Radiometals 2013 in Sonoma Valley

Thursday 13 June 2013 - Sunday 16 June 2013

Santa Rosa, California USA

Book of abstracts

0 - Testing the system

Presenter: Ms. THOMSON, Jana (TRIUMF)

This is a a test abstract

1 - An Automated Module for Remote Separation of 86Y from a 86SrO Powder Target

Production and Automation - Friday 14 June 2013 12:00

Presenter: WOOTEN, A. Lake (Mallinckrodt Institute of Radiology, Washington University School of Medicine AND Department of Biomedical Engineering, Washington University in St. Louis)

Purpose: One of several radiometals used for PET, 86Y (t1/2=14.7 h; Eβ+,avg=660 keV; BR=32%) is used as an imaging analogue for the radiotherapeutic isotope 90Y (t1/2=64.0 h; Eβ-,avg=934 keV; BR=100%). In this work, we produced 86Y via the 86Sr(p,n)86Y reaction using a remote system. Methods: 86SrCO3 was baked in a furnace, producing 86SrO that was pressed into a Pt target holder and bombarded. 86Y was separated from the target using a process that was mentioned by Friedlander et al.1 (1981) and developed by Avila-Rodriguez, et al.2 (2008). Since 86Y has a large γ radiation emission (Γ15 keV=18.9 R cm2/mCi h), we developed an automated module to perform the process inside a lead hot cell. Liquids were transported through the system by vacuum maintained by a Venturi pump, and flow speeds were regulated by actuating valves in the system at various intervals and durations. Both the target dissolution and drying processes could be accelerated using heating elements via digital temperature controllers. The process was monitored using video cameras, radiation detectors, thermocouples, and a pressure transducer. Signals from all of the controls and sensors were integrated in a graphical user interface (GUI) that included an interactive schematic for liquid paths and a clickable step-by-step process that personnel could follow. The separation process involved dissolving the irradiated powder in acid followed by the addition of base, which produced 86Sr(OH)2 in solution and 86Y(OH)3 as a colloid. The liquid was then pulled by vacuum through filter paper that passed the 86Sr(OH)2 through to a vial for recycling, while catching the 86Y(OH)3 colloid. Following two additional rinses with base, acid was added, redissolving the 86Y(OH)3, which was then passed through the filter and collected in a product vial. Results: We have successfully separated 86Y in two preliminary test runs and continue troubleshooting of the system. As testing of the module continues, we will process larger amounts of 86Y and determine effective specific activity (ESA). This module has successfully isolated 86Y as 86YCl3 and recovered the enriched 86Sr as 86Sr(OH)2(aq), which will be recycled for future productions. In the long term, this automated module will be used for future larger-scale productions of 86Y for PET studies at our institution and elsewhere. References: 1. Friedlander, J.; et al Nuclear and Radiochemistry, 3rd ed., Wiley: New York, 1981. 2. Avila-Rodriguez, M.A.; Nye, J.A.; Nickles, R.J. Appl. Radiat. Isot. 2008, 66, 9-13. All nuclear data accessed via NNDC.

2 - Distribution of the Radionuclides 64Cu, 89Zr, 76Br and 86Y in North America: an Academic Center’s Perspective

Production and Automation - Friday 14 June 2013 11:43

Presenter: VOLLER, Tom (Washington University)

Washington University in St. Louis, has been producing and distributing non-standard PET radionuclides to the research community for over 15 years. The radionuclides that have been produced include copper-64, bromine-76, yttrium-86, bromine-77, iodine-124 and zirconium-89. Presently, copper-64 is produced on a regular (weekly) basis and yttrium-86, bromine-76 and zirconium-89 sporadically in lower quantities. The increase in shipping of copper-64 to external institutions is mainly due to the increasing in clinical trials with this isotope. To date, the Division of Radiological Sciences has shipped to 132 researchers at 103 institutions in twenty seven States and two Canadian provinces. This presentation will give an overview of our infrastructure and logistics associated with this endeavor.

3 - Cyclotron Produced Tc-99m from Mo (II) Compounds

Tc - Saturday 15 June 2013 10:03

Presenter: Dr. RICHARDS, Vernal (Washington University in St. Louis Medical School)

Purpose: 99mTc, a γ-emitting isotope with a γ-energy of 140 keV and a half-life of six hours, is used worldwide in over 80% of nuclear medicine imaging procedures. It is typically available via a 99Mo generator. Shortages of this radio-isotope can be traced back to primarily age related problems associated with nuclear reactors, which are the production source of 99Mo. To alleviate the current and impending shortages, focus has been on alternative non-reactor methods to produce the 99Mo. Methods: We have focused on direct production 99mTc via cyclotron bombardment of 100Mo (II) targets. We have shown that 100Mo (II) compounds like Mo2C can be easily prepared to facilitate large routine production of 99mTc on a medical cyclotron. Unlike 94MoO3 that was used as the previously target material for the medical cyclotron production of 94mTc, our 100Mo2C is sufficiently robust to withstand the high temperatures that come with bombardment at high beam currents. To date, we have employed currents of up to 10μA. Use of this compound also facilitates the facile separation of the radionuclide from the target material via the efficient thermo-chromatographic technique. Results: We have demonstrated that the use of 100Mo2C as the target material has produced tens of mCi of 99mTc. This has exciting possibilities as it points to the production of patient quantities on a consistent manner. We have also demonstrated that the cyclotron produced 99mTc can be processed and concentrated for easy labeling, producing images that are of no less a quality than generator produced 99mTc. Recovery of the 100Mo as 100MoO3, the material from which the target is made, stands at 85%. This augurs well for this particular process, as recycling of the expensive 100Mo target material is of prime importance. Activity yields for the produced 99mTc are on average 84% of the calculated theoretical yields pointing to the feasibility in using 100Mo2C in the cyclotron production of 99mTc.

4 - Automated Systems for the Large-Scale Production of 64Cu and 89Zr Radioisotopes

Production and Automation - Friday 14 June 2013 11:17

Presenter: MADRID, Evelyn (Department of Radiology, Washington University Medical of School, St Louis MO)

Purpose: 64Cu and 89Zr are radioisotopes for Positron Emission Tomography (PET). We have developed automated system for routine production of 64Cu and 89Zr to reduce exposure dose, contamination risks, and time spent effecting the separation. We have been operating this systems continually on a weekly and biweekly basis; for in house and for off-site external users. Methods: 64Cu is produced by irradiation of 64Ni electroplated on a gold disk. The target material is introduced into a heated PTFE vessel, and is dissolved in 6M HCl for 35 minutes. After cooling, the solution is remotely pushed into an ion exchange column. The 64Ni is collected into the nickel collection vial using vacuum. Once all the nickel is removed from the column, 0.5M HCl is added to collect the 64Cu. Finally the 64Cu solution is dried under argon. 89Zr is produced via the irradiation of an 89Y foil held in a niobium (Nb) target holder. The irradiated target is introduced into the system, and the yttrium foil is dissolved in a PTFE vessel with 10 ml of 2M HCl. Next the solution is pushed remotely onto a hydroxamate resin column. The 2M HCl is collected with positive pressure into a waste vial, and then the hydroxamate resin is washed with 10ml of 2M HCl, and 10ml of Milli Q water. Finally 89Zr is collected with 1ml of Oxalic acid (1.0M) Results: The automated systems have enabled us to effectively purify 64Cu and 89Zr remotely. Using the systems the overall recovery of each isotope is 80-90%. Both automation systems reduced total processing time and exposure as the hot cell doors are only opened for introduction of the target and for product removal.

