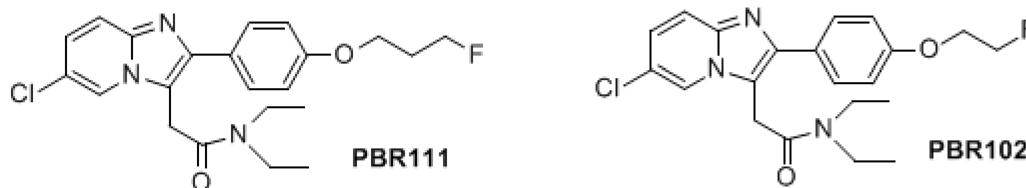
Objectives: [^{18}F]PBR111 ([^{18}F]-1, 2-(6-chloro-2-(4-(3-[^{18}F]fluoropropoxy)phenyl)imidazo[1,2-a]pyridin-3-yl)-N,N-diethylacetamide) and [^{18}F]PBR102 ([^{18}F]-1, 2-(6-chloro-2-(4-(3-[^{18}F]fluoroethoxy)phenyl)imidazo[1,2-a]pyridin-3-yl)-N,N-diethylacetamide) (Fig1) are selective radioligands for imaging of the peripheral benzodiazepine receptor (PBR), also known as the translocator protein (18 kDA) or TSPO (K_i 4.2 nM for PBR111 and 3.3 nM for PBR102)(K_i 800 nM for central benzodiazepine receptor (CBR) for both compounds)[1]. Its synthesis and evaluation in rodents[1] and primates have shown promising results for further investigation in the clinic. As a consequence, a reproducible automated radiosynthesis of [^{18}F]PBR111 and [^{18}F]PBR102 was desired. The radiosynthesis of [^{18}F]PBR111 using a Zymate-XP robotic system has already been reported.[2] Here we compare the automated radiosynthesis of [^{18}F]PBR111 and [^{18}F]PBR102 in 2 GE modules; Tracerlab FX FN and Trcaerlab MX FDG

Methods: Using no carrier added [^{18}F]fluoride, [^{18}F]PBR111 and [^{18}F]PBR102 were synthesised from their p-toluenesulfonyl precursor, via an aliphatic nucleophilic substitution reaction in each of the automated GE modules; the Tracerlab FX FN and Tracerlab MX FDG with a modified reaction sequence in conjunction with an in house remotely controlled HPLC injection module and a sep paking module. In each case, the p-toluenesulfonyl precursor (3.5 – 7.0 μmol) was reacted with the pre dried Kryptofix 222, K_2CO_3, K[^{18}F]F mixture in anhydrous acetonitrile and heated to 100 °C for 5 mins, using activity that ranged from 37 GBq – 148 GBq (1 – 4 Ci). The reaction mixture was purified on a Grace Alltima C18 (10 μ, 250 x 22 mm) before the product underwent sep pak trapping with subsequent formulation ready for evaluation

Results: [^{18}F]PBR111 and [^{18}F]PBR102 was synthesised in 38 – 45% yield (n=30)(decay corrected) from the Tracerlab FX, while both radioligands were synthesised in 10 – 15 % yield (n=12)(decay corrected) from the Tracerlab MX FDG. The specific activity for both radioligands from both synthesis modules ranged from 148 – 370 GBq/mmol (4 – 10 Ci/mmol) at EOS (55 – 60 mins including HPLC purification and sep pak based formulation). Radiochemical purity in each synthesis was > 99%.

Conclusions: It was demonstrated that the the radiosynthesis of [^{18}F]PBR111 and [^{18}F]PBR102 could be fully automated in the Tracerlab FX FN and easily adapted to the Tacerlab MX FDG with reproducible yields, high specific activity and with an average synthesis time of 60 mins. However, the radiochemical yields from both modules could be further optimised. Both [^{18}F] PBR111 and [^{18}F]PBR102 are currently being evaluated in primates and several rodent models.

References: 1. C. J. Fookes et. al, J. Med. Chem., 2008, 51, 3700-3712 2. F. Dolle et. al., J. Label Compd. Radiopharm, 2008, 51, 435439



P211 LYOPHILIZED DMSA (V) KIT FOR LABELING WITH 99mTc

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Objectives: The aim of this work is the development of a lyophilized DMSA (V) kit for labeling with ^{99m}Tc. The study consisted of the definition of the radiochemical quality control methodology and evaluation of the labeling yields of ^{99m}Tc-DMSA (V) and the kit stability.

