Abstracts

IS1

Production of Radiohalogens: Where's the beef?

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The excitation functions for the production of the radioisotopes for the elements in the halogen chemical family have been well delineated. However, a number of radiohalogens are not readily available, for example ^{76,77}Br, ^{124}I, and ^{211}At. While the production parameters have been defined including separation chemistry for these and the other radiohalogens have been published there is still a gap between what is needed for research and routine use and what is available to the community at large.

This presentation will review what is and what is not available with an emphasis on how to solve this roadblock to integrating the non-F-18 radioisotopes into our programs.

CS1

New Nuclear Data for Production of ^{76}Br and ^{124}I

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The positron emitting radionuclides ^{76}Br($T_{1/2}$ = 16.2 h; $I_{\beta+}$ = 54 %) and ^{124}I($T_{1/2}$ = 4.18 d; $I_{\beta+}$ = 22.5 %) are of interest both in diagnosis and therapy. Their production methods at small-sized cyclotrons are well established. However, the increasing demands for the two radionuclides call upon optimisation of existing methods as well as search for new production routes.

The production of ^{76}Br is generally performed via the ^{76}Se(p,n)^{76}Br reaction using highly enriched target material [1,2]. The cross section data base in the energy region below 10 MeV was, however, not strong. We now performed detailed measurements on this reaction over the proton energy range of 4.6 to 20 MeV using the conventional stacked-foil technique and highly enriched target material. The new data allow a better estimation of the theoretical thick target yield of ^{76}Br [3].

In a search for a new production route of ^{76}Br, we also studied the hitherto uninvestigated route ^{78}Kr(d,α)^{76}Br. Utilizing ^{78}Kr of ultrahigh enrichment and the gas-cell technique described earlier, cross sections were measured for the formation of ^{76}Br over the deuteron energy range up to 13 MeV. The calculated thick target yield of ^{76}Br amounts to 59 kBq/μA·h; for production purposes it is rather low [4].

The radionuclide ^{124}I is commonly produced via the ^{124}Te(p,n)^{124}I process [cf.5-7]. The purity is high but the yield is low. We therefore investigated the ^{126}Te(p,3n)^{124}I reaction using highly enriched target material, thin source preparation via electrolytic deposition and the stacked-foil technique. The excitation function of this reaction as well as those of a few competing reactions were measured over the proton energy up to 70 MeV. The yield of ^{124}I over the energy range E_p = 38 → 28 MeV amounts to 148 MBq/μA h, i.e. about six times more than via the (p,n) reaction. The expected level of impurities is, however, higher.

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CS2

Production of ^{38,39}Cl for Botany Tracer Studies

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Chlorine is an essential micronutrient for plants, although it often accumulates in soils to levels much higher than required for optimal plant growth. Given the increasing occurrence of saline conditions in many soils, salt tolerance in plants has become a major research concern. In order to conduct studies in following chlorine ion kinetics in plants, researchers from the University of British Columbia in conjunction with researchers from the University of Toronto required a radiochlorine isotope.

A system was developed for the production of ^{38}Cl ($t_{1/2}$ = 37 m) and ^{39}Cl ($t_{1/2}$ = 56 m) via the ^{40}Ar(p,2pn)^{38}Cl and the ^{40}Ar(p,2p)^{39}Cl reactions. A natural argon gas target at a pressure of 250 psi was irradiated with 41 MeV protons accelerated by the CP42 cyclotron at TRIUMF in Vancouver, Canada. Beam currents ranged from 5 to 7 μA. The Cl isotopes adhered to the walls of the target chamber and were rinsed off with a slightly alkaline solution. The Cl isotopes were purified from other radioactive contaminants (^{38}K) with an anion exchange column. Experimental details and results will be discussed.

CS3

Strategies in Choosing Binary Alloys for the Production of I-124: Proof-of-Principle studies using Al_2Te_3

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The promising clinical viability of I-124 has led to large investments among a few research institutions and, recently, commercial companies to produce multi-millicurie quantities for distribution purposes. The most favorable production path is the ^{124}Te(p,n) reaction at proton energies ≥16MeV. Irradiation of elemental tellurium powder suffers from poor beam ballistics resulting in sputtering effects and large losses of valuable target feedstock (≈$10/mg). The thermal and physical behavior of the target material is significantly improved by alloying elemental tellurium with a low-Z element. Reduction in yield due to the decreased mass fraction of the enriched isotope is considered an acceptable sacrifice for improved irradiation conditions and recovery methods. In practice, the prevailing target material, TeO_2, is limited to beam currents ≤10μA, due to its poor thermal conductivity and low melting point. These factors suggest that sufficient quantities can only be made with higher energy (≥ 16MeV) cyclotrons possibly under thin target conditions where the yield remains high and power input is minimal.

Recent interest in using I-124 to label cancer seeking tracers at our institution has led to the development of a new solid target and supporting system for a CTI RDS 112 negative-ion cyclotron. The choice of a binary target material depends on the ability of the substrate matrix to satisfy three major conditions. First, the melting point of the binary alloy is higher than the elemental substrate alone. Second, the partner element is light such that the mass fraction of the element of interest is as high as possible. Third, the binary compound solidifies to a crystalline matrix reducing volatilization and improving thermal behavior during irradiation.

These criteria motivated the development of a novel binary substrate Al_2Te_3 (Aluminum Telluride) for production of I-124, properties show in Table 1. The binary substrate is annealed prior to irradiation in a gold-plated nickel crucible forming a glassy black solid matrix. The supporting target system includes an external beam line coupled to a 90-degree vertical switching magnet. The target surface is cooled with chilled helium (-15°C) recirculating at ≈1L/sec**,** as well as with forced water on the rear of the crucible.

Table 1. Known properties of target materials for production of I-124.

Compound	Color	Crystalline State	Melting Point [°C]	Wt % [Te]	Density [kg/m^3]
TeO_2	White powder	Green glass	~730	79%	5900
Al_2Te_3	Black crystal	Black glass	~900	87%	4500

Preliminary measurements using natural aluminum telluride show yields approaching 70% of the theoretical 38mCi/μA on pure Te-124 at 11MeV. The glassy black solid matrix appears stable for thick target irradiations at 5μA of 2hrs with mass and iodine product losses of a few percent. Post processing of the target material follows conventional dry distillation techniques with a recoverable yield of 85% compared to 62% with TeO_2.

CS4

Cyclotron Production of iodine-123

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The ^{123}I($T_{1/2}$=13.2h, Eγ=159keV) radioisotope has found wide application in diagnostic nuclear medicine. The $^{124}Te \rightarrow ^{123}I$ reaction is more suitable for production at low-energy cyclotrons. Precise excitation function measurements for the $^{124}Te(p, n)^{124}I$ and $^{124}Te(p, 2n)^{123}I$ reactions showed that highly enriched ^{124}Te is necessary to produce ^{123}I containing relatively ^{124}I impurity. Considerable advances in targetry and chemical separation of radioiodine have been reported.

The enriched ^{124}Te was electrodeposited on a 10cm^2 area of electroplated Ni on a Cu plate. The Ni surface provided greatly increased adhesion for electrodeposited ^{124}Te and did not interfere in the radiochemical separation. The thickness of ^{124}Te was 10~12mg/cm^2. The target was irradiated with a proton beam of 25 MeV energy at the currents of 30~50uA. The method for the separation of iodine-123 from tellurium was adapted from “wet” methods. The overall radiochemical yield was typically greater than 92%.

CS5

2-[^{18}F]FDG Production Using a High Intensity Laser-Induced Flourine-18

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Currently, the method of PET radioisotope generation involves electromagnetic acceleration of charged particles within a cyclotron. Recently it has been shown that when an intense laser beam interacts with solid targets, MeV protons are generated capable of producing PET isotopes. We show here the production of ^{18}F using the petawatt laser beam at VULCAN and also for the first time laser production of 2-[^{18}F]FDG.

The new petawatt arm of the VULCAN Nd:Glass laser at the Rutherford Appleton Laboratory was used in this experimental study. The 0.60m beam was focussed to a 5.5 μm diameter spot using a 1.8 m focal length off-axis parabolic mirror, in a vacuum chamber evacuated to ~10^{-4} mbar. The average pulse duration was 7.5×10^{-13} s and the energy on target was between 220 and 300 J. The peak intensity was of the order of 4×10^{20} Wcm^{-2}. Aluminium foil primary targets of various thicknesses were irradiated by the p-polarised laser beam at an angle of 45^{o}. The protons emanated from a plasma produced by the vaporisation of contamination layers of water and hydrocarbons on the primary target surface. This beam of non-colimated protons (1-30 MeV) was used to irradiate a secondary ^{18}O enriched (96.5%) [^{18}O]H_2O target.

It was firstly necessary to determine how much ^{18}F could be produced per laser shot. The isotope is generated from a (p,n) reaction on ^{18}O enriched (96.5%) [^{18}O]H_2O target. At the highest laser pulse energies (300J), 10^5Bq of ^{18}F was produced at EOB. Yield and radionuclide purity were confirmed by gamma-ray spectroscopy.We have demonstrated for the first time the synthesis of trace quantities 2-[^{18}F]FDG using laser induced ^{18}F activity. 2-[^{18}F]FDG was synthesised using the TRACERlab MX FDG Synthesizer (GE Medical Systems) and the laser generated ^{18}F. Briefly, a mannose triflate precursor was fluorinated following the recovery of ^{18}F-fluorine from the [^{18}O]H_2O. Subsequent hydrolysis and purifications yielded 2-[^{18}F]FDG in 80% radiochemical purity as confirmed by radio-TLC.

IS2

Fluorine-18-Labelled Fluoropyridines : Advances in Radiopharmaceutical Design

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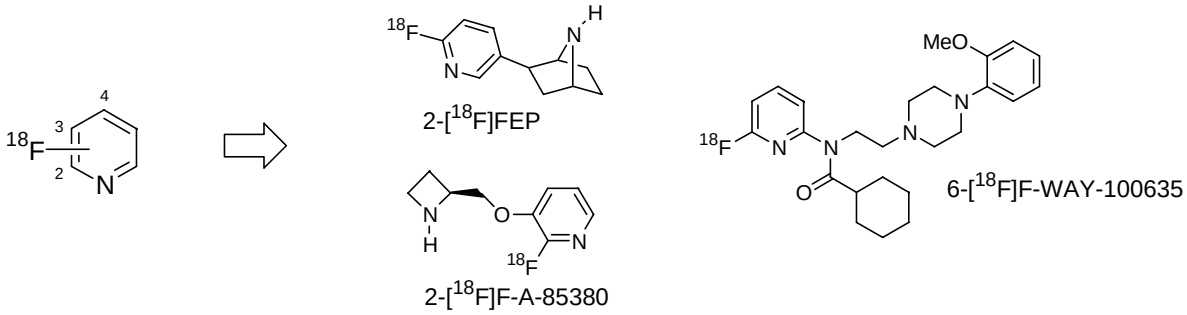
Positron Emission Tomography is a high-resolution, sensitive, functional imaging technique, which can efficiently give access to the distribution, pharmacokinetics and -dynamics of a drug *in vivo* and which can therefore advantageously play a key-role in both drug discovery and development. This molecular imaging technique requires the preparation of a positron-emitting radiolabelled probe or radiotracer and for this purpose, fluorine-18 is becoming, more and more often, the radionuclide of choice (adequate physical and nuclear characteristics and potential wide use and -distribution of fluorine-18-labelled radiopharmaceuticals).

Considering chemical structures showing a fluoropyridinyl moiety, nucleophilic *hetero*aromatic substitution at the *ortho*-position with no-carrier-added [^{18}F]fluoride appears today as the most efficient method for the radiosynthesis of radiotracers and radiopharmaceuticals of high specific radioactivity when compared to *homo*aromatic-, but also aliphatic, nucleophilic radiofluorination. Like for the aliphatic nucleophilic radiofluorinations, only a good leaving group is required (a halogen, or better a nitro- or a trimethylammonium group). There is no need for an additional strong electron-withdrawing substituent for activation of the aromatic ring such as in the *homo*aromatic nucleophilic radiofluorinations, except if one considers *meta*-fluorination. Nucleophilic *hetero*aromatic substitution and consequent fluorine-18 incorporation are generally performed in DMSO with the no-carrier-added, activated K[^{18}F]F-K_{222} complex using conventional heating at a moderately high temperature (120-150°C) or microwave irradiation (100 Watt) for a short period of time (1-2 minutes) and often lead to high radiochemical yields.