5 - Targeting the L-Type Amino Acid Transporter-1 (LAT1) with Zr-89 ImmunoPET

Imaging - Friday 14 June 2013 14:15

Presenter: Dr. IKOTUN, Oluwatayo (Tayo) (Washington University School of Medicine)

Purpose: Amino acid derivatives have been radiolabeled and investigated for imaging many types of cancer. Radiolabeled amino acids targeting system L amino acid transport such as [11C]methionine, [18F]FET and [18F]DOPA are effective brain tumor imaging agents but have shown limited utility for most neoplasms outside of the brain due to low tumor-to-background contrast [1]. The L-type amino acid transporter-1 (LAT1), a member of the system L family, is of particular interest in oncologic imaging due to its a key role in cell proliferation and its up-regulation in a wide variety of tumors including gliomas as well as breast, ovarian, prostate, gastric, and non-small cell lung carcinomas [2,3]. Additionally, increased expression of LAT1 in human cancers has been shown to positively correlate with increased tumor aggressiveness and decreased survival [4]. The goal of this project is to develop an immunoPET agent comprised of an anti-LAT1 monoclonal antibody (mAb) labeled with Zr-89 for imaging LAT1 in cancer. Methods: The anti-LAT 1 mAb, Ab2-LAT1, was conjugated with the chelator desferoxamine (DFO) in 0.1 M sodium carbonate buffer (pH 9) at 37 °C. Zr-89 incorporation was conducted in 1 M HEPES (pH 7) at 37 °C for 1 hour. Labeling efficiency was determine by ITLC. In vitro and in vivo studies were conducted in the human colorectal cancer cell line HCT 116 which has been shown to express high levels of LAT-1 [3]. Results: The modified anti-LAT1 antibody, Ab2-LAT1-DFO was labeled with Zr-89 with a radiochemical purity of ≥95% and used without further purification. Our immunoPET agent was synthesized with a specific activity of 7.95 x 105 Ci/mol. PET imaging and biodistribution studies in in xenograft mice showed high tumor uptake, with optimal tumor-to-non target contrast achieved at 7 days post administration, with tumor associated activity of 10.49 ± 1.78 %ID/g. Specificity of the tracer was shown via blocking studies with 30-fold excess of unmodified antibody, where the tumor uptake was 4.70 ± 0.08 %ID/g. Conclusion: We present herein the first example of immunoPET imaging of the LAT1 amino acid transporter. High tumor-to non-tumor contrast in PET images was achieved at 7 days after administration of tracer. Furthermore, in vivo tracer specificity was shown via blocking studies, where the tracer accumulation was decreased 2-fold in the presence of excess antibody. Our results show immunoPET is a viable approach for directly probing the LAT-1 protein levels in tumors, a strategy that may overcome some of the limitations of substrate-based imaging of system L transport with radiolabeled amino acids.

6 - Development of a Radiolabeled Irreversible Peptide (RIP) as a PET Imaging Agent for Vascular Endothelial Growth Factor

Imaging - Friday 14 June 2013 16:06

Presenter: MARQUEZ, Bernadette (Washington University School of Medicine)

Vascular Endothelial Growth Factor (VEGF) plays an important role in angiogenesis, the formation of new blood vessels, and is upregulated in a variety of cancers. Imaging VEGF expression using Positron Emission Tomography (PET) may aid in patient stratification and in monitoring response to anti-angiogenesis therapy. Recently, we enhanced the binding of a peptide ligand1,2 to VEGF by incorporating cross-linkers so that it binds specifically and covalently to VEGF3. In this work, we re-designed the lead peptide, namely FDNB, to incorporate a NOTA chelator for radiolabeling with 64Cu (t1/2 = 12.7 h). This radiolabeled irreversible peptide (RIP) agent could improve peptide imaging agents by prolonging the probe's residence time in VEGF-associated tumors, providing a better quality image. We developed the first example of a RIP agent, referred to as [64Cu]-FDNB, for PET imaging of VEGF expression in vivo. Tumor uptake in HCT-116 colon cancer xenografts (n = 3) was 3.93 ± 0.98 % ID/g after 24 hr and 3.43 ± 0.42 % ID/g after 48 hr. Tumor uptake for control peptide that binds reversibly to VEGF, namely [64Cu]-L19K, was 2.83 ± 0.80 % ID/g after 24 hr and 2.15 ± 0.30 % ID/g after 48 hr. Tumor uptake comparison of both probes was statistically significant after 48 hr ($p = 0.01$). Similar tumor uptake of [64Cu]-FDNB and [64Cu]-L19K after 24 hr suggests that the cross-linker incorporation does not alter VEGF recognition. However, the increased tumor uptake after 48 hr is suggestive of irreversible binding to VEGF resulting in an improved residence lifetime in the tumor. Our work indicates that cross-linker incorporation may be a viable approach to improved tumor accumulation of peptide probes, and warrants further investigation. References: [1] Fairbrother, W. et al (1998), Biochemistry. 37(51), 17754-64. [2] Pan, B. et al, (2002), J Mol Biol. 316(3), 769-87. [3] Marquez, B. et al (2012), Bioconjugate Chem. 23(5), 1080–1089.

7 - Ag-111: A Radiotracer for the Chemistry and Biochemistry of Silver Antimicrobials

NEW APPROACHES - Sunday 16 June 2013 11:44

Presenter: Dr. AWEDA, Tolulope (Mallinckrodt Institute of Radiology, Washington University School of Medicine)

Objectives: With increasing development of bacteria with resistance to conventional antimicrobial agents, new silver based antimicrobials have been synthesized for direct nebulization into the lungs. Our goal was to develop a radioactive tracer for investigating the biological fate of such compounds. Purified 111Ag was incorporated into the methylated caffeine analogue, IC1 to yield the silver carbene complex designated as [111Ag]SCC1 or shell crosslinked knedel-like nanoparticles (SCKs) and investigated in biodistribution studies. Methods: 111Ag produced from neutron irradiation of Pd targets and subsequent β- decay of 111Pd to 111Ag (110Pd(n, γ) 111Pd ($t_{½}$ = 23.4 min) → 111Ag was purified using anion-exchange chromatography monitored via gamma spectroscopy. Purified 111Ag was incubated with the xanthinium salt, IC1 in methanol or the SCKs in water at room temperature for 2hrs. Biodistribution studies were conducted by administration of aerosol doses to C57BL/6 mice via direct nebulization of the silver radiotracers. Results: The average recovery of pure 111Ag was calculated as (92.9 ± 23.7) %. ICP-MS measurement of the 111Ag product gave a final concentration of <25 ppb of Pd which indicates that >99.9% of the palladium was removed by our purification process. Purified 111Ag was successfully incorporated into the xanthinium salt, IC1 with a radiochemical yield of (25.5 ± 2.5)% while encapsulation into the SCK nanoparticles varied from 70-90%. Nebulization of the reconstituted 111Ag antimicrobials resulted in a total dose received per mouse of (1.07 ± 0.12)% of the aerosolized dose. The average dose taken up in the lungs (% ID/g) of the mice was estimated to be (21.5 ± 1.2)% of the total dose received per mouse. Conclusions: The 111Ag based compounds cleared mostly through feces with good accumulation in the lungs 24 hr after nebulized dose delivery. Pre-clinical studies using 111Ag[SCC1] or 111Ag[SCKs] as antimicrobial compounds show high drug dosing via nebulization and good lung retention up to 70 %ID/g. Autoradiography of the lung sections confirmed residence of the Ag-111 radiotracer.Our results indicate that 111Ag is a useful tool for monitoring the biological activity of silver antimicrobials in vivo.