Methods: The lyophilized formulation of DMSA (V) contained 1.8 mg of DMSA, 0.56 mg of $SnCl_2.2H_2O$, 0.83 mg of ascorbic acid and pH 9. DMSA and ascorbic acid were dissolved in 7% $NaHCO_3$ and $SnCl_2.2H_2O$ was dissolved in 0.1N HCl and left for 20 min under a N_2 gas stream. The pH of the solution was adjusted to about 9 with 1 N NaOH. The solution was made air-free by bubbling with N_2, filtered and then lyophilized. The lyophilized kit was labeled with $^{99m}TcO_4^-$ freshly eluted from a ^{99}Mo-^{99m}Tc generator from IPEN-CNEN/SP. The solution was stirred and incubated at room temperature. Samples were taken to perform the radiochemical quality control. Some labelling parameters were studied such as stability and reaction time (0 and 30 min, 1.0, 2.0 and 4.0 hours), ^{99m}Tc volume (1 and 2 mL) and activity (555-4736 MBq), and kit stability (during 6 months at 2-8 °C). The radiochemical purity was evaluated by thin layer chromatography on silica gel (TLC-SG) and its value also represented the labeling efficiency. TLC-SG strips (1.5 x 12 cm) were developed in two different solvent systems. A solvent system containing: n-butanol/acetic acid/ H_2O (3:2:3 by volume) (S1) was used in order to separate ^{99m}Tc-DMSA (V) from $^{99m}TcO_4^-$ and ^{99m}Tc-DMSA (III). The second system used water (S2) as solvent in order to determine $^{99m}TcO_2$. The R_f of the different species was confirmed experimentally, in particular the R_f for TcO_2 in the first solvent, that was not stated in the original publication. After the TLC run, the strips were cut in 1 cm pieces and the radioactivity determined using a calibrated hyperpure Germanium detector model GX1518 (Canberra Inc., USA). Biological distribution in Wistar rats was evaluated one hour after intravenous dose of 5.5 MBq/0.1 mL ^{99m}Tc-DMSA (V).

Results: Table 1 shows the R_f values for the different species that can be found in the labeling of DMSA (V) with ^{99m}Tc. This lyophilized formulation showed high labeling yields (>95%). High labeling yields were achieved in all reaction times studies. These results also represented the stability of the labeled compound at room temperature that had a high radiochemical purity percentage even 4.0 hours after the labeling. The increase of the activity and volume of ^{99m}Tc did not affect the labelling yield. The lyophilized kit was stable up to 6 months, the period of this study. The biodistribution studies showed that the radiopharmaceutical had the expected in vivo behaviour.

Table 1. Rf of different species of 99mTc

Species	R_f (S1)	R_f (S2)
^{99m}Tc- DMSA (V)	0.6 - 0.7	1
^{99m}Tc- DMSA (III)	0	1
$^{99m}TcO_4^-$	1	1
$^{99m}TcO_2$	0	0

Conclusions: A lyophilized formulation of DMSA (V) was developed for labeling with ^{99m}Tc that could be labeled with ^{99m}Tc activities up to 4736 MBq with high labeling yields (> 95%) and all the quality parameters required. The kit was also stable up to 6 months, essential condition for the commercial production of this kit.

P212 A TIME-EFFECTIVE MICROWAVE ENHANCED FLUORINATION METHOD: ENTRIES FOR HIGH DIRECT LABELLING YIELDS OF TROPANES

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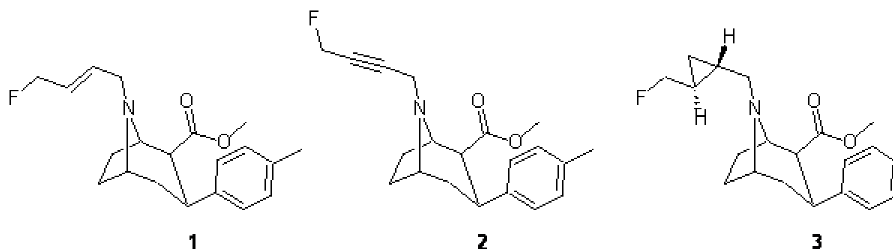
Objectives: The presynaptic dopamine transporter DAT has attracted a veritable interest due to its role in psychiatric and movement disorders. With respect to molecular imaging, cocaine derived, fluorinated tropanes have emerged as the most frequently considered imaging agents for this purpose. However, high-yield routine batch production of fluorine-18 labelled tropanes has often been complicated by adverse effects such as: a) low yields for indirect fluorination via prosthetic groups, b) base mediated exo/endo epimerization at the position 2 carbon center, c) unreasonable low yields with direct labeling. We were interested in a significant improvement of the labeling yields in this class of compounds, to promote the recently developed selective DAT tracers LBT-999 (1), PR04.MZ (2) and PR17.MZ (3).