This presentation summarizes some of the recent applications of these nucleophilic *hetero*aromatic substitutions in the pyridine series and highlights its potential in the design (not seldom by hydrogen, hydroxyl or halogen replacement by fluorine) and preparation, of often drug-based, fluorine-18-labelled radiotracers and radiopharmaceuticals of high specific radioactivity for PET imaging.

IS3

Improved n.c.a. ^{18}F-Fluorination of Electron Rich Arenes via Aryl-Heteroaryl-Iodonium Salts

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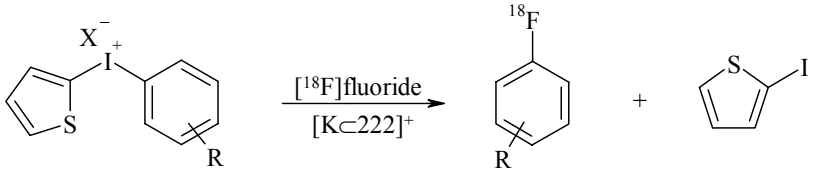
Most of the nucleophilic ^{18}F-labelling reactions only work on electron poor molecules. In case of electron rich and deactivated arenes, [^{18}F]fluoride can normally not be introduced without any activating group, which reduces the electron density in the aromatic ring.

Diaryliodonium salts offer the possibility of a single-step nucleophilic ^{18}F-introduction in electron rich arenes avoiding any activating groups [1, 2]. In this way, a variety of [^{18}F]fluoroarenes have been prepared [1-4]. Hereby the introduction of [^{18}F]fluoride proceeds via the S_NAr-mechanism and leads to [^{18}F]fluoroarenes and the corresponding iodoarenes. The electron deficient ring of the diaryliodonium salt is preferred for the attack of the nucleophile and a steric influence, especially by *ortho*-substituents, could be observed [5]. Thus the substitution can be influenced by the sterics and/or the electron density of the aromatic groups in the precursor. Consequently the use of arene substituents of strongly differing electron density should offer the ^{18}F-labelling of electron rich arenes without the need of further activating groups.

Iodonium salts containing the 2-thienyl group as highly electron rich group and electron rich aromatic rings were earlier found to fulfil these criteria with non-radioactive nucleophiles [6] and were synthesised here as precursors for ^{18}F-labelling of electron rich arenes (Scheme).



X = Br, I, OTos, OTf R = OMe, OBn

The precursors *ortho*-, *meta*- and *para*-methoxyphenyl-2-thienyl-iodonium salts were treated with n.c.a. [^{18}F]fluoride under various conditions. All ^{18}F-labelling reactions showed a very high regioselectivity and led only to the desired n.c.a. [^{18}F]fluoroanisoles without any radioactive side-products. The radiochemical yields (RCY) show a strong dependence on solvent, temperature, sterics, counter ion and purity of the precursor. The best results were obtained with freshly prepared 2-methoxyphenyl(2-thienyl)iodonium bromide as precursor, with a RCY up to 60 %. Optimised conditions are DMF at 130 °C and 20-25 min reaction time. Present studies concentrate on the use of triflate and tosylate as counter ions and 4-benzyloxyphenyl(2-thienyl)iodonium salts as precursors.

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IS4

Radiohalogenated Tropanes: Imaging Agents For The Serotonin Transporter

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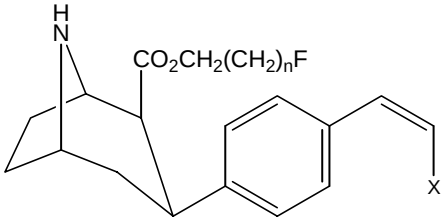
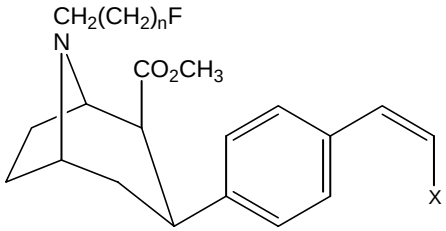
The serotonin transporter (SERT) has been implicated in the pathophysiology of major depression and suicide. Decreased numbers of SERT binding sites in cortical regions in postmortem brain tissue of depressed patients and suicide victims have been measured with the serotonin uptake inhibitors [^{3}H]imipramine and [^{3}H]citalopram. Therefore, development of subnanomolar affinity ligands with optimal physiochemical properties is especially important for measuring binding in cortical regions where serotonin transporter (SERT) density is low and can be masked using less potent lipophilic ligands. Among the various PET and SPECT radioisotopes available for incorporation into SERT ligands fluorine-18 (half-life=110 min), iodine-123 (half-life=13.3 h) and bromine-76 (half-life=16 h) are attractive candidates from the organic chemist's perspective. Their long half-lives allow: (a) ample time for the radioligand to reach a state of quasi equilibrium at the target binding site, a condition when the ratio of region of interest to reference region stays constant, which is crucial in tracer kinetic modeling; (b) sufficient time for incorporation into the tracer molecule and for purification of the final product suitable for regional distribution to be shared by a consortium of research sites and (c) for analysis of the presence of radiolabeled metabolites in plasma samples over a relatively long period of time. Finally, fluorine-18, iodine-123 and bromine-76 can be incorporated into the tracer molecule in high specific activity by no-carrier added nucleophilic and electrophilic substitution reactions, respectively.

In this presentation, we report the synthesis, in vitro and in vivo characterization and radiosynthesis of several new 2β-carbo-ω-fluoroalkoxy-3β-(4'-((Z)-2-iodoethenyl)phenyl)nortropanes (I), 2β-carbo-ω-fluoroalkoxy-3β-(4'-((Z)-2-bromoethenyl)phenyl)nortropanes (II), *N*-ω-fluoroalkyl-2β-carbomethoxy-3β-(4'-((Z)-2-iodoethenyl)phenyl)tropanes (III) and *N*-ω-fluoroalkyl-2β-carbomethoxy-3β-(4'-((Z)-2-bromoethenyl)phenyl)tropanes (IV) developed in our laboratories as potential PET and SPECT SERT imaging agents. Several of these candidate SERT imaging agents exhibited a combination of physiochemical and pharmacokinetic properties that may enhance our ability to determine the role of the SERT in the pathophysiology of depression and suicide in cortical, forebrain and midbrain regions. Research funded by NIMH and DOE.



I: X = I, n=1 or 2
II: X = Br, n=1 or 2



III: X= I, n=1, 2 or 3
IV: X = Br, n=1, 2 or 3

CS6

Fluorine-18 and Iodine-124 Radiohalogenation Using a polymer Micro-Reactor

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Size really does matter. Nanotechnology, the miniaturization of macroscale processes and devices, offers distinct advantages to PET radiochemistry. In particular, the intrinsic reduction in resources and logistics required for PET radiochemical preparations. Here we show the first application of a microfabricated reaction system to PET radiochemistry, we term "microfluidic PET". The short half-life of the positron-emitting isotopes and the trace chemical quantities used in radiolabelling make PET radiochemistry amenable to miniaturization.

Microfluidic, technologies are capable of controlling and transferring tiny quantities of liquids which allow chemical and biochemical assays to be integrated and carried out on a small scale. Such technologies provide distinct advantages over current methods of PET radiochemical synthesis. Significantly, radiochemical reactions on-chip can be easily shielded and will not require the space and resources required for conventional hot cell synthesis. Secondly, it provides a scope for an integrated total system (synthesis, separation and analysis). Thirdly, due to the rapid and thorough mixing achieved in miniaturised reactors, the speed and specific activities of radiochemical syntheses could be enhanced. Finally, the photolithographic fabrication of the microfabricated device allows the manufacture of complex, yet relatively inexpensive and disposable devices.

To demonstrate "proof of principle" we have investigated the radiohalogenation of small and large molecular weight molecules using the microfluidic device. These reactions involved the direct radioiodination of the apoptosis marker Annexin-V using Iodine-124, the indirect radioiodination of the anticancer drug doxorubicin from a tin-butyl precursor, and the radiosynthesis of 2-[^{18}F]FDG from a mannose triflate precursor and fluorine-18 and hence provide a test bed for microfluidic reactions.

We demonstrate the rapid radioiodination of the protein Annexin V (40% radiochemical yield within 1 min) and the rapid radiofluorination of 2-[^{18}F]FDG (60% radiochemical yield within 4 seconds) using a polymer micro-reactor chip. Chromatographic analysis showed that the labelling efficiency of the microfluidic chip is comparable to conventional PET radiolabelling reactions. This development represents a major breakthrough and has the potential to revolutionise PET radiochemistry.

CS7

Initial Assessment of Different Methods of [^{18}F]F$^-$ Radiofluorination in a Small Volume: A Step Towards Miniaturization of Radiosynthesis

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The mass/volume quantities of the radiolabled materials involved in the syntheses of no carrier added PET radiotracers are very small. In principle, reactions with [^{18}F]F$^-$ and ^{18}F-labeled compounds could be conducted in <1 μL solvent volumes with μg quantities of reagents. However, reported [^{18}F]F$^-$ radiosyntheses use >200 μL- (typically 0.4-1 mL) total volume of solvent and mg quantities of reagents. The use of smaller amounts of reagents/solvents can save time/money/materials involved in preparation of precursors. It is possible that higher concentrations of reagents, resulting from the use of smaller solvent volumes, will lead to increased radiochemical yields. The future application of "on-the-chip" technology may enable previously unattainable or impractical multi-step radiosyntheses.

In order to perform ^{18}F-radiofluorination in a small volume three successive steps must be accomplished. [^{18}F]F$^-$ must be concentrated in a reactive form, a radiolabeling reaction performed, and the reaction products removed from the system (preferably in a small volume of solvent) for further processing. A number of systems were setup to explore the reaction of [^{18}F]F$^-$ with a precursor in ≤50 μL solvent volume.[a]

System	Concentration Method	Encountered Problem(s)
Flat bottom shallow vessel	Evaporation of water from slowly introduced aqueous [^{18}F]F$^-$ on the open flat surface of hot tantalum [b]	Significant loss of radioactivity during evaporation. Low extraction of product from the system.[a]
Silver wool reactor	Evaporation of water from slowly introduced aqueous [^{18}F]F$^-$ on hot silver wool [b]	Low radiochemical yield of the product
Glassy carbon "needle"	Electrochemical adsorption of [^{18}F]F$^-$ on the surface/tip of a thin rod immersed in aqueous [^{18}F]F$^-$ [c]	Insufficient trapping of [^{18}F]F$^-$
Electrochemical flow-through cell	Electrochemical adsorption of [^{18}F]F$^-$ on a flat glassy carbon surface [c]	Difficult to extract product due to increased solution viscosity upon heating, low product radiochemical yield

[a] Radiosynthesis of [^{18}F]4-fluorobenzophenone from its trimethylammonium triflate precursor was used as a model reaction. Methods based on: [b] slow evaporation of solvent, [c] electrochemistry, [d] ion exchange.

CS8

An improved radiochemical synthesis of N-succinimidyl 4-^{18}F-(fluoromethyl)benzoate and its application

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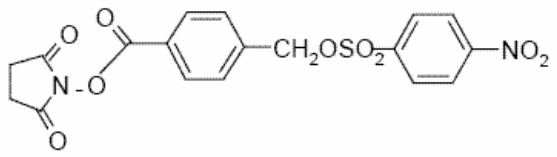
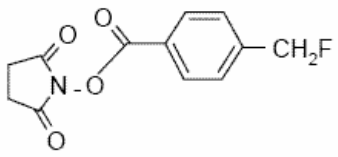
The application of biologically active peptides labelled with position-emitting nuclides has emerged as a useful and interesting field in nuclear medicine. Among a number of PET nuclides, fluorine-18 appears to be the best candidate for labeling by virtue of its favorable physical and nuclear characteristics. However, the progress of bioactive molecule labeling with ^{18}F is laborious and time-consuming. *N*-succinimidyl 4-(^{18}F) (fluoromethyl)-benzoate (S^{18}F MB) was found to be a very useful acylation agent in labeling biologically active molecule.