8 - Production, Separation and Labeling of Ti-45

NEW APPROACHES - Sunday 16 June 2013 11:26

Presenter: Mr. SIIKANEN, Jonathan (Medical Radiation Physics, Lund University)

Objectives : 45Ti (T1/2=3.08 h, β+=84.8%) is a metallic PET radionuclide. With a half-life comparable to 18F, 45Ti is an attractive alternative for labeling of proteins. The objective is to investigate production yield, separation and labeling. Methods : Two stacked scandium foils (~12x12x0.25mm3, ~110 mg each) are irradiated with 12.5 MeV, 10 µA protons (GE PETtrace) producing 45Ti via the 44Sc(p,n)45Ti reaction. With 16 MeV protons low levels of 44Sc are co-produced in the front foil, useful to study scandium break-through into the titanium elution. Non-irradiated bulk scandium is trimmed and beam strike of the foils (~30-50 mg) is dissolved in 12.1 N HCl and then filtered. Titanium is separated from scandium using solvent extraction with octanol. The product is tested for labeling either on antibodies pre-conjugated with Df-NCS or on transferrin [Vavare A.L and Welch M.J., JNM 2005;46(4):683-9]. Results : Typically 45Ti productions are 12.5 ± 0.9 GBq (337 ± 24 mCi) (n=4) for 2 h irradiation. The calculated thick target saturated yield at 12.5 MeV is 5.5 GBq/µA (149 mCi/µA). Solvent extraction takes about 2 h to perform and yields are 45.8 ±0.8 % (n=3). Activity concentrations up to 1.2 GBq (30 mCi) in 200 µl, 0.1 N HCl (end of separation) are delivered. The decay corrected radio labeling yield for transferrin is 66.5 ± 9.5 % (n=4) based on 15 µg transferrin per 37 MBq (1mCi) 45Ti. For Df-antibody the decay-corrected yield is 38.6 ± 10.9 % (n=5) based on 40 µg Df-antibody per 37 MBq (1mCi) 45Ti.

9 - Exploring a Pretargeted Approach for Imaging Hyperactivated Metabolism in Breast Cancer

Imaging - Friday 14 June 2013 14:51

Presenter: Dr. VIOLA-VILLEGAS, Nerissa (MSKCC)

Purpose: The peptide pHLIP localizes to the surface of acidic tumors via transmembrane insertion. With long-circulating in vivo kinetics, a pre-targeting platform is ideal especially with the peptide's N-terminus exposed to the extracellular milieu. Here, we describe the validation of a pretargeting strategy via ligation of pHLIP-tetrazine (Tz) and 64Cu-NOTA-trans-cyclo-octene (TCO) in breast cancer. Method: NOTA-TCO was labeled with 64Cu (t1/2=12.7 h) via incubation at room temperature for 5 min and purified via C18 radio-HPLC. In in vitro studies, 4T1 breast cancer cells were incubated with pHLIP-Tz (0.1 nmol) at 1 h at 37 °C before adding 64Cu-NOTA-TCO (2.5 μCi, 0.1 nmol). A separate group with no pHLIP-Tz served as a negative control. In vivo ligation was demonstrated through PET imaging experiments in mice bearing 4T1 orthothopic tumors. First, pHLIP-Tz (~50 μg, 10 nmol) was injected intratumorally followed by intravenous injection of 64Cu-NOTA-TCO (~100 μCi) 1 h later. PET imaging was performed after 1-24 h post-tracer administration. Results: 64Cu-radiolabeling of NOTA-TCO obtained >80% radiochemical yield with a 20±2.0 mCi/μmol specific activity. In vitro assays reveal minimal activity (0.34±0.10%) in the negative control whereas in cells exposed to pHLIP-Tz, a 7.4±0.5% binding relative to the total activity added was displayed. The PET images show tumor delineation with a 5.9±2.7%ID/g tracer uptake at 1 h post-tracer injection whereas, in the absence of pHLIP-Tz, no radiotracer uptake in the tumor was shown. Clearance of 64Cu-NOTA-TCO proceeded via the hepatobiliary organs. At 24 h, PET images display just tumor delineation (2.7±1.4%ID/g) with minimal activity in healthy tissues. Conclusion: We have confirmed proof-of-principle that a pretargeting strategy is applicable to a transmembrane peptide. Work is underway toward optimization of this technique with a view of rapid radioactivity clearance and site-selective targeting of pHLIP.

10 - Cyclotron Produced Ga-66/68 with Thermal Diffusion-Assisted Bulk Separation and AG50W-X8/UTEVA Purification

NEW APPROACHES - Sunday 16 June 2013 11:08

Presenter: Mr. SIIKANEN, Jonathan (Medical Radiation Physics, Lund University, Sweden)

Purpose: An alternative route to generator produced Ga-68 (T1/2=68 min, β+=87.7 %, Emean=353 keV) is to use charged particle activation of zinc. Ga-68 generators are widely available and easy to use. However availability of a cyclotron and the limited activity output of commercial generators (≤ 2.8 GBq (75mCi)) can motivate direct production. Also for Ga-66, (T1/2=9.49 h, β+=51 %, Emean=1904keV),no generator is available. Methods: Possible Ga-68 production on Zn-68 is calculated from already published cross sections [F. Szelecsényi et al., JARI, 1998, (49)]. Natural zinc foils (0.1 &0.25 mm) are irradiated with 5-10 μA, 13.6 MeV protons (GE-PETtrace) to produce Ga-66/68. After irradiation the foils are heated in a tube furnace at 400 ° C for 30 min (0.1 mm) and 2 h (0.25 mm) under argon environment to diffuse gallium out to the foil surface [V. Tolmachev et. al., JARI, 1996, (47)]. The cooled foils are etched with 2 ml of 0.05 N HCl, which is then loaded onto a cation exchange (90mg, AG50W-X8, 200-400 mesh) and extraction column (15mg UTEVA®, 400 mesh) system (connected in series with a three-way stopcock) originally developed for purification of generator produced Ga-68 [A. A Coarasa et al., J Nucl Med. 2012; 53 (Supplement 1):1742]. The flow through of the 0.05 N HCl solutions is discarded. After loading, the three-way stopcock is opened to UTEVA column and 2 ml of 5 N HCl (which elutes Ga from the AG50W-X8) is pushed through both columns to re-trap Ga on UTEVA and further eliminate Zn and other contaminants. Ga is eluted with 0.1 N HCl ready for further labeling. Ga-66 reactivity is measured by titration with NOTA. Results: Ga-68 saturation yield for 0.1 mm (71.4 mg/cm2) Zn-68 (~1 USD/mg) enriched foil is 2GBq/μA which correspond to 50GBq (1.4Ci) Ga-68 (50 μA, 68 min irradiation). More than 60 % of foil activity (< 2 % without heating) is extracted in the acid after diffusion process with <0.5 % of foil mass lost. Ga-trapping in AG50 is ~100 % and 85 % is re-trapped in UTEVA. More than 90 % of the UTEVA-trapped Ga is eluted with 200 μl 0.1 N HCl. Ga-66-reactivity is 0.6-2.2Ci/μmol NOTA (at EOB). Diffusion and purification takes ~45 min(0.1 mm foil).