Methods: A microwave (MW) enhanced labelling protocoll for direct aliphatic radiofluorination of cocaine derived labelling precursors in high radiochemical yield has been developed. The fluoride sources [18F]CsF, [18F]TBAF and [18F][K+ÌK222] were compared in MeCN in terms of labelling yield and byproducts formed.

Results: The labelling yields were remarkably higher than under conventional conditions. Reaction times were efficiently reduced. All final radiotracers were efficiently isolated from the reaction mixture via HPLC and solid-phase extraction.

Conclusions: A novel MW-enhanced labeling protocol is reported which overcomes the reported issues upon direct labelling of tropanes with [^{18}F]fluoride. This time-effective high yield fluorination method may also be beneficial in other cases.



P213 CAPTIVE SOLVENT METHYLATIONS IN THE INJECTOR LOOP OF THE TRACERLAB CARBON-11 MODULE

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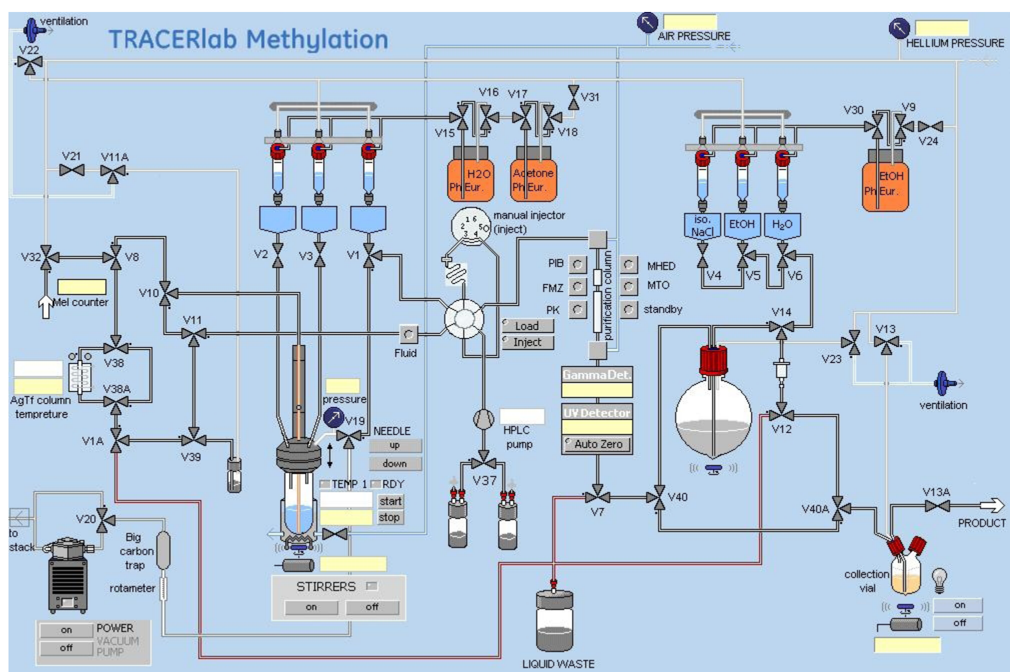
Objectives: We set to develop fast and reliable methods of carbon-11 radiopharmaceutical production on a TRACERLAB-FX-C module providing possibility of back-to-back syntheses of several different tracers in a same day without exposure of an operator to the risk of irradiation and facilitating GMP compliant radiopharmaceutical production. The major focus was made to provide flexibility to choose between captive solvent and bulk solution methylation without any alteration of tubing connections.

Methods: The standard configuration of the module as supplied by the manufacturer (GE) was modified by installing additional valves, feed-back digital input and re-arranging capillary line interconnections. No additional electronic control cards were required, as we used the spare inputs and outputs available in the system. The main additional features provided in the novel setup of the synthesizer are as follows:The flow path of the [^{11}C]methyl iodide was re-routed so as to allow the methylation reaction occur inside the built-in injector loop of the preparative HPLC system. This allows to perform "captive solvent" methylations followed by direct injection onto the HPLC preparative column, which adds the reliability to the synthesis routine.Automatic clean-up procedure with acetone, water and 70% ethanol. All solvents used are of pharmaceutical grade to provide GMP compliance. The automatic clean-up starts immediately after the end of synthesis and allows to prepare the module for the next production cycle in less than 30 minutes.Automatic 6-position column selector switch. This provides the possibility to use different HPLC semi-preparative columns for each tracer without the need of dismounting connections.