S^{18}FMB was synthesized by one step reaction of N-succinimidyl-4-[(4-nitrobenzensulfonyl)oxymethyl]benzoate(SNOB) with $^{18}F^-$. SNOB could be obtained with the yield of 75% by the reaction of silver 4-nitrobenzene sulfonate and N-succinimidyl 4-(bromomethyl)benzoate at room temperature for 6 days. After optimizing the radiosyntheses parameters, the radiochemical yield of S^{18}F MB is up to 57%(corrected for decay), in addition, a simple separation method on small Sep-Pak silica was used to substitute for complicated HPLC and high radiochemical purity could be obtained. In order to provide methodology research for the labelling of other expensive biological molecules, we labeled IgG with S^{18}F MB successfully. Under the optimal labeling condition (0.2g/L of IgG, pH=7.8-8.5,25℃,and reaction time 15 minutes), the yield of S^{18}F MB labelling IgG was above 80%. To peptide, on the basis of the conjugation of octreotide with S^{18}FMB, we realized the S^{18}FMB labeling VIP, which is a useful PET imaging agent in diagnosing many kinds of tumor.



SNOB



SFMB

CS9

Radiosynthesis of 3-(3-[18F] Fluoropropoxy)-4-(benzyloxy)-N-[(1-(dimethylamino)cyclopentyl)methyl]-5-methoxybenzamide, a PET Radiotracer for the Glycine Transporters GlyT-2

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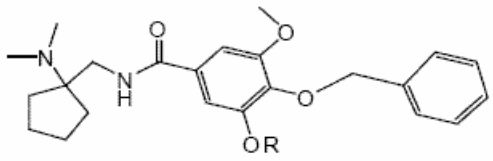
The recently described selective and potent GlyT2 antagonist, 4-benzyloxy-3,5-dimethoxy-N-[(1-dimethylaminocyclopentyl)methyl] benzamide (IC50 =16 nM) provided an important additional tool to further characterize GlyT2 pharmacology. In order to identify an effective PET radioligand for in vivo assessment of the GlyT-2 transporter, 3-(3-[$_{18}$F]Fluoropropoxy)-4-(benzyloxy)-N-((1-(dimethylamino)cyclopentyl)methyl)-5-methoxybenzamide ([$_{18}$F]**3**), a novel analogues of 4-benzyloxy-3,5-dimethoxy-N-[(1-dimethylaminocyclopentyl)methyl]benzamide was labeled with fluorine-18 using a one-pot, two-step method. The NCA radiofluorination of 1,3-Propanediol di-*p*-tosylate in the presence of potassium carbonate and kryptofix-222 in acetonitrile gave 81% 3-[$_{18}$F]fluoropropyl tosylate, which was subsequently coupled with4-benzyloxy-3-hydroxy-5-methoxy-N-[(1-dimethylaminocyclopentyl) methyl]benzamide in the same reaction vessel. Solvent extraction and HPLC (Eclipse XDB-C8 column, 80/20/0.1 MeOH/H_2O/Et_3N, 3.0 ml/min) gave [$_{18}$F]**3** in 98.5% radiochemical purity. The radiochemical yield was determined to be 14.0-16.2 % at EOS (decay-corrected). and the specific activity was 1462.5 GBq/μmol. The time of synthesis and purifcation was128 min. The final product was prepared as a sterile saline solution suitable for in vivo use.

Key words: glycine transporter 2(GlyT2), PET, fluorine-18, radiotracer



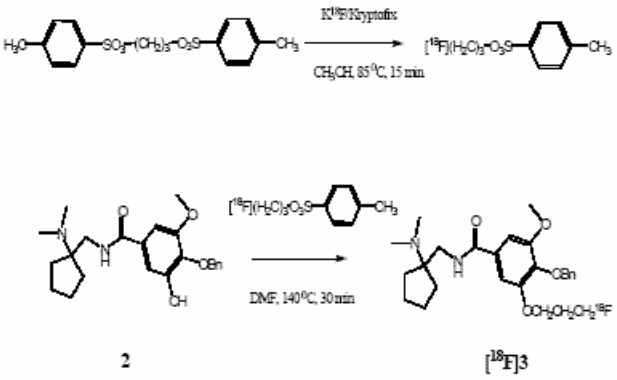
1: R= CH_3

2: R= H

3: R= $CH_2CH_2CH_2F$

[^{18}F]**3**: $CH_2CH_2CH_2[^{18}F]$

Figure 1. Chemical Structures of **1** and novel analogues **2, 3**, [^{18}F]**3**



2 [^{18}F]**3**

Scheme 2. Radiosynthesis of [^{18}F]**3**

CS10

Radiosynthesis and PET studies of ^{18}F-EF5 as a hypoxia imaging agent in spontaneous canine tumours

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Non-invasive methods for the early assessment of tumors that are potentially resistant to radiotherapy and/ or chemotherapy because of their hypoxic state are of clinical interest in human medicine. There has been considerable interest in imaging hypoxia with radiolabeled derivatives of nitroimidazoles and positron emission tomography (PET) in the last years.
Among others, EF5 [2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3-pentafluoropropyl)-acetamide] has been used to assess tumor hypoxia in animals and humans using immunohistochemical methods.

The aim of the present study was to synthesize and validate the potential of [^{18}F]EF5 as an imaging agent for tumor hypoxia using PET. The synthesis of [^{18}F]EF5 was accomplished by the electrophilic addition of [^{18}F]fluorine gas across the double bond of an allyl precursor in trifluoroacetic acid at 0°C as was previously reported. [^{18}F]EF5 was purified by semi-preparative HPLC. After removal of the HPLC solvent by evaporation, the final product was formulated for i.v. injection. The whole procedure is fully automated and the total synthesis time was ca. 90 minutes after irradiation.

PET studies were acquired in 11 dogs suffering from various spontaneous tumors. In 7 animals double tracer studies using [^{15}O]H_2O (perfusion) and [^{18}F]EF5 (hypoxia) were performed. The animals were examined in a whole body PET scanner (Advance, GE Medical Systems). At different time points urine and arterial blood samples were collected. In 6 dogs invasive pO_2 Eppendorf needle electrode measurements were performed.

Tumor hypoxia was detected in 4 of 11 (36 %) spontaneous canine tumors by [^{18}F]EF5 PET. PET images demonstrated correlation with Eppendorf measurements in 3 cases, with 3 discordant cases. As expected [^{18}F]EF5 accumulation occurred in low perfused areas, but low perfusion did not lead to tumor hypoxia in every case. HPLC analysis showed that [^{18}F]EF5 was metabolically stable in plasma, while metabolites were found in urine.

[^{18}F]EF5 may be a potential hypoxia imaging agent, however further in vivo PET studies are needed before conclusive statements can be made.

CS11

Examining the Use of PET and ^{18}F-EF5 to Evaluate Tumour Hypoxia

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Background: Our group has recently shown[a] that hypoxia in the Shionogi tumour model for prostate cancer initially decreases following interruption of androgen supplies in the mice, but increases significantly when the tumours become androgen independent (AI). Thus, it may be possible to monitor progression in Shionogi tumours by following changes in hypoxia. The hypoxia marker system (EF5/ELK3-51) was used with flow-cytometry (cell suspensions from disaggregated tumours) and immunohistochemical methods (tumour sections) to evaluate these changes in tumours harvested at selected time points following castration of the mouse. However, the use of positron emission tomography (PET) with a tracer for hypoxia would also allow evaluation of changes in hypoxia 1) non-invasively, 2) over the entire tumour and 3) within the same tumour over time. We report here a preliminary study examining the use of PET and ^{18}F-EF5 to evaluate tumour hypoxia at two stages in the Shionogi tumour model non-invasively.

Methodology: Shionogi tumours were grown on the upper back of DD/S male mice subcutaneously. Androgen dependent (AD) tumours were evaluated before mice were castrated and AI tumours were evaluated ~40 days after castration of the mouse, by which time the tumour had regressed and re-grown in an AI manner. Mice (~ 30-40g) bearing either AD or AI tumours (~450 – 550 mm^3) were anaesthetized prior to and during scanning procedures (Halothane, 5% and 2% for induction and maintenance, respectively). The mice were immobilized on the scanning bed, and EF5 radiolabelled with ^{18}F (~ 40 – 60 μCi) was co-injected with unlabelled EF5 (30 mg/kg). The Concorde MicroPET R4 system was used to scan the mouse and tumour (dynamic and static scans). ^{18}F-fluorodeoxyglucose (~50 μCi, FDG) was injected after completion of the EF5 scans, and a second scan carried out. Data were collected in list mode, and the images (^{18}F-EF5 and FDG) were reconstructed using attenuation scans carried out before injection of the tracer.

Results: ^{18}F-radiolabelled EF5 was well-distributed through the animal's tissue initially including the brain and was eventually cleared through the bladder. Uptake in the kidneys, liver and intestines was high at two hours. However, time activity curves generated from regions of interest within the tumour mass and normal leg muscle indicated that ^{18}F-EF5 accumulated preferentially in tumour tissue over the period of the scan. The tumour to non-tumour tissue ratio for ^{18}F-EF5 was ~2, four hours post-injection. The uptake of FDG helped define the limits of the tumour. Of some interest, ^{18}F-EF5 activity in the tumour tissue appeared to be heterogeneous perhaps reflecting different levels of hypoxia within the same tumour.

Acknowledgements: The authors thank H. Adomat, M. Bowden, S. McCormick, M-L. Camborde, J. Woo and V. H Dragowska for expert technical assistance and useful discussions

[a] K. Skov, H. Adomat, M. Bowden, V. Dragowska, M. Gleave, C. Koch, J. Woo, D. Yapp. Radiation Research, 2004. In press.

*DTY is Adjunct Professor, Div. of Biopharmaceutics and Pharmaceutics, Faculty of Pharmaceutical Sciences, UBC.

CS12

[^{18}F]Fluorine substitution at the 16α-position of fulvestrant (Faslodex; ICI 182,780): Impact on estrogen receptor binding and target tissue uptake.

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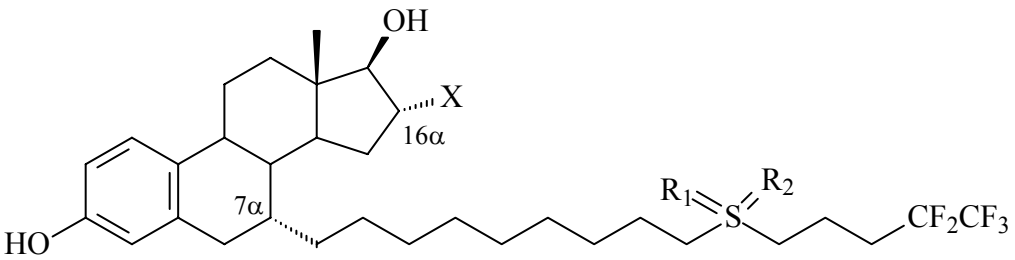
Fulvestrant (Faslodex; ICI 182,780) (X = H; R_1 = O; R_2 = -) is a pure estrogen receptor (ER) antagonist recently approved for the treatment of hormone-sensitive breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Fulvestrant strongly binds to the ER and its mode of action consists of inhibition of ER dimerization leading to a down regulation of ER protein cellular levels. With the aim to develop a probe for positron emission tomography (PET) imaging capable of predicting the potential therapeutic efficacy of selective ER modulators (SERM), we prepared three new 16α-[^{18}F]fluorofulvestrant derivatives. These new radiopharmaceuticals were evaluated for their binding affinity to the human ERα and for their target tissue uptake in immature female rats.

Substitution of one of the side-chain F-atoms of fulvestrant for ^{18}F would have led to a product of low specific activity; instead we selected the 16α-position for ^{18}F-labeling, which at least in the case of estradiol (ES) is well tolerated by the ER. Radiochemical synthesis proceeds by stereoselective introduction of the [^{18}F]fluoride at the 16□-position of fulvestrant via opening of an intermediate *O*-cyclic sulfate followed by hydrolysis of the protecting methoxymethyl (MOM) ether and sulfate groups. Three analogs with different oxidation states of the side chain sulfur, i.e. sulfide (R_1 = R_2 = -), sulfone (R_1 = R_2 = O) or sulfoxide (i.e. fulvestrant) were prepared.

Introduction of the 16□-fluorine led to a dramatic decrease of the apparent binding affinity for ER. Likewise, *in vivo* ER-mediated uterus uptake values in immature female rats were disappointing. Overall, our findings suggest that these potentially new PET radiopharmaceuticals are not suitable as tracers to predict ER(+) breast cancer response to hormonal therapy with selective ER modulators.



CS13

Studies of Tumour Microenvironment and Metabolic Activity in Breast Cancer Xenografts by Non-Invasive Small Animal PET and MRI

Wieslawa H. Dragowska[1], Thomas J. Ruth[2], Michael J. Adam[2], Piotr Kozlowski[3], Kirsten Skov[1], Marcel B. Bally[1] and Donald T.T. Yapp[1]*

[1]Department of Advanced Therapeutics, B.C. Cancer Agency; [2]TRIUMF; [3]The Prostate Center at Vancouver General Hospital, Vancouver, British Columbia.