11 - 72As for ImmunoPET: Production, Isolation, and Labeling Conditions

Production and Automation - Friday 14 June 2013 10:59

Presenter: Dr. ELLISON, Paul (Department of Medical Physics, University of Wisconsin)

Objectives: Arsenic has several radioisotopes with nuclear decay properties that are of interest to the medical research community. Its positron emitting isotopes 72As (t1/2 = 26.0 h) and 74As (t1/2 = 17.8 h) are useful as PET imaging agents and 76As (t1/2 = 26.4 h), a β- emitter, has radiotherapy potential. Arsenic also has unique chemical properties allowing for its covalent bonding to thiol groups. The present work investigates the use of 72As in monitoring the biodistribution of monoclonal antibodies (mAbs). Methods: 72As was produced by proton-irradiating natGeO2 targets in a GE PETtrace cyclotron, followed by their caustic dissolution, reprecipitation of GeO2, anion exchange chromatography, reduction to As(III), and solvent extraction. The product was then used to examine a variety of radiolabeling conditions using the mAbs TRC105 and bevacizumab. The effects of tris(2-carboxyethyl)phosphine (TCEP) reduction and primary amine thiolation of the mAbs were investigated. The efficacy of 72As radiolabeling was monitored with thin-layer chromatography (TLC) and size-exclusion chromatography (SEC). Purified 72As-TRC105 was injected into control (n=2) and 4T1-tumor bearing (n=2) mice. Results: Labeling yields of TCEP-reduced TRC105 and bevacizumab were observed to be 70 - 95%, as determined by the SEC 72As elution profile (n=6). An attempt to label thiolated TRC105 without the addition of TCEP as a disulfide bond reducing agent was unsuccessful. Preliminary results of the biodistribution of the [72As]-TRC105 in mice are indicative that the As-mAb bonds are not stable in vivo. In all experiments (n=4), the radioactivity was observed to rapidly pass through the kidneys and bladder, with >65% of the injected dose excreted by 24 hours post injection. Conclusions: Radiolabeling yields of [72As]As(III) with TCEP-reduced mAbs were favorable. However, progress still needs to be made to understand the mechanism and increase the stability of the As-mAb bond before the tracer finds utility as an immunoPET agent.

12 - Transition Metal Ion Chromatography to Measure True Specific Activity of 64Cu

NEW APPROACHES - Sunday 16 June 2013 12:02

Presenter: Ms. MASTREN, Tara (Washington University in St Louis)

Purpose: True specific activity measurements are very important in radiometal productions to determine the effectiveness of the separation method and to assist with batch to batch consistency and reliability. Current methods to measure true specific activity involve using ICP mass spectrometry which is not readily available at all institutions. Using an ion chromatography method we can determine the amount and types of metal contaminants as low as 1ppb in our 64Cu productions. Method: 5-20 µCi of 64Cu is diluted into 3mL of TraceSELECT Ultra, ACS reagent for ultratrace analysis, water and injected into a 1mL injection loop. A metal free high pressure liquid chromatography system is used with a Dionex CS5A 2-mm Transition Metal Column. The eluent (1.4 mM pyridine-2,6-dicarboxylate / 13.2 mM Potassium hydroxide / 1.12 mM Potassium sulfate / 14.8 mM Formic acid) is passed through the column at 0.30 mL/min. As the metals elute from the column they pass through a mixing loop where they are mixed with 1.0 M 2-dimethylaminoethanol/0.50 M Ammonium hydroxide/0.30 M Sodium bicarbonate containing 0.06g/L 4-(2-pyridylazo)resorcinol (PAR) flowing at 0.15mL/min. During this time the metals complex with the PAR dye and then they are passed through a UV detector and measured at 530nm. Calibration curves have been made for copper, nickel, zinc, cobalt, and iron using TraceCERT atomic absorption standards, 1000 mg/L in nitric acid and range in final concentration from 1µg/L to 10µg/L. Results: Using this method we are able to see the amounts and types of metal contaminants that are present in our 64Cu productions. The main contaminant is the target material, 64Ni, followed by cold copper, iron, and zinc. Experiments are in progress to compare the results of this method and results obtained from TETA titrations and ICP measurements.

14 - 89Zr Production with Solution Target: Seeking Alternatives to Oxalic Acid in Final Product

Production and Automation - Friday 14 June 2013 10:03

Presenter: Dr. DEGRADO, Timothy (Mayo Clinic)

Objectives: The PET radiometal 89Zr (T1/2=3.3 d) has recently received growing attention for radiolabeling antibodies to accomplish ImmunoPET. To enable more self-shielded cyclotrons the ability to access this isotope and to reduce processing time, we have developed a solution target approach that avoids dissolution of solid target materials. We also began to address the potential toxicity issues associated with use of oxalic acid as the eluent of the commonly utilized hydroxamate column. Methods: The Y(NO3)3·6H2O salt (89Y, 100% natural abundance) was dissolved in 1.7 M HNO3 (3 mL) to prevent precipitation of the target material. The 89Y / 89Zn solution was trapped on an in-house produced hydroxamate column (75 mg) that trapped the 89Zr. The column was washed with 72 mL 2M HCl to remove Y. The 89Zr was eluted with oxalic acid (1 M) or the following experimental solutions: citric acid, acetic acid, malonic acid, succinic acid, ascorbic acid (1 M), EDTA (0.01 M), DTPA (0.05 M), NaH2PO4 (1 M) and NaH2PO4/Na2HPO4 (1 M, pH 7). The resulting solution was neutralized as needed with Na2CO3, and utilized for labeling of DFO-conjugated antibodies. Results: After irradiation of the Y(NO3)3 solution for 2 h at 20 µA, ~ 4 mCi of 89Zr was produced. 89Zr was quantitatively trapped on the hydroxamate column. Following washing of the column with 2M HCl, >95% 89Zr was eluted with oxalic acid. Elution efficiency was suboptimal for citric acid, acetic acid, malonic acid, succinic acid, ascorbic acid, EDTA, and DTPA. The use of NaH2PO4 (1 M) and NaH2PO4/Na2HPO4 (1 M, pH 7) resulted in 65-80% elution efficiency, but was dependent on elution time. Conclusions: 89Zr production using a solution target is feasible, although yields are moderate at low beam currents. The use of NaH2PO4 (1 M) and NaH2PO4/Na2HPO4 (1 M, pH 7) as elution agents simplifies the 89Zr labeling conditions in relationship to oxalic acid. Neutralization of the labeling solution is no longer required, and problems caused by precipitation and/or toxicity of oxalate salts are avoided.