Results: Modifications of the commercial synthesizer described above allowed us to produce multiple tracers on the same module within the same day reliably without the need to alter the connections in the system. Both captive solvent (in-loop) and bulk solution (in the reaction vessel) methylations are performed with the same setup. In-loop methylations can be performed either by [^{11}C]methyl iodide or [^{11}C]methyl triflate depending on the tracer. Currently we produce routinely for our clinical research programs following radiopharmaceuticals: [^{11}C]PIB, [^{11}C]metomidate, [^{11}C]MHED, [^{11}C]PK-11195, [^{11}C]flumazenil.

Conclusions: Additional features added to the commercial synthesizer described in this work have improved the reliability of the routine production of different radiopharmaceuticals, allowing multiple tracer production on a same day and reducing the radiation exposure of an operator. The system was validated and is GMP compliant.



P214 A VERSATILE RADIONUCLIDE DELIVERY SYSTEM FOR PET OPERATIONS

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Objectives: The GSK Clinical Imaging Centre opened in December 2006 with the mission to make a difference for patients by accelerating translation of basic science discoveries into clinically meaningful results. The focus of the centre will be on PET and fMRI imaging. For this work, the centre is equipped with the following: 2 Siemens PET CT systems, 2 Siemens 3T MRI systems, 2 Siemens Eclipse HP cyclotrons, 2 blood analysis laboratories, organic chemistry lab, raw material quarantine lab, NMR suite, 6 hotlabs (each containing: 2 hotcells, 1 double cavity minicell with commercially available and in-house designed radiochemistry equipment), quality control lab, Isolator room, In vitro labs, In vivo labs, engineering workshop and a radioactive engineering workshop. Remote operation of the cyclotrons is possible from 8 separate locations in addition to the master control which is situated in the radioactive engineering workshop. The majority of the work will focus on the use of carbon-11 (70%) and fluorine-18 (15-20%). To this end, both cyclotrons are equipped with two carbon-11 targets and one fluorine-18 fluoride target. In addition, the cyclotrons are equipped with one oxygen-15 target each and a nitrogen-13 ammonia and fluorine-18 fluorine target respectively. Provision had to be made for an automated radionuclide delivery system (RNDS) to safely send activity to each of the 8 locations as well as allow for within lab transfer of activity from the minicells to the hotcells, resulting in a total demand for more than 100 distinct routes.

Methods: The backbone of the RNDS consists of Valco 16 position multiway valves and Valco 2 position 4 port valves, linked up through a RS485 serial connection controlled using Siemens Simatic PCS7 software. User access is either through touch screen (hotlabs) or personal computer interface (PET control room) and the system is interlocked with e.g. hotcell/minicell port opening and pressure alarms. Finally, the RNDS incorporates a trap and release system for automated delivery of gaseous oxygen-15 products and adequate means for passive waste abatement. As the cyclotrons and chemistry facilities are located on the first floor, we had the opportunity to route the delivery lines through an extended ceiling void between the clinical ground floor and the first floor with easy access and shielded using 20mm lead.

Results: Following installation, the system was pressure tested for all possible routes. During initial use, infrequent valve failure was observed for the last 16 position multiway valve on the RS-485 daisy chain. This error proved to be due to a timing issue on the interrogation of the actual valve position. Once resolved, the system has been working without technical failure.

Conclusions: We have designed, built and validated a safe and flexible system for the routing of PET radionuclides within our facility.

P215 FULLY AUTOMATED SYSTEM FOR [18F]FALLYPRIDE ROUTINE PRODUCTION WITH TRACERLAB MX MODULE

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Objectives: In recent years big efforts have been devoted to the preclinical research of dopaminergic system with [^{18}F] Fallypride. [^{18}F]Fallypride is highly selective radioligand and can be used for visualisation of D_2/D_3 receptors by PET in both striatal and extrastriatal regions of the brain. Functionality of these receptors is very important in terms of human behaviour. [^{18}F]Fallypride is a [^{18}F]fluorinated substituted benzamide and it can be conventionally synthesized from a tosyl-precursor by a standard ^{18}F nucleophilic displacement reaction.