Background: HER-2/*neu* overexpression in breast cancers is correlated with resistance to treatment and poor prognosis. Recently we have shown (IHC and flow cytometry (FCM)) that LCC6 breast cancer xenografts overexpressing HER-2/*neu* ($LCC6^{HER-2}$) are more viable and contain a significant population of hypoxic viable cells compared to their size-matched isogenic controls ($LCC6^{Vector}$). No changes in tumour vascularization were observed, and levels of hypoxia were not related to tumour size. These initial studies led us to explore selected tumour parameters *in situ* in an attempt to explain the observed differences between the $LCC6^{HER-2}$ and $LCC6^{Vector}$ tumours.

Experimental Approach and Methods: $LCC6^{HER-2}$ and $LCC6^{Vector}$ tumours, grown s.c. in SCID mice, were studied when they reached a volume of 200-300 mm^3. Animals were anesthesized (halothane) during all PET and MRI procedures. The Conforde MicroPET R4 was used for PET scans, and data were collected in list mode. ^{18}F-EF5 (~60μCi) was co-injected i.v. with unlabelled EF5 (30mg/Kg) 3 hours prior to scanning to evaluate tumour hypoxia. FDG (~60μCi) was subsequently injected i.v. following EF5 scans and the data collected immediately to assess the metabolic activity of the tumour. The following day the same animals were imaged with MRI to assess pH and tumour perfusion. Mice were re-injected with unlabelled EF5 and tumours were harvested a day after MRI procedures for examination with histology and flow cytometry.

Results: Preliminary PET data show that the EF5 uptake was ~2 fold higher in $LCC6^{HER-2}$ compared to $LCC6^{Vector}$ tumour. FDG uptake was faster, and the maximum activity per pixel was ~1.4-fold higher in $LCC6^{HER-2}$ *vs.* $LCC6^{Vector}$ tumour. The degree of EF5 and FDG uptake in LCC6 tumours correlated well with the percentage of viable hypoxic cells found in cell suspensions from disaggregated tumours. The preliminary data from MRI images indicated that perfusion appears to be greater in the $LCC6^{HER-2}$ tumour and that the intracellular pH in the $LCC6^{Vector}$ tumour was elevated slightly (7.5 *vs*. 7.1 for $LCC6^{Vector}$ and $LCC6^{HER-2}$, respectively).

Conclusions: PET and MRI were used successfully to evaluate the *in vivo* environmental and metabolic status of human breast cancer xenografts in SCID mice. The preliminary PET (hypoxia) results correlated well with our previous findings (histology and flow cytometry). The metabolic activities, of $LCC6^{HER-2}$ tumours appear to be higher than in $LCC6^{Vector}$ tumours based on FDG data.

The authors gratefully acknowledge the expert technical assistance of Siobhan McCormick, David Green^ and Andrew Yung. This project funded in part by NCIC.

EF5 = [2-(2-nitro-1H-imidazol-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl)-acetamide]; *DTTY is Adjunct Professor at the Dept. of Pharmaceutical Sciences, Division of Biopharmaceutics/Pharmaceutics, UBC; ^DG supported by the Michael Smith Foundation for Health Sciences.

CS14

^{18}F-FESB: A novel ^{18}F-labelled PET tracer for β-amyloid plaques, its synthesis and automated radiofluorination

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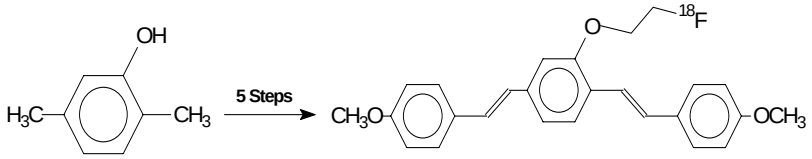
In spite of recent advances in new radiopharmaceuticals for the clinical evaluation of Alzheimer's disease (AD), positron emission tomography (PET) and single photon emission computed tomography (SPECT) are not currently in routine use. [^{18}F]Fluorodeoxyglucose, a PET tracer for evaluating metabolic disorders, serves as an indirect tool to detect the presence and progression of AD. The significant roles of amyloid cascades and neurofibrillary tangles (NFTs) in the pathogenesis of AD necessitate the development of a biomarker that facilitates early diagnosis of the disease and is receptor specific so that it serves as a true diagnostic tool for anti-amyloid therapies. A recent study suggests that anti-amyloid therapies, when co-investigated in combination with PET or SPECT amyloid imaging tracers, could facilitate in vivo evaluation of the efficacy of therapy in the aging human brain. Earlier reports on [^{11}C]-labelled Congo Red, [^{11}C]-Methoxy-XO4 (2.3-6.7% RCY) and [^{99m}Tc]-Chrysamine-G analogs as PET markers of β-amyloid plaques indicated high uptake in the brain and their specific binding to β-amyloid plaques but suffered either from poor detection of the disease due to marginal entry in the brain or very low radiochemical yields.

The first human study with Pittsburgh Compound-B (PIB), in limited number of patients diagnosed with mild AD, showed marked retention in the areas known to contain large amounts of amyloid deposits in AD and further supports the role of a PET AD diagnostic radiotracer in AD therapy management.

The present work describes the automated synthesis of 1-(2`-fluoroethoxy)-2,5-bis(4`-methoxystyryl)benzene (FESB) and its ^{18}F- analog using an ASU. It was observed that use of 'ionic fluids' in the radiochemical synthesis significantly enhanced the labeling efficiency of the product. ^{18}F-FESB, being a fluorinated analog, has much longer half life than other ^{11}C-labelled members of this class and, therefore, will have a direct impact on the patients radiation doses and delineation of β-amyloid plaques from other regions in the brain. The biological properties of ^{18}F-FESB are currently under investigation.



^{18}F-FESB

CS15

Fluorine-18 Labeling and Baboon PET Imaging of MCL322 and MCL301, Novel Tropane Dopamine Ligands

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[1]Yale University School of Medicine, Departments of Psychiatry and Diagnostic Radiology, [2]VAHCS West Haven CT, [3]ADARC, McLean Hospital, Harvard Medical School, MA, and [4]NPI, McLean Hospital, Belmont MA.

Measurement of dopamine transporters (DAT) in vivo by noninvasive imaging with radiolabeled cocaine analogs has applications in the study of neuropsychiatric diseases such as movement disorders, substance abuse, and psychosis. Despite a plethora of radiolabeled analogs, there is still need for selective, specific ligands. The purpose of these experiments was to label two novel ligands, 2-fluoroethyl 3-(4-bromo-and 4-iodophenyl)-8-methyl-8-aza-bicyclo[3.2.1]-octane-2-carboxylate, MCL322 and MCL301, with fluorine-18 and evaluate their brain uptake in a nonhuman primate model.

METHODS. The 2-tosyloxyethyl ester precursor was reacted with anhydrous K[^{18}F]F generated by azeotropic distillation of CH_3CN with K_2CO_3 and Kryptofix-222 for 3 min in a 600-watt microwave oven and the product was purified by semi-preparative HPLC (C_{18}, CH_3OH/-H_2O/Et_3N, 75/25/0.1, 2.0 mL/min). After isolation on a C_{18} solid phase extraction cartridge, product was eluted with EtOH, diluted to 5% EtOH with normal saline containing 0.1 mM L-ascorbic acid, and sterilized by 0.22 μ membrane filtration. For PET imaging, ^{18}F tracer was ad-ministered iv in a single bolus to female baboons under isoflurane anesthesia and images were acquired on a CTI/Siemens ECAT HR+, collecting images over 3 h post injection (pi). Data were reconstructed, realigned, and scaled to provide quantitative 3-D projections. Lipophilicity was estimated by octanol-buffer (pH 7.4) partition using Wilson's back-correction method.

RESULTS. In a typical run, 25 min bombardment at 40 μamp gave a final activity of 56 mCi [^{18}F]MCL-322 in a synthesis time of 52 min, radiochemical yield 23.2%, radiochemical purity >99% and specific activity 16,800 Ci/mmol. For both tracers, PET images showed initial uptake in both striatum and midbrain (diencephalon) regions, corresponding primarily to the location of dopamine (DAT) and serotonin transporter (SERT), respectively, but within 15 min pi, midbrain activity decreased, whereas striatal activity continued to increase over the 3 h scanning session. The ratio of midbrain to cerebellum peaked at about 30 min with a value of 1.8 and remained at 1.7–1.8 throughout the study. In contrast, the striatum: cerebellum ratio increased from 1.7 at 15 min pi to a value of 5.6-5.8 at 3 h. This selectivity is in keeping with in vitro binding data, which showed selective binding to DAT versus SERT or norepinephrine transporter (NET).

CONCLUSION. The initial results with these tracers indicate in vivo selectivity for DAT compared to competing monoamine transporters, in keeping with in vitro affinity data. Additional experiments are under way to verify pharmacological specificity of tracer uptake. Supported by National Institutes of Health (NS40587) and Veteran's Affairs (REAP and MIRECC).

IS5

Preparation of ^{124}I labeled Imaging Agents

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Recent interests in developing new molecular imaging agents labeled with ^{124}I has prompted us to investigate iodinated probes previously reported for ^{123}I labeling. It is well known that ^{124}I emits positrons and has a relatively long half-life ($T_{1/2}$ = 4 d) suitable for PET imaging. In order to expand the potential of radioiodinated radiopharmaceuticals, we have investigated the ^{124}I radiochemistry of several new ^{123}I labeled imaging agents developed in our laboratory for different purposes. To test the iodination reaction of ^{124}I we have used a general procedure described below. To a serum vial containing a tributyltin derivative (100-200 μg), 50 □l ethanol was added and then followed by 50-100 μl of 1N HCl (adjusting the volume based on the concentration of radioactive iodide solution) and ^{124}I (10-20 μl). The ^{124}I is a carrier-added preparation obtained from Washington University. The reaction was initiated by adding hydrogen peroxide and then stood at room temperature for 10 min. At the end of reaction, 0.1 ml of sat. sodium bisulfite was added to stop the reaction. The reaction was neutralized with 1.5 ml of saturated solution of sodium bicarbonate. Purification was carried out by using a C-4 mini-column or a C-18 cartridge. The desired product was eluted from the column or cartridge with a small amount of ethanol (0.5-1.0 ml). The radiochemical purity was obtained with TLC or HPLC. Using this procedure we have tested four compounds: IMPY (a ß amyloid imaging agent), ADAM and OB-ADAM (SERT imaging agents) and FIAU (tumor proliferation or thymidine kinase gene expression imaging agent) and the results are listed on Table 1. As indicated the radiolabeling yields as well as radiochemical purities were excellent. There was no distinctive differences between which isotope was used for the experiments. Our preliminary studies suggest that ^{123}I labeling procedures can be readily transferred for ^{124}I labeling without any significant deviation. If the supply of ^{124}I can be secured, it is likely that ^{124}I imaging agents can be readily prepared and supplied for clinical testing.

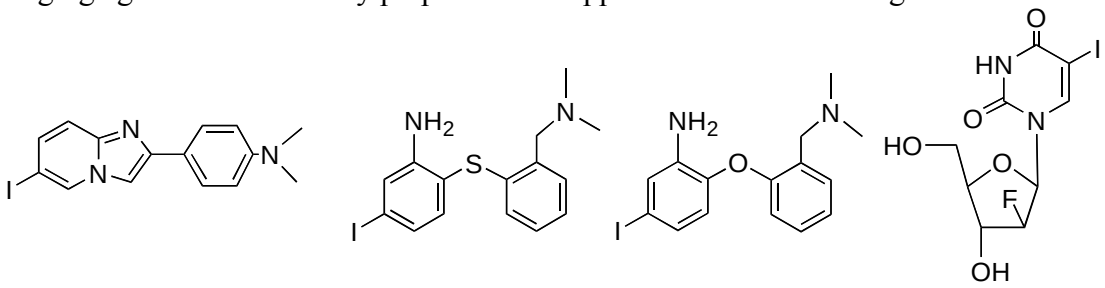

Table 1. Comparison of ^{123}I and ^{124}I radiolabeling

Ligand	I-123	I-124	RCP
IMPY (ß-amyloid)	50-80%	76%	>98%
ADAM (SERT)	50-70%	60%	>96%
OB-ADAM (SERT)	80-90%	87%	>99%
FIAU (Tumor/Gene expression)	40-60%	61%	>99%

IS6

Development of Facile No-Carrier-Added Radioiodination Procedures

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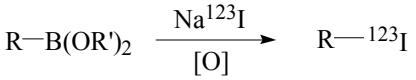
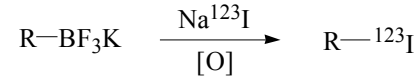
The preparation of high specific activity, no-carrier-added radioiodinated agents has become increasingly important in nuclear medicine imaging. Organometallic reagents are popular precursors in radioiodination reactions but the separation of the starting materials from the desired products can be tedious and time consuming due to the lipophilic character of many of the organometallic reagents.