15 - Nanoscale Production of Molybdenum-99: Parasitic Neutron Irradiation and Chemical Partitioning of Uranyl Sulfate Solutions

Tc - Saturday 15 June 2013 10:40

Presenter: Dr. ELLISON, Paul (University of Wisconsin)

Objectives: Recently there has been considerable interest in the production of molybdenum-99 without the use of highly-enriched uranium [1]. By taking advantage of aqueous uranyl-salt solution fission fuel, the process of molybdenum isolation from the fuel can be significantly simplified. In the present work, parasitic neutrons from routine copper-64 production are used to create low levels of 99Mo and other fission products in a uranyl sulfate solution, allowing for their use in tracer-level chemistry experiments. Methods: Natural uranium nitrate hexahydrate was used to prepare 100 mL of 60 mM uranyl sulfate in 0.1 M H2SO4. An annular irradiation vessel was used to contain this solution in close proximity to the copper-64 production target on the University of Wisconsin RDS-112 cyclotron. After irradiation with parasitic neutrons produced in the 64Ni(p,n)64Cu nuclear reaction, the solution is passed through a column of porous titania resin, followed by washing with 0.1 M H2SO4, water, and 0.1 M NaOH. High-purity germanium gamma spectroscopy is used to quantify 99Mo and other radionuclides and monitor their partitioning across the procedure. Results: A six hour 64Cu production irradiation of the uranium solution produces 650 ± 50 nCi of molybdenum, allowing for accurate quantification of its behavior on the titania extraction process. Other neutron-activation products that partially extract onto the titania resin include 239Np, 132Te, 97Zr, and 131, 132, 133, 35I. The efficacy of this chemical procedure at extracting and isolating 99Mo is being monitored after subsequent, weekly re-irradiations of the uranyl sulfate solution. Conclusions: The parasitic neutron irradiation of uranyl sulfate solutions allows for the nanoscale production of molybdenum-99 and other neutron-induced reaction products for useful chemical partitioning studies. [1] U.S. Department of Energy Office of Inspector General Office of Audits and Inspections. The Global Threat Reduction Initiative's Molybdenum-99 Program. OAS-L-12-07, Washington, July 2012.

16 - The Neurotensin Analogue Ac-K(NOTA)-P-NMeArg-RPY-Tle-L for PET Imaging and Therapy of NT Expressing Cancer Cell Lines

Imaging - Friday 14 June 2013 16:24

Presenter: Dr. MEBRAHTU, Efrem (Washington University School of Medicine)

Objective: Neurotensin receptors (NTR) are expressed in a number of cancers such as human ductal pancreatic adenocarcinoma (75%), colon adenocarcinoma, and invasive ductal breast cancer (91%). This work aims to develop PET imaging and therapy agents using the neurotensin analogue NT(6-13), Ac-K(NOTA)-P-NMeArg-RPY-Tle-L (NTA1) for early detection and therapy of neurotensin receptor (NTR) positive cancers. Methods: NTA1 was obtained from CPC scientific. In vitro and in vivo studies of [64Cu] and [68Ga] labeled NTA1 were conducted using human colon adenocarcinoma HT29 cell lines. For in vivo studies nude mice bearing HT29 xenograft were employed. Results: The neurotensin analogue was labeled with 64Cu and 68Ga with high binding Kds of 4.8 + 2.8 nM and 9.8 + 5.4 nm respectively, with HT29 cells. Bound activity was internalized quickly. A blocking study with “cold” peptides confirmed the specificity of binding. PET imaging and post-PET biodistribution analysis demonstrated high tumor uptake, though significant kidney and liver uptakes were also observed.

17 - Automated Module for the Separation of Radiometals

Production and Automation - Friday 14 June 2013 10:21

Presenter: Mr. VALDOVINOS, Hector (University of Wisconsin-Madison)

Objectives : To automate the separation of radiometals monitoring radioactivity for PET tracer labeling. Methods : Modular radiochemistry systems have evolved following the automation design of Siikanen et al, fitted with compact radiation detectors. A peristaltic pump drives fluid through a low-volume manifold, with two-way pinch valves accessing reservoirs for reagents and ion exchange resin mini-columns. The valves and pump are controlled by a relay card programmable with LabVIEW software, which also acquires time-activity curves from three point-like detectors (10x10 mm CsI / HTV S9269 PIN diodes) at key points on the fluid path. Hydroxamate resin (100mg) was used for the separation of 45Ti and 89Zr from irradiated and then dissolved scandium and yttrium foils, respectively; and a dual column system of AG50-x8 (125 mg) and UTEVA (100mg) resins was used to purify 66/68Ga separated from a zinc foil by thermally assisted diffusion (. The Zn foils are placed inside a 15mm ID glass tube coupled with the module for automatic delivery of solvents, and then heated at 400°C for 15-60 min under an argon atmosphere. Gallium is etched from the Zn foil with 4 mL 0.05M HCl and then run through the dual column system for purification. The three isotopes were eluted in sequential 200 µl fractions: 45Ti in 3M HCl / 3% H2O2 mobile phase, 89Zr in 1M oxalic acid and 66/68Ga in 0.1M HCl. Reactivities with DFO and NOTA were measured by competitive titration. Results : The reproducibility and reliability of the automatic separation of 89Zr, 45Ti and 66/68Ga has been proven. The trapping and eluting efficiency (in the three most concentrated fractions) for 89Zr was 98±2% and 62±5% (n=7), respectively; and for 45Ti, 49±5% and 41±2% (n=3), respectively. For 66/68Ga the thermal diffusion efficiency was 39% for a 250um foil, trapping was 100% efficient in both columns and the elution in the two most concentrated fractions was 74%. The separation of Zr and Ti takes ~30 min, and for Ga the separation takes ~45min plus the heating time for thermal diffusion. 89Zr and 66/68Ga had reactivities >1Ci/umol.

18 - Target Preparation and Yield Measurements for the natCr(p,n)52Mn Reaction for Proton Energies <15 MeV

NEW APPROACHES - Sunday 16 June 2013 10:50

Presenter: WOOTEN, A. Lake (Mallinckrodt Institute of Radiology, Washington University School of Medicine AND Department of Biomedical Engineering, Washington University in St. Louis)

The radioisotope 52Mn has favorable half-life (t1/2=5.6 d) and positron-emission (Eβ+,avg=242 keV; BR=29.6%) characteristics to be a highly useful tool for PET-based molecular imaging of important processes in numerous areas of biomedical research. Although its relatively high emission of γ radiation (Γ15 keV=18.4 R cm2/mCi h[1]) would likely disqualify 52Mn from clinical use, the research and development applications for a traceable isotope of Mn are abundant. Currently, the CSISRS/NNDC database includes only 2 cross-section data sets with more than 5 data points for this reaction, and only one of those data sets extends above a proton beam energy (Ep) of 11 MeV. That data set shows—just like many other (p,n) reactions—a local excitation peak at Ep~15 MeV, which bodes well for scaled-up production of 52Mn using biomedical cyclotrons with similar energies. Perhaps one reason for the limited supply of cross-section data is the difficulty in fabricating Cr targets that lend themselves to cross-section measurement. Since Cr is too hard and brittle to be hot-rolled into a thin foil, we used an alternative method for fabricating such a foil that was similar to previously reported work by Tanaka and Furukawa[2] (1959). In our work, natural “hard” Cr was electroplated in an industrial bath onto a disc that had been cut into a piece of Cu sheet and then masked on one side with a vinyl lacquer. The resulting Cu disc, with Cr on one side, was placed in concentrated nitric acid, which rapidly dissolved the Cu disc, leaving a clean disc of thin Cr foil. This disc was bombarded briefly with 14.7 MeV protons at a very low current and allowed to decay for a few days. Gamma spectroscopy of the foil confirmed production of 52Mn in the Cr, but this preliminary cross-section was substantially less than expected. In ongoing work, the data analysis calculations will be revisited, and numerous stacked foil targets will be bombarded to yield more data and results. References: [1] Smith, D.S.; Stabin, M.G. Health Phys. 2012, 102, 271-291. [2] Tanaka, S.; Furukawa, M. J. Phys. Soc. Jap. 1959, 14, 1269-1275. All nuclear data accessed via NNDC, unless otherwise indicated.