Methods: Produced no-carrier-added [^{18}F]fluoride was transferred to the TracerLab MX synthesizer and extracted from the ^{18}O-enriched water on the activated QMA cartridge. Trapped radioactivity was then eluted by a mixture of $K_2CO_3/K_{2.2.2}$ in CH_3CN/H_2O and transferred into the reaction vessel. [^{18}F]fluoride was consequently dried by performing three successive azeotropic distillations at 95°C with CH_3CN. The dried residue was mixed with a solution of tosyl-fallypride in 3 ml of acetonitrile. Thereafter [^{18}F]fluorination was performed at 85 ^{0}C for 20 min. After the labeling reaction, the radioactivity was diluted with 20 ml of water and passed through activated C18 Sep-Pak cartridge. Retained [^{18}F]Fallypride was then rinsed with 15 ml of water, eluted with 3 ml of ethanol and injected onto HPLC. The product fraction was purified on HPLC with 50% CH_3CN/Triethylamine (94:6). Isolated activity was collected in 50 ml of isotonic sodium chloride and passed through a C18 Sep-Pak. The cartridge was rinsed three times with 10 ml of water and then eluted with 2 ml of ethanol. [^{18}F]Fallypride was diluted with 7 ml of isotonic saline and the pH was adjusted by adding ascorbic acid. Complete QC was performed and specific radioactivity was determined by analytical HPLC.

Results: In order to meet incoming demands we selected TracerLab MX for automation of [^{18}FFallypride production since it is widely present in many radiochemistry facilities and can easily comply GMP requirements. Sterile disposable cassettes used for FDG production can be easily adapted to routine [^{18}F]Fallypride synthesis. In addition, the analogic box of the module allows programmable manipulation of add-on devices such HPLC system and a reformulation box. Production of [^{18}F]Fallypride was conducted within 70 min with an overall radiochemical yield of 32%. The best yield was obtained for 4 mg of precursor, and no significant influence due to initial level of [^{18}F]fluorine activity was observed. Chemical and radiochemical impurities analyzed by HPLC could not be detected. Specific activity was >5000 Ci/mmol (decay corrected). The residual organic solvents were quantified by GC and were within GMP specifications. The pH was neutral and the final solution was pyrogen free.

Conclusions: A fully automated production of [^{18}F]Fallypride was established on TracerLab MX module coupled with semi-preparative HPLC system and home-made reformulation box. The entire process was strongly reliable and reproducible on routine basis providing thus radioactive product of high chemical and radiochemical purity according to the GMP requirements.

P216 AUTOMATED PRODUCTION OF [18F]F-A-85380 USING TRACERLAB MX SYNTHESIZER

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Objectives: [^{18}F]F-A-85380 (2-[^{18}F]F-A-85380) is a highly selective radioligand used for visualization of nicotinic acetylcholine receptors (nAChRs) by PET. By using commercially available TacerLab MX module we developed an automated process for routine synthesis of this radiotracer. The synthesis was performed in two steps starting with the standard nucleophilic exchange of [^{18}F]fluoride with an activated trimethyl ammonium triflate precursor followed by a rapid removal of the N-BOC protective group. After HPLC purification [^{18}F]F-A-85380 was successfully reformulated for human use.

Methods: After irradiation of enriched [^{18}O]water, no carrier-added [^{18}F]fluoride was isolated on QMA cartridge and eluted with a mixture of $K_2CO_2/K_{2.2.2}$ into the reactor. [^{18}F]fluoride was consequently dried by performing three successive azeotropic distillations at 95°C with CH_3CN. A solution of 4 mg of 2-TMA-A-85380 in 3 ml of CH_3CN was added to the dry residue and the reactor was heated at 95°C for 10 min to yield N-BOC protected [^{18}F]F-A-85380. The product was then hydrolyzed at 100°C for 4 min by adding 3 ml of 1M HCl/EtOH (1:1). The reaction mixture was neutralized with 1 ml of 2M of NaOH diluted with 5 ml of water and applied onto reversed-phase HPLC column. Elution was performed with CH_3CN/H_2O/TFA (10:89.85:0.15) as mobile phase and the fraction of [^{18}F]F-A-85380 was collected. Subsequently, the HPLC solvent was removed by trapping activity onto a Sep-Pak cartridge, and retained [^{18}F]F-A-85380 was eluted with 1.5 ml of ethanol and rinsed with 13.5 ml of saline.

Results: TracerLab MX is actually the most commonly used synthesizer for production of [^{18}F]FDG since it fully complies GMP requirements. Therefore, we found extremely interesting to adapt this module to [^{18}F]F-A-85380 routine production by using sterile disposable cassettes. Conditions for the fluorination step were optimized and a radiochemical yield of 78% could be obtained when the reaction was performed at 95 °C for 10 min. Lower temperature resulted in reduced fluorination yield while an increase of the temperature and/or the time of the reaction showed no significant improvement. Hydrolysis of N-BOC protected [^{18}F]F-A-85380 with an ethanolic acidic solution was quantitative within 4 min at 100°C. During HPLC purification of the crude [^{18}F]F-A-85380 two major peaks corresponding to [^{18}F]fluoride and [^{18}F]F-A-85380 were observed with retention times of 5.7 min and 15.5 min, respectively. Typically, total synthesis procedure was accomplished in 65 min with an overall radiochemical yield of 38% (decay corrected). Analytical HPLC and radio-TLC did not show radiochemical and chemical impurities. Residual organic solvents, such as acetonitrile and TFA, were analyzed by GC and were according to GMP specifications. The final solution was pyrogen free.