The use of organoboranes as precursors to radiohalogenated pharmaceuticals has been of continuous interest in our laboratory for over 20 years. Although boronic acids can be prepared containing a wide variety of functional groups and are generally easier to separate from the radioiodinated products, their use in radiopharmaceutical chemistry has not kept pace with that of other organometallic reagents. The situation has changed in recent years due to the popularity of Suzuki coupling chemistry that has made the precursor boronic esters readily available in the laboratory (and commercially). [Kabalka, et al. *Nucl. Med. Biol.* **2003**, *30*, 369.] We have developed radioiodination reactions that tolerate a wide variety of functional groups that utilize organoboronic esters as starting materials.

Trifluoroborates have also proven to be versatile intermediates in organic synthesis because of their remarkable chemical reactivity. Interestingly, they are crystalline ionic solids that are stable to both air and water for extended periods, and they are readily prepared from the corresponding boronic acids by addition of KHF_2. [Kabalka, and Mereddy. *Tetrahedron Lett.* **2004**, *45,* 343.] In addition, trifluoroborate salts have proven to be as versatile as boronic acids in organic synthesis and are simpler to remove from reaction mixtures due to their ionic nature. We also wish to report a rapid and high yield synthesis of high specific activity, iodine-123 labeled aryl and vinyl iodides from the corresponding organotrifluoroborates. The fact that only the products are lipophilic makes the new reaction ideal for kit applications since a simple Sep-Pak filtration results in radiochemically pure products.





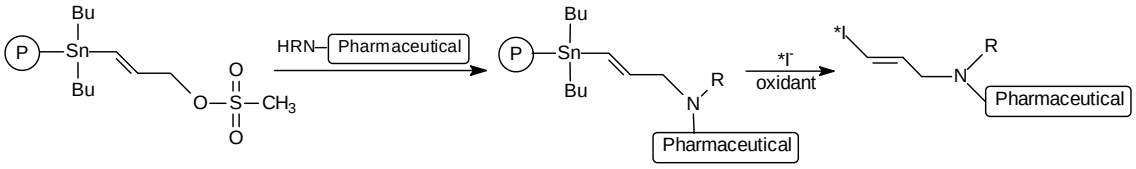
CS16

A Polymer-Supported Stannyl Propenyl Mesylate: A Platform for Radiohalogenation of Amines

M.K.J. Gagnon, D.H. Hunter.
Department of Chemistry, The University of Western Ontario, London, Ontario, N6H 5B7.

Vinylstannanes act as precursors for a wide range of radiohalogenated pharmaceuticals. In order to circumvent the problems associated with these soluble organotin reagents, we have developed an insoluble polymeric analogue whereby the precursor to the radiopharmaceutical is tethered to a polymeric backbone. Specifically, a polymer-supported 3-stannyl-2-propenyl mesylate **1** acts as the site of attachment for biological species of interest which contain an amine, thiol or alcohol as nucleophiles. The development of the polymer-supported propenyl mesylate will be presented, as well as the reaction of this polymer with amines to produce precursors to potential cardiac imaging agents **2**.

The polymers were analysed by specialized solid state techniques such as MAS ^{119}Sn NMR and DRIFT IR spectroscopies. As well, the resins were reacted with iodine and were shown to release the iodinated amines in good yield as the sole soluble product. The results of the analogous radioiodination reactions of these polymers will also be presented.



1 **2** **3**

CS17

Custom Labelling with Radioiodines and Custom Synthesis of Precursors for Medical Imaging

S.Lu, JML Biopharm Inc., 4004 Wesbrook Mall, Vancouver, British Columbia, Canada V6T 2A3

A. Custom labeling of radioiodine:

Radiolabeling with iodine (^{123}I, ^{124}I, ^{125}I, and ^{131}I) has a wide range of applications in nuclear medicine. For example, the iodo-labeling can be used for the labeling of antibodies, DNA, nucleosides, and drugs. Five common methods for radio iodination will be reviewed in the presentation:

a. Chloramines-T (e.g. steroid labeling)
b. Lactoperoxidase (e.g. LH and other peptide/protein labeling)
c. Bolton-Hunter Reagent (e.g. FSH and other peptide/protein labeling)
d. Iodine Exchange (e.g. MIBG and iodine-dopa labeling)
e. Tin Compound (e.g. IduR, tzdm labeling)

B. Custom synthesis of precursors:

Also, in this presentation, a number of innovative methods for the synthesis of precursors to the radiolabelling a variety of PET and SPECT agents will be discussed. A list of available, standard precursors will be provided.

CS18

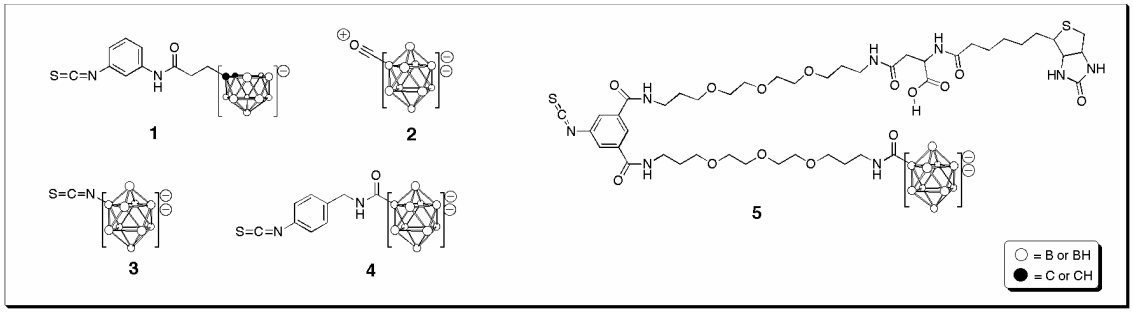
A METHOD FOR DIRECT RADIOIODINATION OF BORON CAGE PENDANT GROUPS ON PROTEINS.

Donald K. Hamlin*, Ming-Kuan Chyan, and D. Scott Wilbur
Department of Radiation Oncology, University of Washington, Seattle, WA 98103

The most common method for radioiodination of proteins is the "direct labeling" procedure. While this method is very efficient, for therapy applications (e.g. using ^{131}I) it suffers from release of the ^{131}I from the (metabolized) protein, after which it localizes in the thyroid. Although there are methods for blocking uptake of ^{131}I in the thyroid, these do not provide full blockade. As the amount of ^{131}I used in the therapy protocol is very high, localization of only a small percentage in the thyroid can cause significant radiation dose to that organ.

Investigations in our laboratory have shown that anionic boron cage molecules are stable to in vivo deiodination and can effectively compete with phenol in electrophilic iodination reactions. In fact, a *nido*-carborane studied appears to be some 50x more reactive than the phenol in tyrosine. Based on this information, we investigated some *nido*-carborane derivatives (e.g. **1**) as potential direct radioiodination pendant groups for proteins. Proteins conjugated with **1** did not appear to have all of the radioiodine on the carborane cage, since thyroid localization of radioiodine was noted in vivo. Further, the *nido*-carborane caused significant non-specific association in vivo. We also studied conjugation of two simple decaborate(2-) molecules, **2** & **3**. These molecules were not very reactive with proteins, so the conjugates obtained were non-optimal. Following those studies, we chose to prepare and evaluate a phenylisothiocyanate derivative, **4**. It appeared that this worked better and did not cause non-specific localization of the protein. However, it was difficult to determine how many conjugates were on the protein. To aid our studies, and for potential application to extracorporeal affinity adsorption (*Bioconjugate Chem. 13*, 1079, 2002), a decaborate(2-) derivative that also contained a biotin moiety and a protein conjugation moiety, compound **5**, was prepared.

To evaluate whether compound **5** allowed selective radioiodination, two different types of competitive reactions were conducted. In the first, an antibody Fab´ fragment was conjugated with **5** (2/Fab´) and was radioiodinated in the presence of a $F(ab')_2$ fragment. Evaluation of radiochromatograms obtained on size-exclusion chromatography indicated that the tyrosines reacted as well as the decaborate(2-) moiety. To decrease the reactivity of the phenols, the conjugate of **5** was treated with N-acetylimidazole. In a second competitive reaction, tyrosine-blocked Fab´ conjugate of **5** was reacted in the presence of Fab´ that had been treated in the same manner, but did not have **5**. After the reaction, the mixture was run over an avidin column, and about 90% of the protein-bound radioactivity remained on it. This finding indicates that the radioiodination was not completely selective for the decaborate(2-) moiety containing Fab´ after blocking its tyrosines. Additional in vitro and in vivo studies are being conducted to determine if 100% selectivity can be attained, and to assess the usefulness of this approach for radioiodination of proteins. Issues such as removal of the acetyl esters (with base) and retention of immunoreactivity will be assessed.



IS7

Radioiodines: Versatile Radionuclides for Molecular Medicine Applications

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Department of Nuclear Medicine and Functional Imaging, Lawrence Berkeley National Laboratory, Berkeley CA 94720, USA

From diagnostics to therapeutics to biomedical research, from SPECT to PET, radioiodines are found in a wide variety of molecular medicine applications. This talk will highlight three representative approaches involving radioiodine relative to myocardial perfusion imaging.

The first involves the application of polymer-supported stannanes for the rapid regioselective preparation of radioiodinated probes, a collaboration with Dr. Duncan Hunter of The University of Western Ontario. Utilizing submilligram quantities of the polymer-bound precursor, high specific activity, radiochemically pure, tin free iodophenyl-piperazinium salts were synthesized. The expanded potential of these polymer precursors was realized in an effort to find a suitable strategy for rapid iodine-122 labeling and purification. While largely used for radioiodinations, these stannyl precursors provide a platform for the production of the full spectrum of radiohalogenated probes.

Second, iodorotenone, a radioiodinated analog of the natural product rotenone, was labeled with iodine-125 and iodine-123 by the iododestannylation and evaluated in several animal species, showing great potential as a myocardial perfusion tracer. Iodorotenone exhibited high extraction and better linearity with flow versus the current SPECT cardiac flow tracers, thallium-201 and ^{99m}Tc-sestamibi.

The latest studies, subject of a collaboration with Drs. Grant Gullberg, LBNL and Bruce Hasegawa, UCSF, involve whole body small animal imaging of iodine-125 labeled compounds. Using pinhole collimators on the Gamma Medica X-SPECT and GE Hawkeye SPECT/CT systems, moderate resolution images of ^{125}I-iodorotenone distribution were obtained. Given the availability, affordability and half-life of iodine-125, this isotope may find utility in small animal imaging applications related to both drug and imaging agent development.

As a group radioiodines display the broadest array of nuclear properties compared to the other radiohalogens. These properties may be appropriately matched to the application allowing seamless translation of studies from the benchtop to the clinic.