19 - Pycup – a New Cage-Like Chelate for the Coordination of Cu Radioisotopes

CHELATES - Sunday 16 June 2013 09:15

Presenter: Dr. BOROS, Eszter (Massachusetts General Hospital / Harvard Medical School)

Cu-64 has gathered great interest over the past decade for PET imaging of peptides and antibodies due to its favorable emission characteristics. One of the great challenges for employing Cu-64 for targeted imaging is in overcoming the high lability of the Cu(II) ion. In the body, Cu(II) rapidly undergoes ligand exchange, even when complexed with ligands that form chelates with very high thermodynamic stability. Macrocyclic, cross-bridged (CB-TE2A) or cage-like (SarAr) complexes provide high thermodynamic stability, and importantly, high kinetic inertness with respect to dissociation. These ligands, however, are synthesized using low-yielding, multi-step procedures which can limit donor atom versatility and subsequently labeling conditions. Here we describe the ligand system pycup and its corresponding derivatives as alternative bifunctional Cu-64 chelators. The Cu-64 complex of the non-derivatized di-acetato derivative showed rapid clearance from all organs including only 0.04 % ID/g activity in the blood after 2h in mice. A bifunctional version of this ligand (pycup1A1R) was also synthesized and successfully conjugated to a fibrin-targeted peptide for thrombus imaging. We will describe the labeling conditions, inertness, and biodistribution of these Cu-64 derivatives and their application in imaging of models of thromboembolic disease.

20 - Solid-Metal Targetry on a GE PETtrace for the Production of High-Valent Metal Radionuclides

Production and Automation - Friday 14 June 2013 09:45

Presenter: Dr. HOLLAND, Jason (Massachusetts General Hospital)

As the number and type of radiotracers continues to expand, access to a broad range of radionuclides is becoming increasingly important. Here we report the design and implementation of a new, first generation solid-metal target for use on a clinical 16.5 MeV GE PETtrace cyclotron. The water-cooled aluminium target holder can accommodate multiple solid-metal foils of variable thickness (0.1 – 2.0 mm; diameter = 25 mm), orientated at a 90° angle of incidence to the beam, and allows for a versatile target geometry (single or stacked foils). The utility of our target design has been demonstrated by the production of clinically relevant quantities of the high-valent metal radionuclides 89Zr and 90Nb at beam currents ranging from 2 to 10 μA. Zirconium-89 was produced and isolated in accordance with established procedures (1). Niobium-90 (t1/2 = 14.60 h; I(beta+) = 51.2%; E(beta+, mean) = 0.66 MeV; E(beta+, max.) = 1.50 MeV), a promising radionuclide for use in positron emission tomography (PET), was produced by the natZr(p,n)90Nb transmutation reaction on natural Zr foils (0.15 mm; 90Zr abundance = 51.45%) (2, 3). Use of natural Zr targets yielded a range of Nb radionuclides including 90Nb (t1/2 = 14.60 h; 97.86%), 92mNb (t1/2 = 10.15 d; 0.47%), 95mNb (t1/2 = 3.61 d; 0.51%), and 96Nb (t1/2 = 23.35 h; 0.27%), as well as the radionuclidic impurities 89Zr (t1/2 = 78.41 h; 0.77%) and 87mY (t1/2 = 13.37 h; 0.11%), and daughter nuclides 95Nb (t1/2 = 34.991 d) and 87Y (t1/2 = 79.8 h). In addition, we have developed a new, simple, one-step method for separating niobium radionuclides from bulk Zr and other chemical impurities which will facilitate future radiochemical studies using 90Nb-based PET radiotracers. In conclusion, development of solid-metal targetry for the GE PETtrace offers the exciting possibility for many radiochemistry sites to expand their portfolio to include a wide range of metal radionuclides. References (1) Holland et al., Standardized methods for the production of high specific-activity zirconium-89; Nucl. Med. Biol., 2009, 36, 729-739. (2) Busse et al., Radiochemical separation of no-carrier-added radioniobium from zirconium targets for application of 90Nb-labelled compounds; Radiochim. Acta, 2002, 90, 411-415. (3) Radchenko et al, 90Nb – a potential PET nuclide: production and labeling of monoclonal antibodies; Radiochim. Acta. 2012, 100, 857-863.

21 - Molecular Imaging of Multiple Myeloma

Imaging - Friday 14 June 2013 14:33

Presenter: Dr. SHOKEEN, Monica (Washington University)

Multiple myeloma is the second most commonly diagnosed hematologic cancer characterized by immunoglobulin secreting malignant plasma B-cells. Myeloma arises from post-germinal center B-cells and its pathogenesis involves both acquired intrinsic genetic abnormalities as well as changes to the bone marrow microenvironment. Interactions between myeloma cells and bone marrow stroma enhance tumor survival. Clinical and pre-clinical data demonstrate that changes in the expression of adhesion molecules facilitate the dissemination of plasma cells out of the bone marrow, leading to malignant transformation, tumor spreading and immortalization. Very late antigen-4 (VLA-4; also called α4β1 integrin) is a non-covalent, heterodimeric, transmembrane receptor that recognizes the QIDS (Gln-Ile-Asp-Ser) and ILDV (Ile-leu-Asp-Val) motifs of two widely known ligands, the vascular cell adhesion molecule-1 (VCAM-1) and fibronection respectively VLA-4 is implicated in tumor cell trafficking, osteoclast stimulation and drug resistance in multiple myeloma. Biomedical imaging techniques such as 18F-fluorodeoxyglucose (FDG)/Positron Emission Tomography (PET), skeletal survey, bone scintigraphy and magnetic resonance imaging (MRI) are routinely used for staging and post-treatment follow up in multiple myeloma patients. However, there are no specific multiple myeloma imaging agents used clinically. VLA-4 targeted novel molecular imaging of multiple myeloma has the potential to improve early-stage diagnosis and management of patients receiving compounds that affect the tumor cells as well as the microenvironment. In this meeting, we will present a proof-of-principle study that demonstrates novel imaging of VLA-4 positive 5TGM1 murine myeloma cells using a high-affinity, VLA-4 targeted PET probe respectively in vitro, and in vivo using small animal PET/CT imaging in a subcutaneous and intraperitoneal (extra-osseous) immunocompetent mouse model of multiple myeloma (PLoS ONE 8(2): e55841). Additionally, potential of small animal MRI, near-infrared (NIR) optical imaging and Gallium-68 PET agents for multiple myeloma imaging in orthotopic mouse models of murine myeloma will be presented.