Conclusions: Using the commercially available TracerLab MX we developed an automated process for routine synthesis of [^{18}F]F-A-85380 under GMP requirements. Conditions for radiosynthesis are suitable for preparation of [^{18}F]F-A-85380 in quantities and times practical for use as a PET radiopharmaceutical.

P217 PET IMAGING OF MELANOMA WITH 18F-LABELED RECCMSH(ARG11)

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Objectives: The goal of this project was to evaluate the PET tumor-imaging potential of the peptide Ac-D-Lys(^{18}F-FB) ReCCMSH(Arg^{11}) that targets the melanocortin-1 receptor over-expressed on melanoma cells.

Methods: The peptide Ac-D-Lys-CCMSH(Arg^{11}) was synthesized using solid phase Fmoc synthesis. Ac-D-Lys-ReCCMSH(Arg^{11}) peptide was prepared with $[(C_6H_5)_3P]_2ReOCl_3$ and Ac-D-Lys-ReCCMSH(Arg^{11}) in DMF, using a ligand exchange reaction. The peptide Ac-D-Lys-ReCCMSH(Arg^{11}) was radiolabeled with N-succinimidyl 4-[^{18}F]fluorobenzonate ([^{18}F]SFB) in DMSO, synthesized with three radio-synthesis steps, and purified by C-18 reverse phase HPLC. PET/CT imaging studies were performed with Ac-D-Lys(^{18}F-FB)ReCCMSH(Arg^{11}) in B16/F1 melanoma tumor bearing C57 mice.

Results: The decay corrected radiolabeling yield of [^{18}F]SFB was 40% over a 1.5 hour reaction period. The radiochemical purity was more than 95% by using a radio-HPLC assay. The radiolabeling yield of Ac-D-Lys-ReCCMSH(Arg^{11}) was about approximately 15% and its radiochemical purity was more than 90%. Melanoma tumors were clearly visualized with Ac-D-Lys(^{18}F-FB)ReCCMSH(Arg^{11}) by PET/CT imaging at 1 h post injection. Injection of 20 ug of a competitor peptide NDP blocked tumor uptake of the radiolabeled peptide confirming receptor specificity.

Conclusions: The radiolabeled peptide Ac-D-Lys(^{18}F-FB)ReCCMSH(Arg^{11}) exhibited rapid receptor mediated tumor uptake in vivo. PET/CT studies demonstrated excellent tumor localization and high tumor to background. The initial tumor imaging results warrant further studies to define the compounds biodistribution and clearance kinetics.

Research Support: The MURR Research Partnership Initiatives (MURRPI) program, Univeristy of Missouri-Columbia. PET/CT imaging studies were performed at the Biomolecular Imaging Core, Harry S. Truman Veterans Administration Hospital, Columbia MO

P218 ONE POT SYNTHESIS OF [18F]FPEB IN A SEMI-AUTOMATED MODULE

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Objectives: To simplify the synthesis of 3-[^{18}F]fluoro-5-(2-pyridinylethynyl)benzonitrile without intermediate isolation and purification in a one-pot process using a semi-automated fluorination module.

Methods: The process was carried out in a GE Medical TRACERlab® FX-FN module. Aqueous [^{18}F]fluoride (105-131 GBq) from a Siemens/CTI RDS 112 cyclotron was collected on an anion exchange cartridge (QMA, Waters) and eluted with 0.6 mL solution of Kryptofix-222 and K_2CO_3 in CH_3CN/H_2O into a glass reaction vessel and dried with He(g) flow at 85-105°C followed by one 1 mL CH_3CN treatment and drying again. Nitro precursor 3-nitro-5-(2-pyridinylethynyl)benzonitrile (2 mg) in 0.5 mL DMSO was added and reacted for 15 min at 120°C. HPLC mobile phase (4.8 mL) was added and injected on an HPLC equipped with semi-prep column, eluting with either CH_3CN/ H_2O/ CF_3CO_2H (50/50/0.1) or EtOH/(10 mM NaH_2PO_4 pH 6.7), 40/60. The eluate was diluted with H_2O (6x volume), trapped on a C_{18} Sep-Pak® (Waters) and eluted with 1 mL EtOH followed by 10 mL normal saline, then filtered through a 0.22 mm membrane filter. Specific activity and radiochemical purity were determined by analytical HPLC.