CS19

Synthesis and in vitro evaluation of O^6-3[^{131}/^{125}I]iodobenzyl-2'-deoxyguanosine ([^{131}/^{125}I]IBdG), a potential agent for the quantification of alkylguanine-DNA alkyltransferase (AGT)

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The DNA repair protein AGT is responsible primarily for the drug resistance seen in alkylator chemotherapy. A method to quantify AGT in vivo by noninvasive means could help individualize cancer alkylator chemotherapy. We previously reported that O^6-[^{131}I]iodobenzylguanine ([^{131}I]IBG) was not ideal for this purpose because this compound exhibited considerable nonspecific uptake in cells *in vitro* and in xenografts *in vivo*. In search of a better analog, we have synthesized the corresponding guanosine derivative, [^{125}I]IBdG, and evaluated it *in vitro.* IBdG was synthesized in 3 steps from commercially available 2'-deoxyguanosine and converted to its trimethylstannyl analogue, TBdG. TBdG was radioiodinated using N-chlorosuccinimide as the oxidant to give [$^{125/131}$I]IBdG in 80-90% radiochemical yield. The binding of [^{131}I]IBG and [^{125}I]IBdG to purified AGT was studied in a paired-label format in the absence or presence of graded concentrations of O^6-benzylguanine (BG), which is a potent inactivating agent of AGT. In the absence of BG, 48.8 ± 2.9% of input [^{125}I]IBdG radioactivity was bound to AGT; in comparison, the percent of input [^{131}I]IBG bound to AGT was 99.4 ± 0.4. In both cases, BG inhibited the uptake in a concentration-dependent manner with IC_{50} values of 3.3 μM and 1.4 μM for [^{131}I]IBG and [^{125}I]IBdG, respectively. About 15-17% of input activity in each case bound to the nonspecific protein BSA. In other parallel paired-label studies, the uptake of [^{131}I]IBG and [^{125}I]IBdG by AGT-rich DAOY medulloblastoma cells was determined in the absence or presence of increasing concentrations of either BG or IBdG. In the absence of any unlabeled agent, a 3-fold higher uptake of [^{125}I]IBdG by this cell line was seen compared to that of [^{131}I]IBG (30.7 ± 0.5% versus 11.4 ± 0.5% of respective input counts; $p < 0.05$), which is presumably due to the higher transmembrane transport of the sugar derivative. The uptake of [^{131}I]IBG and [^{125}I]IBdG was reduced to half-maximal values by BG at concentrations of 8.0 μM and 19.0 μM, respectively. When unlabeled IBdG was used to deplete AGT, these values were less than 1 μM for both tracers. These results indicate that radiolabeled and unlabeled IBdG warrant further investigation as reagents for AGT imaging and depletion, respectively.

CS20

Radioiodination of high specific activity ß-CIT with ^{123}I

Sami S. Zoghbi,*[1,2,3] Gilles D. Tamagnan,[1,2] Yolanda Zea-Ponce,[1,2] Robert B. Innis,[1,2,3] Ronald M. Baldwin[1,2]

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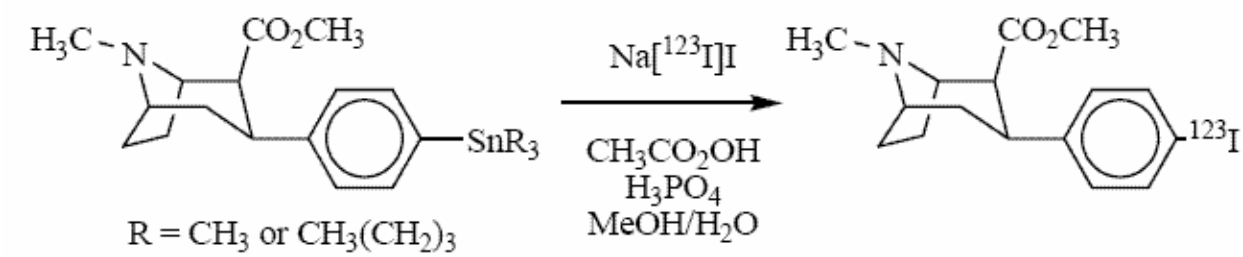
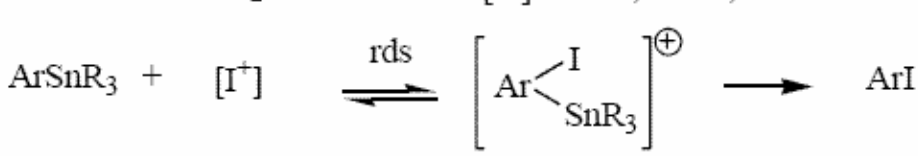
[^{123}I]β-CIT radiopharmaceutical is of important diagnostic utility in imaging the dopamine transporter in health and disease. Its production from no-carrier-added iodine-123 and at high specific activity is of major importance in detecting the targets at low levels of receptor density. Routine radioiodination of large quantities of radioactivity (30-100 mCi) tended to produce lower and more variable radiochemical yield than when small amounts of radioiodine were used. We hypothesized that the inhibitors may be reducing agents present in the no-carrier-added Na[^{123}I]I. Others have had success in high radiochemical yield when carrier halogen (iodine or other halogen) was used in the reaction such as chlorine, but careful separation of the chlorinated species would have to be implemented to ensure high specific activity preparations. Thus we investigated the effect of oxidizing agent on the radiochemical yield in the absence of other nonradioactive halogens. The radioiodination of ß-CIT was characterized in the presence of phosphoric acid and peracetic acid as an oxidizing agent as an electrophilic substitution (iododestannylation) of iodine for trialkylstannyl group, with the rate-limiting step being driven by generation of the electrophilic iodine species by the oxidizing agent.

Methodical adjustment of the level of oxidizing agent in the radioiodination reaction was sufficient to result in consistently high radiochemical yield and further investigations into the physicochemical properties of the ^{123}I-ß-CIT allowed the development of the proper conditions for high yield recoveries of product.

Supported by National Institutes of Health and US Veteran's Affairs.





CS21

Small Molecule Inhibition of Viral Fusion of Respiratory Syncytial Virus (RSV) - Targeting the Binding Pocket within the Trimer-of-Hairpins

C. Cianci, D.R. Langley, D.D. Dischino*, Y. Sun, K.-L. Yu[1], A. Stanley, J Roach, Z. Li, R, Dalterio, R. Colonno, N. Meanwell, and M. Krystal
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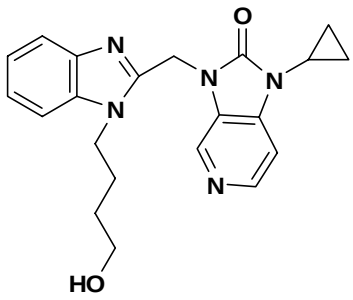
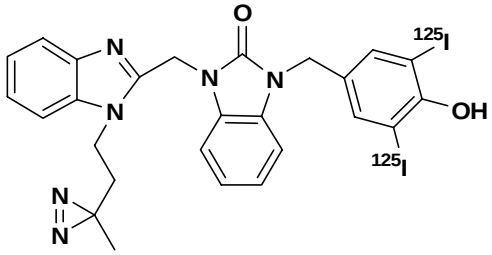
Respiratory syncytial virus (RSV) has been recognized as a leading cause of virus-induced lower respiratory tract disease in infants and children. Recently we described BMS-433771 as an orally active small molecule inhibitor of RSV fusion (C. Cianci et al, *Antimicrob. Agents Chemo*, **48**, 413-422, 2004). An ^{125}I- labeled photoaffinity label, BMS-356188, was developed and then used to confirm the identity of the virus protein targeted by this class of RSV inhibitors and to label the specific amino acid residues intimately involved in the binding interactions.

Photoactivation of the photoaffinity label in the presence of virus obtained from the supernatant of infected cells, demonstrated that the RSV fusion protein was the only protein covalently labeled. Subsequent mapping studies demonstrated labeling of a 5,998 Dalton F1 fragment comprising amino acids 164-218 of the fusion protein. Peptide sequencing demonstrated that BMS-356188 was attached primarily to tyrosine-198, a residue found inside the binding pocket proposed as a potential target for small molecules. The high potency of this class of inhibitor suggests that interruption of the association of the Phe-483 and Phe-488 of the C-terminal with the N-terminal pocket is sufficient to disrupt the precise conformation within the fusion hairpin configuration that is critical for the fusion of viral and cellular envelopes.



BMS-433771



^{125}I-BMS-356188

CS22

Radioiodination of 3-Hydroxy-4-pyridinones

M. Bowen, T. Storr, D. Green, K. Böhmerle, M. Adam and C. Orvig.
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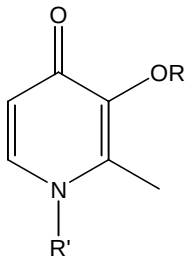
3-Hydroxy-4-pyridinones have proved useful as metal chelators in a variety of applications.[1] Of great importance is their ability to chelate strongly to iron, which has lead to their use as orally active therapeutic agents for iron overload diseases. Studies have found that 1,2-dimethyl-3-hydroxy-4-pyridinone (R = H, R' = methyl) is an effective drug for reducing high iron levels in patients suffering from thalassaemia major.[2] More recently, studies have focussed on varying the R groups shown to improve the properties and specificity of these molecules.[3] Our group has synthesized a wide range of 3-hydroxy-4-pyridinone derivatives, with many different groups in the R and R' positions.



3-Hydroxy-4-pyridinones;
R = H, various substituents
R' = alkyl, aryl

The reported work investigates the addition of a radioactive iodine atom to a range of pyridinones. ^{125}I labeled analogues of these molecules will be used to obtain data on biodistribution and accumulation of 3-hydroxy-4-pyridinones *in vivo*.

[1] Kline, M., Orvig, C. *Clin. Chem.* **1992**, *38*, 562.
[2] a) Kontoghiorghes, G., Bartlett, A., Hoffbrand, A., Goddard, J., Sheppard, L., Barr, J., Nortey, P. *Brit. J. Haematol.* **1990**, *76*, 295. b) Bartlett, A., Hoffbrand, A., Kontoghiorghes, G. *Brit. J. Haematol.* **1990**, *76*, 301. c) Anderson, L., Wonke, B., Prescott, E., Holden, S., Walker, M., Pennell, D. *Lancet* **2002**, *360*, 516.
[3] For summary see: Martell, A., Motekaitis, R., Sun, Y., Ma, R., Welch, M., Pajeau, T. *Inorg. Chim. Acta* **1999**, *291*, 238.

CS23

A Comparison of the Synthesis, iodination, and Biodistribution of Compounds Which Contain a Decaborate(2-) or Dodecaborate(2-) Functional Group.

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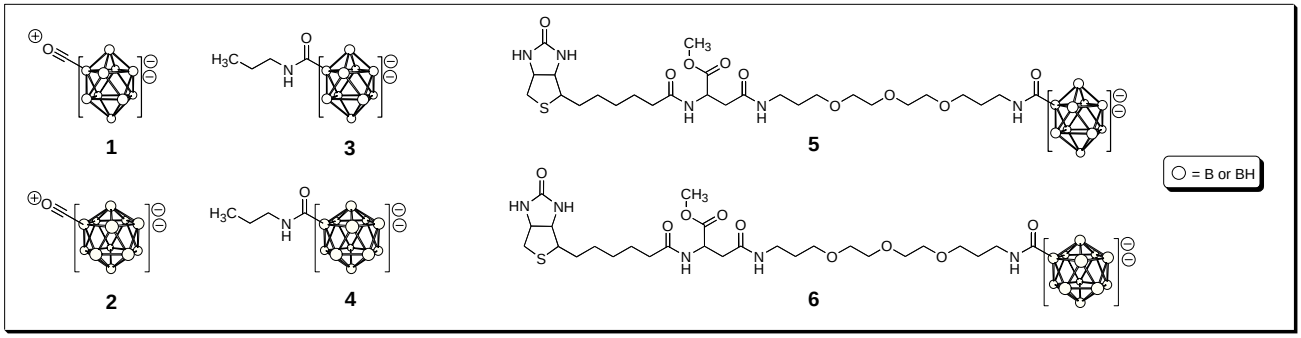
Department of Radiation Oncology, University of Washington, Seattle, WA 98103

We are investigating the use of dianionic borate cage moieties as pendant groups for incorporation of radiohalogens into biomolecules. Two borane cage molecules of particular interest are the decaborate(2-) ($[B_{10}H_{10}]^{2-}$) and dodecaborate(2-) ($[B_{12}H_{12}]^{2-}$) cage moieties. Both are highly water soluble and readily halogenated. Carbonylation of these dianionic species, to prepare compounds **1** and **2**, is readily accomplished using oxalyl chloride in anhydrous acetonitrile at room temperature for 30 min – 4 h. The longer reaction time (i.e. 4 h) was required to carbonylate the dodecaborate(2-) cage. Due to the unique nature of the boron cage moiety, the reactivity of the acylboranes with nucleophiles is low. However, primary amines, such as *n*-propylamine, can provide amide derivatives (e.g. **3** and **4**) if **1** or **2** is stirred with the neat amine at room temperature for 16 h to 3 days. In this reaction, the longer time (i.e. 3 days) is required for reaction with the acylated decaborate(2-) moiety, **1**. Additionally, reactions **1** and **2** with diamines can provide borate cage amido adducts that have a free amine for further modification. This approach was taken to prepare the complex biotin derivatives, **5** and **6**. Their preparation employed the reaction of 4,7,10-trioxa-1,13-tridecanediamine with **1** or **2** to provide adducts. In a second step, the borate cage adducts containing free amines were reacted with a biotin derivative that had an activated ester.