22 - Nitroimidazole Derivatives of an Acyclic Chelator as Potential PET Imaging Agents of Hypoxia Using Ga-68

CHELATES - Sunday 16 June 2013 09:33

Presenter: RAMOGIDA, Caterina F. (University of British Columbia; TRIUMF)

Purpose: Positron-emission tomography (PET) is an important imaging modality employed extensively in nuclear medicine. Traditionally, PET imaging agents were dominated by use of organic nuclides such as F-18, whose production is dependent on an on-site cyclotron. With a half-life of 68 min, Ga-68 is an attractive alternative to conventional F-18 labeled PET imaging agents, since Ga-68 is produced from a commercially available 68Ge/68Ga generator system, making PET a less expensive and more accessible technique. Recently, our group has developed the linear chelating agent, H2dedpa (N4O2) that binds Ga(III) quickly under mild conditions, and possesses ideal properties to be incorporated into a Ga-68 PET imaging agent [1]. Herein, we report bifunctional derivatives of H2dedpa that incorporate a nitroimidazole (NI) moiety to investigate specific targeting of hypoxic tumour cells, given that in the absence of sufficient oxygen NI will be reduced and retained exclusively in hypoxic cells.[2] Methods: Two families of bifunctional chelators (BFCs) based on the H2dedpa scaffold were synthesized. Firstly, N-alkylated derivatives were prepared via alkylation of the 2° nitrogens of the ethylenediamine backbone with the appropriate 1-(ω-bromoalkyl)-nitroimidazole targeting moiety to produce a small library of compounds. Secondly, a bifunctional derivative of H2dedpa was prepared (H2dedpa-Bn-NCS) to synthesize a small library of backbone functionalized chelates which retained the native binding sphere of H2dedpa via conjugation of the appropriate nitroimidazole-ethylamine in a thiourea bond coupling reaction. The BFCs were screened for their ability to bind gallium, using non-radioactive gallium. The compounds were radio-labeled with both Ga-67 (γ-emitter), and Ga-68, stability studies against human apo-transferrin were performed at 37°C and evaluated via PD-10 column elution. Results: The pro-ligands were labeled with Ga-67 and Ga-68, and all showed labeling efficiencies >95% after only 10 minutes at room temperature. Both classes of compounds (N-alkylated and backbone functionalized) showed excellent stability (>95% intact) against human apo-transferrin after 2 hours at 37 °C. Furthermore, the ability of the compounds to specifically penetrate hypoxic cells will be tested in vitro using a 3D tumour spheroid model of hypoxia in the near future. 1. Boros, E.; Ferreira, C. L.; Cawthray, J. F.; Price, E. W.; Patrick, B. O.; Wester, D. W.; Adam, M. J.; Orvig C. J. Am. Chem. Soc. 2010, 132(44),15726-15733. 2. Wilson, W. R.; Hay, M. P. Nat. Rev. Cancer 2011, 11(6), 393-410.

23 - Producing Radiometals in Solution Targets

Production and Automation - Friday 14 June 2013 12:18

Presenter: Dr. HOEHR, Cornelia (TRIUMF)

We have developed a solution target system for the quick production of various radiometal isotopes using the existing infrastructure of a liquid target. With this approach, the acquisition of costly generators, if available, or solid target stations are avoidable. This is especially important if the quick production of several metal isotopes would be advantageous for preliminary chemical and/or biological studies. Solution target systems can therefore enable the development of new tracers with matched physical and pharmacokinetic properties. All irradiations took place at the TR13, a 13MeV cyclotron at TRIUMF, Vancouver. To date, three different isotope productions have been investigated. Tc-94m was produced via the Mo-94(p,n) reaction starting with a MoO_3 or (NH_4)_6Mo_7O_24 solution of natural abundance. Bombardments were carried out with 5 μA of proton beams for up to one hour and with measured yields of up to 110 MBq at end-of-bombardment (EOB) [1]. A solution of Ca(NO_3)_2 (natural abundance) was irradiated to produce Sc-44 via the Ca-44(p,n) reaction with a proton current of 2-7 μA for one hour. Up to 9.25 MBq at EOB were produced. Finally, a ZnCl_2 solution was irradiated to produce Ga-68 via the Zn-68(p,n) reaction. Details about target design, loading systems and solution concentrations and lessons learned for all three isotopes will be presented. [1] C. Hoehr et al., Appl. Radiat. Isot. Vol. 70, p. 2308, 2012

24 - Purification, Characterization and Radiolabelling of Radiometals (94mTc, 44Sc) Obtained from Liquid Targets

NEW APPROACHES - Sunday 16 June 2013 10:09

Presenter: OEHLKE, Elisabeth (TRIUMF)

The production of radiometal isotopes using a liquid target system leverages readily available systems in modern cyclotron facilities and might therefore help to increase the availability of new and promising radiometals, especially for preliminary studies. Here we present the isolation and radiolabelling of two positron-emitting radiometals, 94mTc and 44Sc, from salt solutions which were irradiated at the TR13, a 13 MeV cyclotron at TRIUMF, Vancouver. 94mTcO4 was extracted from irradiated ammonium heptamolybdate tetrahydrate solutions using Aqueous Biphasic Extraction (ABEC) resin [1]. The overall isolation efficiency was 70%. The final product was characterized by radio-TLC, which indicated that it consisted predominantly (>99%) of free pertechnetate. The time from end-of-bombardment (EOB) to having the purified 94mTc was approximately 50 min [2]. For the separation of 44Sc from irradiated natCa(NO3)2 solutions, a DGA (N,N,N',N'-tetra-n-octyl-diglycolamide) resin [3] was used. Sc3+ in 6M HCl is quantitatively absorbed on the resin and can be eluted using a small volume of 0.05M HCl. The separation process can be accomplished within 30 min. The final product was characterized for isotopic and chemical composition. 44Sc produced using this method was successfully incorporated into DOTA-containing constructs (20 nmol DOTA (0.1 mM), 95°C, pH 4, 30 min, 97% yield). Efforts are also underway to explore the feasibility of alternative chelates. [1] T. J. Morley et al., Nucl. Med. Biol. Vol. 39, p. 551 – 559. [2] C. Hoehr et al., Appl. Radiat. Isot. Vol. 70, p. 2308 – 2012. [3] M. Bunka et al., Annual Report 2011, Paul Scherrer Institut, p.59.