Results: Using the CH_3CN mobile phase resulted in low isolated yields because of incomplete separation of product. Using the EtOH system, [^{18}F]FPEB was obtained in average 16% radiochemical labeling yield and 9% overall isolated yield from [^{18}F] fluoride (n = 16). Specific activity was 125 GBq/mmol and radiochemical purity was >98%. Overall time of synthesis from end of bombardment was 240 min.

Conclusions: Initial low yield from incomplete resolution of the product and precursor peaks on HPLC was solved by switching to an ethanolic mobile phase. This system has proved to be reliable in routine production.

Research Support: Supported in part by Vanderbilt Department of Radiology.

P219 APPLICATION OF MICROWAVE ACCELERATION TO RADIOFLUORINATION OF RADIOPHARMACEUTICALS

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Objectives: To apply a dedicated single-mode microwave accelerator to production of representative fluorine-18 labeled radiopharmaceuticals.

Methods: A GE Medical TRACERlab® FX-FN module was modified to accept a V-vial that fit the cavity of a dedicated single-mode microwave accelerator. Aqueous [^{18}F]fluoride (112-135 GBq) from a Siemens RDS 112 cyclotron was collected on an anion exchange cartridge (QMA, Waters) and eluted with 0.6 mL solution of Kryptofix-222 and K_2CO_3 in CH_3CN/H_2O into the reaction vessel and dried with He(g) flow at 85-105°C thermal heating; 1 mL CH_3CN was added and heating/drying cycle repeated. Precursor (tosylate for fallypride and FP-DTBZ and nitro for setoperone and altanserin, 1-3 mg) in 0.5 mL solvent (see table) was added. The thermal reactions were heated 25 min at 99º. For microwave, the reaction vessel was moved to the microwave cavity and pulsed with temperature, power (watts) and times as shown in the table. HPLC mobile phase (4.8 mL) was added and injected on an HPLC equipped with semi-prep column, eluting with EtOH/(10 mM NaH_2PO_4 pH 6.7) (47/53) for fallypride and FP-DTBZ, and MeOH/ THF/ (10 mM NaOAc pH 4.5), 9/21/70 for setoperone and altanserin. The eluate was diluted with H_2O (6x volume), trapped on a C_{18} Sep-Pak® (Waters) and eluted with 1 mL EtOH followed by 10 mL normal saline, then filtered through a 0.22 mm membrane filter. Specific activity and radiochemical purity were determined by analytical HPLC.

Results: For [^{18}F]fallypride, the microwave method gave higher yield and higher specific activity than the thermal method. Microwave heating also gave higher specific activity of [^{18}F]FP-DTBZ, but the radiochemical yield was lower, possibly because of using lower quantities of precursor. Reaction times were <3 min for microwave compared to 25 min for thermal. [^{18}F]Setoperone and [^{18}F]altanserin were obtained in high specific activities with good yields by the microwave process; both compounds are known not to react well with thermal heating.

Conclusions: These experiments provide further support that microwave acceleration provides a means to obtain fluorine-18 radiopharmaceuticals in a shorter time in high specific activity.

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Tracer	Solvent	Conditions		Yield (%)		Specific Activity (GBq/µmol)	
		Thermal	µWave	Thermal	µWave	Thermal	µWave
Fallypride	CH_3CN	99º 25 m	120º 100W 3x60s	30%	49%	377	1,738
FP-DTBZ	CH_3CN	99º 25 m	120º 100W 3x45s	17%	11%	291	1,092
Setoperone	DMF/ sulfolane		165º 120W 2x15s		11%		447
Altanserin	DMSO		140º 120W 3x30s		32%		>370

P220 DUAL PET ISOTOPE LABELING A σ_2 RECEPTOR LIGAND FOR IMAGING STUDIES OF SOLID TUMORS

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Objectives: 5-bromo-N-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butyl)-2-(2-fluoroethoxy)-benzamide (BDBFB) was found to have a high affinity and high selectivity for σ_2 versus σ_1 receptors in vitro (Ki-σ_2 = 0.65 ± 0.22 nM, Ki-σ_1 = 1,076 ± 88 nM, the ratio of $\sigma_{2\,:}$? σ_1 = 1656 fold, Log D =3.89). We previously radiolabeled this compound with F-18 for PET imaging of solid tumors (Tu, 2007). The presence of bromine in the structure of this ligand permits labeling with Br-76. The purpose of this study was to compare [^{76}Br]BDBFB with [^{18}F]BDBFB as a potential PET radiotracers for imaging the σ_2 receptor status of solid tumors using the EMT-6 murine model of breast cancer