Iodination of compounds **1**-**6** (di-Et_3NH^+ salts) was conducted in a 5% HOAc/MeOH/H_2O mixture using NaI and chloramine-T (ChT) as the oxidant. The iodination reactions are very rapid, with color dissipating within 1 second for all reactions. It appears that iodination reactions are somewhat faster on the decaborate(2-) cage as no color is observed, whereas a yellow color is present, albeit briefly, when iodinating the dodecaborate derivatives. Radioiodinations are facile (within 1 min) at room temperature using no-carrier-added $Na[^{125,131}I]I$ and ChT in the 5% HOAc/MeOH/H_2O solvent mixture. Using the same conditions, radioiodination of **5** provided a 98% radiochemical yield (by HPLC) and radioiodination of **6** provided a 69% radiochemical yield. Although the reaction conditions were not optimized for each compound, one explanation for the difference in labeling yield is the slower radioiodination reaction rate of the dodecaborate(2-) cage in **6**. In binding studies, >90% of either [^{125}I]**5** or [^{125}I]**6** was bound to an avidin column, indicating that the radioiodination did not affect their biotin binding. A comparison of the biodistributions at 1 and 4 h post injection of the two biotin derivatives ([^{131}I]**5** and [^{125}I]**6**) coinjected in athymic mice will be presented.



CS24

[^{123}I]YP428, First SPECT Imaging Agent of mGluR5 Receptors. Evaluation in Nonhuman Primate.

David Alagille[1], Kelly Cosgrove[1,] Ronald Baldwin[1],Louis Amici[1], Julie Staley[1], Gilles Tamagnan[1,2]*.

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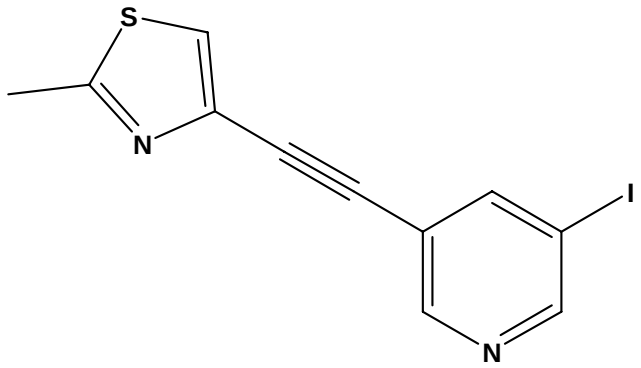
The role for glutamatergic neurotransmission in the behavioral and reinforcing effects of cocaine is becoming increasingly evident[1,2], especially for the type 5 metabotropic receptor (mGluR5). Chiamulera and co workers[3] demonstrated that genetic deletion of mGluR5 in mice resulted in reduction of intravenous cocaine self-administration. These investigators also found that cocaine self administration was reduced following administration of the selective mGluR5 antagonist MPEP. In our continuous effort to better understand the biological process of cocaine reward and craving, we initiated a program of mGluR5 imaging agent discovery.

We will report in detail the synthesis of different mGluR5 antagonists leading to the discovery of [^{123}I]YP428 and the evaluation of this compound as the first SPECT imaging agent for the mGluR5 receptor in nonhuman primate.



YP428

1: Cornish, J. L. and Kalivas, P. W. Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J. Neurosci.* **2000**, *20*, 1-5.

2: Di Ciano, P. and Everitt, B. J. Dissociable effects of antagonism of NMDA and AMPA/KA receptors in the nucleus accumbens core and shell on cocaine-seeking behavior. *Neuropsychopharmacology* **2001**, *25*, 341-360.

3: Chiamulera, C.; Epping-Jordan, M. P.; Zocchi, A.; Marcon, C.; Cottiny, C. et al. Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. *Nature Neurosci.* **2001**, *4*, 873-874.

CS25

A FLEXIBLE STRATEGY FOR RADIOLABELLING INSULIN WITH RADIOHALOGENS

K. J. Guenther[a], P. Schaffer[a], S. Yoganathan[a], R. Chirakal[b], M. Dolovich[c], J. Zubieta[d], S. R. Banerjee[d], J. W. Babich[e], J. F. Valliant[a].

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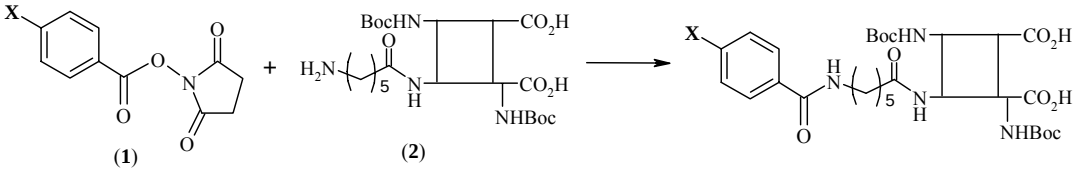
[d]Department of Chemistry, Syracuse University, Syracuse, NY.
[e]Molecular Insight Pharmaceuticals Inc., Cambridge, MA.

One of the keys to making significant advances in the field of nuclear medicine involves the development of new radiopharmaceuticals that can target specific receptors. Consequently, there is an interest in developing novel radiolabelling strategies, which would facilitate attachment of a radioactive tag to a biomolecule, while maintaining the physiochemical properties.

The objective of this study was the development of a flexible and robust strategy for labelling insulin with both diagnostic and therapeutic radionuclides including ^{18}F, ^{99m}Tc, ^{125}I, and ^{131}I. A radiolabelled insulin tracer would afford the opportunity to study the distribution and metabolism of the hormone *in vivo*. Furthermore, the probe would also be used to detect tumour metastases, as insulin receptors are over-expressed on cancer cells.

The methodologies involve conjugating a series of different prosthetic groups, through a short spacer to the Phe(B1) residue of a protected form of insulin. The prosthetic groups include 4-^{18}F-fluoro-succinimidylbenzoate and 4-^{131,125}I- iodo-succinimidylbenzoate (**1**). To confirm formation of the radiolabelled insulin derivatives, non-radioactive standards were prepared and characterized by HPLC, mass spectrometry, and enzymatic digestion experiments.

The approach utilized a regioselective conjugation of the aforementioned prosthetic groups to the Phe(B1) residue of a Boc-protected insulin precursor (**2**). We found that direct conjugation did not yield the desired conjugates, however, incorporation of a suitable spacer enables rapid synthesis of the preferred bioconjugates without a detrimental impact on the RBA. Following removal of the Boc groups and purification by HPLC, the desired insulin analogues were isolated.



X = ^{18}F, ^{131,125}I

CS26

New Approach of Using Artificial Neural Networks for Crosstalk Correction in Simultaneous Dual-Radionuclide SPECT: A Monte Carlo Study

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Simultaneous dual-radionuclide SPECT has a great potential in nuclear medicine imaging. The main obstacle toward clinical applications is cross-talk contamination. Artificial Neural Networks (ANNs) have been used to remove scatter and crosstalk contamination from photopeak photons within the dual-radionuclide images. We have previously proposed an approach of using ANNs for correcting crosstalk based on experimental acquisitions. The aim of this work was to further study this approach by using Monte Carlo simulation.

Materials & Methods: The Monte Carlo software package, SimSET from Washington University, was used to generate the projection data from digital phantoms and the artificial neural network package SNNS, from the University of Stuttgart, was employed to train neural network and correct crosstalk contaminations. The right elliptical cylinder torso phantom within the SimSET package was used for the network training and three other digital phantoms were created for the crosstalk correction tasks. The first digital phantom was the Cylindrical Striatal Phantom, which was used in our previous experiments. The second Circle phantom was designed to test various ratios of dual radionuclide activities and the third one was the well-known Zubal phantom. The dual radionuclides modelled in this study were ^{99m}Tc and ^{123}I. A parallel collimator and a detector with clinical geometry were included in these Monte Carlo simulations. An artificial neural network with 24 input nodes, 10 hidden nodes and 2 output nodes, was implemented in this work. The input nodes cover the energy range from 79 to 183 keV. The corrected projection data were reconstructed using the filtered backprojection algorithm. A quantity P, the percentage crosstalk contamination defined in our previous study, was used to assess the image improvement.

Results: The percentage crosstalk contaminations at various Regions of Interest were reduced significantly. The P was reduced from 400% to a negligible value for the Cylindrical Striatal Phantom. For the Circle phantom, the P values were reduced from 25%, 20%, 10%, 5% and 1% to around 0% , respectively. There are slight variations of the P values for the Zubal phantom, but all had a substantial reduction.

Conclusions: The new approach of using ANNs to correct crosstalk contamination should be a simple but effective tool in dual-radionuclide imaging applications.

IS8

Progress in Development and Evaluation of New Radiopharmaceuticals Labeled with Iodine-124 and Bromine-76 at Washington University.

Michael J. Welch
Washington University School of Medicine, Division of Radiological Sciences, St. Louis, MO 63110

At Washington University St. Louis three areas of research related to the radionuclides iodine-124 and bromine-76 are being carried out. These are:

1) **The development of automated separation and preparation units for the radionuclides**. Simple, easy to use targetry for the preparation of these cyclotron produced nuclides bromine-76, bromine-77 and iodine-124 have been developed. Automated processing systems for the separation of these nuclides from the target material are under development. Supported by the National Cancer Institute, bromine-76 and iodine-124 are being distributed to several researchers in the United States for various research applications.

2) **Quantification of PET imaging utilizing bromine-76 and iodine-124**. Bromine-76 and iodine-124 both have complicated decay schemes and high energy positrons that can degrade the image quality, particularly when utilizing small animal imaging systems. Various approaches are being taken to improve quantification with these nuclides. One approach is the use of an interactive reconstruction algorithm developed at the University of Southern California that corrects from the positron range. The application of this technique will be described.

3) **Radiopharmaceutical development with bromine and iodine radionuclides**. Several types of compounds are being labeled with these long-lived halogen radionuclides. These include ligands for the σ-2 receptor, ligands for steroid hormone receptor and compounds to measure cellular proliferation. The application of agents in all three of these types of applications will be described.

Acknowledgements: The work described in this presentation involve collaboration with many members of the radiopharmaceutical chemistry group at Washington University. The work was supported by NCI grant R24CA86307 and DOE grant DEFG02-84ER-60218.

CS27

A Comparison of Distillation Methods for the Recovery of Bromine-76

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Keywords: bromine-76, distillation

Bromine-76 is prepared at Washington University School of Medicine on a small biomedical cyclotron (15 MeV). Solid tungsten targets containing annealed $^{63}Cu_2{}^{76}Se$ are bombarded at either 5 microAmps (disc target) or 20 microAmps (inclined target) to make ^{76}Br via the (p,n) reaction. The radionuclide is removed from the target via dry distillation, deposits in a narrow band on a quartz tube and is recovered with small volume washes of dilute NH_4OH.

A historic review of distillation methodology was performed to identify differences in recoveries between induction and conventional furnaces. In both scenarios, the target was placed in a quartz tube and the sealed system was flushed with argon gas during heating. Distillation temperatures ranged from 1000º-1090ºC. In the induction furnace the target was heated for 5-10 minutes while in the conventional furnace the distillation time was 1-1.5 hours.

There was little difference in recoveries between the two systems. The percent distilled from the target averaged 73% using the induction furnace (26% stdev) and 76% using the conventional furnace (stdev 14%). The amount of ^{76}Br recovered from the quartz tube was similar for both systems (63% induction, stdev 23% vs. 60% conventional, stdev 21%). The overall amount of activity recovered from the target ranged from 28%-68% in the induction furnace (average 43%, stdev 17%) and from 12%-78% in the conventional furnace (average 45%, stdev 17%). However, the use of the induction furnace led to visible degradation of the target material after an average of 4 distillations. The resultant target layer was non-uniform and had a crystalline appearance. Additionally, the target material became less adherent to the target backing. It was hypothesized that the rapid heating and cooling of the solid target in the induction furnace led to the degradation of the target material. The conventional furnace presented a milder heating and cooling cycle. The disc target withstood 24 distillations with no visible signs of degradation while the inclined target withstood 20 distillations with similar results. It was apparent that distillations in the conventional furnace were resulting in slight losses in target material as evidenced by decreasing yields with subsequent bombardments. For example, the inclined target yields decreased from 1.09 mCi/microAmp*hour to 0.75 mCi/microAmp*hour after 15 bombardments. Upon replenishment with $^{63}Cu_2{}^{76}Se$ the yield has averaged 1.10 mCi/microAmp*hour (n=14). Taking in to account the high cost of target material and solid target backing coupled with the relatively long half-life of ^{76}Br (16.2 h) we have adopted the conventional furnace as our preferred method for the recovery of ^{76}Br.