Methods: Synthesis of [^{18}F]BDBFB was accomplished by microwave irradiation of the corresponding methanesulfonate ester precursor with [^{18}F]/Fluoride to give [^{18}F]BDBFB in an overall yield of 25% and a specific activity of ~2000 Ci/mmol. The corresponding radiobrominated, [^{76}Br]BDBFB, was successfully prepared via the conventional bromodestannylation reaction (Figure 1). Biodistribution studies were conducted with ~25μCi/110 μl [^{18}F]BDBFB on EMT-6 tumor-bearing female Balb/c mice. Animals (n=4) were sacrificed at 5, 30, 60, and 120 min post-i.v. injection of the radiotracer. The [^{76}Br]BDBFB microPET studies were performed on a microPET-Focus 220 scanner with an additional four EMT-6 tumor-bearing mice. The animals were anesthetized and imaged dynamically for 1 hr immediately after injection of 60~70 μCi, then for 30 minutes at 4 hr post-injection and finally for 60 minutes at 24 hr post-injection.

Results: As previously reported, [^{18}F]BDBFB displayed a high initial uptake in both tumor (3.28 ± 0.41 ID%/g) and blood (3.57 ± 0.43 ID%/g). After 2 hours, only 15% of the initial activity remained in the blood and muscle, while 29% was retained in the tumor, suggesting that later imaging time points might afford better tumor:non-tumor ratios. The microPET study of [^{76}Br] BDBFB displayed only modest visualization imaging of tumor at 4 hours. At 24 hours post-injection, the radioactivity displayed homogeneous distribution, which was confirmed by a post-PET biodistribution.

Conclusions: The results of this initial study indicate that brominated version, [^{76}Br]BDBFB, ofthe previously reported [^{18}F] BDBFB does not have optimal target:non-target contrast for imaging the proliferative status of solid tumors in vivo with PET. This may be due to de-bromination. Although the long half-life of Br-76 has the potential to allow for shipment of labeled compounds to other centers and could provide a useful tool to conduct pharmaceutical kinetics studies, the metabolism of this compound in vivo of rats needs to be further evaluated.

Reference: J. Med. Chem., 2007, 50 (14), pp 3194–3204.

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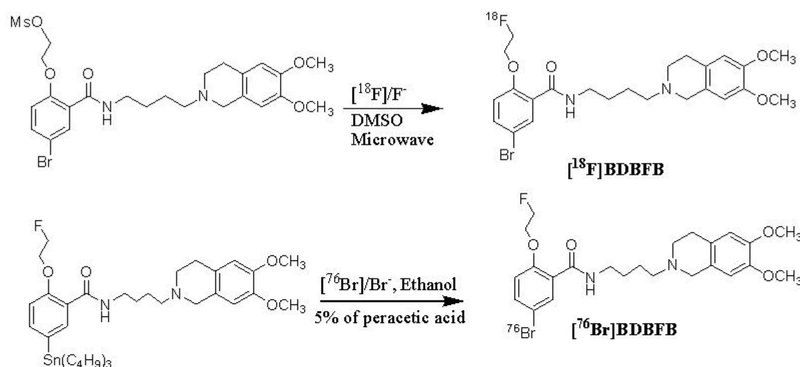

Figure 1. Radiosynthesis of [^{18}F]BDBFB and [^{76}Br]BDBFB

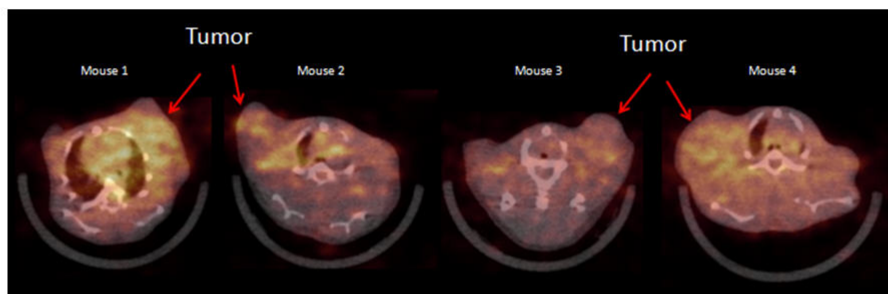

Figure 2. Imaging [^{76}Br]BDBFB in Female Balb/c mice implanted with EMT-6 breast tumors