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IS9

Astatinated Molecule Stability in Vivo: The Challenge of Obtaining High Stability without Affecting the Carrier Molecule

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Astatine-211 is one of only a few α-particle emitting radionuclides that are suitable for in vivo use. At-211 is particularly attractive for cancer therapy as it is a pure α-particle emitter (i.e. has 100% α-emission through a branched decay pathway), does not have α-particle emitting daughters, has a reasonable half-life ($t_{1/2}$ = 7.21 h), and can be readily produced in clinically useful quantities. As with other α-emitters, this radionuclide holds great potential for treatment of micrometastatic disease, cancer retained in compartmental spaces (i.e. ovarian cancer), and solid tumors that are resistant to conventional radiation therapy (i.e. melanoma). However, instability of the At label on cancer targeting agents may preclude its use in many cancer applications.

Monoclonal antibodies (mAbs) have been found to be effective delivery agents for targeted radionuclide therapy of cancer. Early investigations demonstrated that astatination of proteins, such as mAbs, yielded radiolabeled materials that were very unstable towards in vivo deastatination. A solution to this inherent instability was found by attaching the At-211 to an aromatic ring compound, and in a second step, attaching the At-labeled compound to the mAb. While the two-step approach has provided a satisfactory solution for intact mAb and their $F(ab')_2$ fragments, instability of the At-211 label is again a problem with smaller mAb fragments such as Fab´ or scFv. Astatinated rapidly metabolized cancer-targeting agents such as peptides and small molecules are also generally very unstable towards in vivo deastatination.

It seems likely that solutions to this instability reside in alternate methods of bonding the At-211. Methods for chelation of At are under study, but stable chelates have not been reported to date. Alternatively, we have investigated the use of *nido*-carborane cage molecules for attaching At to proteins and small molecules. This labeling approach has proven to be very efficient due to the high reactivity of the *nido*-carborane cage. While the in vivo stability appears to be higher than that of astatinated aryl ring compounds, ultimately it is probably not sufficient for use in patients. Therefore, we have also investigated a number of other boron cage molecules as pendant groups for astatination of compounds. In those investigations, we found that molecules containing bis-*nido*carboranes (also referred to as Venus Flytrap Complexes) were very stable, but these had dramatic effects on the in vivo distribution of the labeled molecule. Subsequently, we found that dianionic decaborate containing molecules have very high in vivo stability and have minimal affect on the in vivo distribution of the labeled molecule. However, the astatinated decaborate(2-) derivatives are effectively residualized in the organ where the carrier molecule is metabolized (e.g. liver or kidney), making these molecules unacceptable for this application. Now that molecules with high stability against in vivo deastatination have been found, the focus is to find chemical modifications that will alleviate the propensity to be residualized in non-target tissues.

While a solution for obtaining high in vivo stability of At-labeled compounds has been found, it is only a partial solution in that the molecules have a profound effect on the in vivo retention of the At. Indeed, it may not be a solution at all unless modifications can be found to alter the in vivo retention. Thus, this presentation will provide an overview of the literature regarding instability of At-211-labeled compounds, will provide a survey of studies with boron cage compounds studied, and (hopefully) will stimulate thought and discussion on possible solutions to this limitation to a potentially very useful radionuclide.

IS10

Astatine-211 and Astatinated Radiopharmaceuticals

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The range in tissue of ∀-particles is only a few cell diameters and, therefore, targeted ∀-particle therapy is ideally suited for the treatment of micrometastases, tumors in circulation and those cancers that spread as thin sheets of compartmental tumors. In addition to their shorter range in tissue, ∀-particles have several radiobiological advantages over the ∃-particles that are typically used in endoradiotherapy. These include higher relative biological effectiveness, low oxygen enhancement ratios, absence of dose rate effects and non-dependence on cell cycle for their therapeutic effectiveness. This talk will cover issues related to the development of astatinated radiopharmaceuticals; brief descriptions of the topics that will be covered are given below.

Astatine-211 Production. Astatine-211 is generally produced by the cyclotron bombardment of natural bismuth by 28 MeV ∀-particles via the ^{209}Bi(∀, 2n)^{211}At nuclear reaction. An internal target system was developed at Duke with which ^{211}At production yields of 0.8 ± 0.1 mCi/μAAh (a 4-fold higher yield than that obtained with the conventional external target system) were obtained. Astatine-211 from the target was isolated by dry distillation in 67 ± 16% distillation yields.

Astatinated Monoclonal Antibodies (mAbs). Chimeric 81C6, an anti tenascin mAb was labeled with ^{211}At using *N*-succinimidyl 3-[^{211}At]astatobenzoate (SAB). Up to 14 mCi of labeled ch81C6 has been prepared, the immunoreactive fraction of which was 83.3 ± 5.3%. A phase I clinical trial involving 17 brain tumor patients to determine the maximum tolerated dose and objective responses was conducted. Median survival in these recurrent brain tumor patients was 60 weeks, significantly higher than those obtained from conventional treatments.

Meta-[^{211}At]astatobenzylguanidine ([^{211}At]MABG). *Meta*-[^{131}I]iodobenzylguanidine ([^{131}I]MIBG) has been used in the treatment of neuroendocrine tumors such as neuroblastoma. Because neuroblastomas undergo extensive metastases, an analogue of MIBG labeled with ^{211}At may be ideal for their treatment. [^{211}At]MABG was synthesized by astatodesilylation of a silicon precursor. It demonstrated a high degree of toxicity to human tumor cells in both monolayer and multi-cellular spheroids at activity concentrations orders of magnitude less than even no-carrier-added [^{131}I]MIBG and equivalent to only a few ^{211}At decays per cell. Recently, the superiority of [^{211}At]MABG in killing cells transfected with the norepinephrine transporter gene has been demonstrated. Preliminary results of [^{211}At]MABG synthesis at a higher level from a solid-phase supported tin precursor also will be discussed.

5-[^{211}At]Astato-2'-deoxyuridine ([^{211}At]AUdR) and Astatinated octreotate. In addition to the above, recent results obtained with these two astatinated radiopharmaceuticals also will be discussed.

IS11

Radiohalogen-Based Targeted Therapies

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Although the same radiobiologic principles underlie therapy with external beam radiation and radionuclides, there are significant differences in the biologic consequences subsequent to such exposures. External beam and brachytherapy emissions are composed of photons, while radiations of interest in radionuclide therapy are particulate. In this talk, the special features that characterize the biologic effects arising from the traversal of charged particles through mammalian cells will be presented. In addition, the outcomes of treatment with radiohalogens in experimental models of cancer will be described.

CS28

Auger therapy for prostate cancer

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Prostate cancer is the most prevalent cancer in men and the second leading cause of cancer death in North America. In early stage prostate cancer both surgery and radiation treatment can be curative. Radioisotope induced therapy is of interest in prostate cancer treatment because Auger electron-emitting androgen may be delivered directly to prostate tumor cells by direct injection where the disease is localized, making the prostate an optimal target for clinical application. Hence when an Auger electron-emitting nuclide is covalently incorporated into DNA it can affect double strand breaks in DNA and cell death. We are interested in using the steroid receptor interaction pathway to direct such radiation to DNA in steroid receptor-containing prostate cancer cells. Radioiodine incorporated into an iodoandrogen steroid is brought into proximity of DNA by the androgen receptor protein (AR); the cancer cell DNA is consequently targeted by the Auger electrons of the radioiodine decay, followed by apoptotic cell death. The iodoandrogen 7-methyl-17-(2'-(E)-iodovinyl)-19-nortestosterone (EMIVNT) was selected for the present Auger therapy trial based on its known high affinity for the androgen receptor and stability in aqueous solution. A novel synthesis starting with 5(10)-estren-7-methyl-17-ethynyl-17-ol-3-one led to the known radiolabelling precursor 7-methyl-17-(2'-(E)-tributylstannylvinyl)-19-nortestosterone. Radioiodination was carried out in the presence of peracetic acid and [^{125}I]NaI or [^{123}I]NaI. High specific activity [^{123,125}I]EMIVNT was recovered by HPLC. Initial androgen receptor binding experiments with [^{125}I]EMIVNT prepared at 2,200 Ci/mmole, demonstrated that [^{125}I]EMIVNT binds AR at the affinity of the natural ligand, dihydrotestosterone. Further *in vitro* experiments using AR-positive and AR-negative prostate cancer cell lines have examined the ability of [^{123,125}I]EMIVNT to cause dose dependent apoptotic cell death using the MTT apoptotic assay. Our results are highly promising for the development of [^{123,125}I]EMIVNT as a novel treatment for prostate cancer.

CS29

Preliminary Clinical Imaging and Pharmacokinetic Results with NM404 in Non-Small Cell Lung Cancer

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Objectives: NM404, a second-generation radioiodinated phospholipid ether (PLE) analog, undergoes prolonged selective retention (>80 days in mouse models) in a wide variety of malignant tumors in animal models (25/25) due to an apparent lack of metabolic enzyme activity in tumor cells relative to normal cells. The aim of this project is to examine the tumor avidity and retention properties of NM404 in human non-small cell lung cancer (NSCLC) patients.

Materials and Methods: Following intravenous injection of ^{131}I-NM404 (1mCi, <20 g), patients with advanced NSCLC were scanned at 3, 6, 24, 48, 96h and at 7 and 11 days on a GE Maxxus dual head SPECT scanner. Blood and urine samples were collected for pharmacokinetic analysis as well as for clinical hematology, renal and hepatic bioanalysis.

Results: Initial qualitative imaging results indicate that ^{131}I-NM404 clearly localizes in pulmonary NSCLC masses as early as 24h after intravenous injection and is selectively retained by these tumors in excess of 11 days. Furthermore, radioactivity associated with the liver and lower abdominal organs including the urinary bladder, kidneys and intestines was significantly less than that observed previously with the iodophenyl-alkylphosphocholine prototype, ^{131}I-NM324, in colon and lung cancer patients. No adverse reactions were observed in any of the patients.

Conclusions: These initial observations suggest that NM404 exhibits tumor uptake and retention properties in human NSCLC similar to that found previously in rodent tumor models. Efforts have been initiated to extend the clinical utility of NM404 to CT-PET imaging by labeling with iodine-124, a newly-available positron-emitting isotope with a 4-day physical half-life. In addition, animal tumor model studies to examine the radiotherapeutic potential of NM404 as a Diapeutic™ agent are currently underway.

IS12

PET in Drug Discovery and Development. A Pharmaceutical Company's Perspective.

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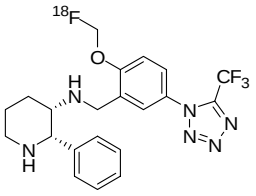
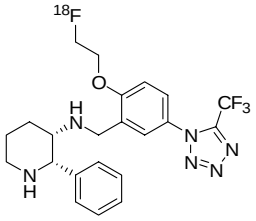
PET is a useful research tool that can be used to reduce the cost of bringing new drugs from the preclinical stage through to final approval by assisting in choosing the dosage level and regimen. PET is extremely useful when there is no easily measurable clinical pharmacodynamic marker or substantial time is required before an indication of efficacy is observed. We have been involved in developing PET tracers for novel CNS targets for use in preclinical imaging studies in monkeys as well as clinical studies. These studies are used to evaluate drug candidates to assist in lead compound evaluation and to measure receptor occupancy of clinical compounds to assist in selecting clinical dosage/regimen.

The development of the neurokinin-1 (NK_1) tracer [^{18}F]SPARQ (**1**) and its use in clinical studies as well as the synthesis and characterization of the NK_1 tracer [^{18}F]fluoroethyl SPARQ (**2**) and the metabotropic glutamate receptor subtype 5 (mGluR5) tracers **3**-**5** will be presented. Uses of other radiohalogens will also be discussed.



1, [^{18}F]SPARQ



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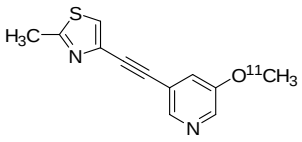

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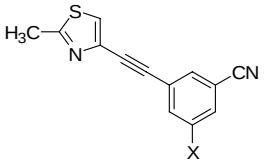

4, X=$^{11}CH_3$
5, X=^{18}F