25 - Isolation of the Auger Emitter Erbium-165

Production and Automation - Friday 14 June 2013 11:35

Presenter: Mr. ELEMA, Dennis (Technical University of Denmark)

Introduction 165Er is a promising radionuclide for internal radiotherapy, decaying via EC with a 10.6h half-life to the ground state of stable 165Ho. Its ionizing radiation emissions are limited to x-rays and auger electrons under 40keV. Of particular interest are the low energy electrons resulting from the auger cascade, which are high-LET with a limited range. This has the potential for maximizing localized dose and leaving untargeted entities relatively dose-free. 165Er is created in cyclotrons via the (p,n) or (d,2n) reaction on naturally monoisotopic 165Ho. Conveniently, deuteron irradiation also populates 166Ho (1.2 days, β-) which acts as a holmium tracer during development. Isolation of trace erbium from bulk holmium is a challenge due to the chemical similarities between neighboring rare-earth elements. However the difference in ionic radii of the +3 cations gives rise to different binding constants for compounds formed with weakly chelating ligands, allowing separation based upon complex charge. The aim of this work is to optimize chromatographic separation of 165Er from 200-400mg quantities of Ho on strong cation exchange resin with α-hydroxyisobutyrate as the complexing ligand. Methods Holmium foils (1mm x 1cm2, 99.9% REA) were irradiated by 10uA 8 MeV deuterons from a GE PETtrace-800. Foils were dissolved in 2M HCl, and dried. The residue was taken up in 0.01M HCl and added to a 20cm by 18mm(ID) column packed with AG 50Wx4 (100-200 mesh) that was equilibrated with the mobile phase, ammonium alpha-hydroxyisobutyrate (0.05M, pH 4.7). The column was then run at a flow rate of 3ml/min with flow controlled by a peristaltic pump. The elution profile was determined by counting fractions in a MikroWin liquid scintillation counter. Energy resolution on the electron emissions discriminated Er-165 decay from that of 166Ho, and half-life analysis of standards made window corrections possible. Results The relative selectivity of Ho to Er by the DOWEX 50WX4 resin is 1.8, and the resolution of the separation described above was 0.99. Many routes are available for further optimization, and these will be explored and the results presented.

26 - 99mTc-Pertechnetate Manufacturing Using a Medium-Energy Cyclotron: from Target Irradiation to Quality Control

Tc - Saturday 15 June 2013 09:45

Presenter: SELIVANOVA, Svetlana (Sherbrooke Molecular Imaging Center, Université de Sherbrooke)

Technetium-99m (^{99m}Tc) is the most widely used radioisotope in nuclear imaging. Currently, ^{99m}Tc is obtained from a ^{99}Mo generator, which, in turn, is produced from highly-enriched ^{235}U (typically 93%) in nuclear reactors. Recent shortage of ^{99m}Tc supply created awareness about the need to develop alternative ^{99m}Tc production technologies in time for the aging nuclear reactors become decommissioned or converted to low-enriched ^{235}U (<20%). Initial theoretical calculations and experimental results suggest that cyclotrons could provide substantial amount of required ^{99m}Tc. We investigated the influence of irradiation parameters (beam energy, beam time) and ^{100}Mo target characteristics on radiochemical yield and radionuclidic purity of ^{99m}Tc using a medium-energy TR24 cyclotron. Enriched (>99%) ^{100}Mo targets (0.67-1.25 mm thickness) were irradiated at 20-24 MeV beam energy and 15-30 μA current to produce ^{99m}Tc via the ^{100}Mo(p,2n)^{99m}Tc nuclear reaction. Irradiated targets were dissolved and ^{99m}Tc was isolated from the crude mixture as sodium ^{99m}Tc-pertechnetate. An automated cassette-based separation unit was developed for this purpose. A variety of resins was tested for optimal ^{99m}Tc separation. ^{99m}Tc-pertechnetate was obtained in >98% radiochemical and >99% radionuclidic purity. It can be used for kit labeling to produce other ^{99m}Tc-radiopharmaceuticals. Inherent to cyclotron-produced ^{99m}Tc presence of longer-lived ^{95}Tc, ^{95m}Tc, and ^{96}Tc will contribute to the additional radiation dose and should be accounted for when establishing new Pharmacopoeia standards.

28 - Opening Remarks

Production and Automation - Friday 14 June 2013 08:55

Presenter:

29 - An Overview of PET Radiometal Production

Production and Automation - Friday 14 June 2013 09:00

Presenter: LAPI, Suzanne (Washington University)

Positron emission tomography, with its high sensitivity and resolution, is growing rapidly as an imaging technology for the diagnosis of many disease states. The success of this modality is reliant on instrumentation and development of effective, novel, targeted probes. Initially, research in this area was focused on the four PET isotopes 11C, 13N, 15O, and 18F, but the short half-lives of these isotopes limit radiopharmaceutical development to those that probe rapid biological processes. To overcome these limitations, there has been a rise in alternative radionuclide development in recent years including 64Cu, 89Zr and many other radionuclides.. An overview of cyclotron radionuclide production in general will be presented and then this talk will focus on the cyclotron production of the radiometals from past to present.

30 - Active Urokinase Plasminogen Activator in Castration-Resistant Prostate Cancer with an Internalizing Antagonistic Human Antibody

Imaging - Friday 14 June 2013 15:10

Presenter: LEBEAU, Aaron

The development of new therapeutics for castration-resistant prostate cancer (CRPC) is greatly hindered by the inability to measure therapeutic response in patients. New imaging agents are desperately needed to aid in drug development. One attractive target for imaging CRPC is the plasminogen activation system (PAS). Consisting of the secreted serine protease urokinase plasminogen activator (uPA), the receptor of uPA (uPAR) and the endogenous inhibitor of uPA (PAI-1), the PAS is highly over-expressed in metastatic CRPC tissue. Using a human fragment of antigen binding phage display library, we have developed a novel human antibody that inhibits secreted and uPAR bound forms of uPA. The anti-uPA antibody, U33 IgG, was found to be a potent competitive inhibitor of uPA and was highly selective demonstrating no cross-reactivity with other secreted prostate cancer-associated proteases. Subsequent in vitro studies, using U33 IgG labeled with 111In (111In-U33 IgG), found that the U33 mimicked the function of PAI-1 resulting in internalization of the uPA-U33 complex when bound to uPAR. As a SPECT/CT imaging probe, 111In-U33 IgG demonstrated a high tumor uptake of 43% ID/g at 72hrs in PC3 xenograft mice. The 111In-U33 IgG probe was able to detect both soft tissue and osseous lesions in a metastatic CRPC model. In summation, we have developed a novel and potent tracer for imaging metastatic CRPC that can be directly translated into the clinic by virtue of its human antibody scaffold.

31 - Synthesis and In Vivo Evaluation of 64Cu-CB-TE1A1-PEG28-A20FMDV2 an alpha-nu-Beta6-

Imaging - Friday 14 June 2013 15:48

Presenter: HU, Lina

Copper-64 is an attractive radionuclide for both imaging and therapy. This study compares the chelator 11-carboxymethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-4-methanephosphonic acid (CB-TE1A1P), a chelator that can be radiolabeled under ambient conditions to the widely used chalator 1,4,7,10-tetra-azacyclododecane-N,N'N",N'"-tetraacetic acid (DOTA) when conjugated to the established integrin alpha_nuBeta_6-targeting peptide, PEG_28-A20FMDV2. PEG_28-A20FMDV2(1) was synthesized using solid-phase Fmoc chemistry and DOTA-tris(tBu)ester) or CB-TE1A1P were conjugated to created DOTA-1 and CB-TE1A1P-1 (see PDF with figure 1A). Following TFA cleavage, the conjugatews were analyzed by HPLC and MALDI. Radiolabeling with copper-64 (37'C, 15 min) was monitored by radio-HPLC. Cell binding and internalization were assessed using Dx3puroBeta_6 (alpha_nuBeta_6-positive) and Dx3puro (alpha_nuBeta_6-negative) cells. Small animal imaging and biodistribution studies were done in female athymic mice with paired Dx3puroBeta_6 and Dx3puro tumours. DOTA-1 (HPLC R_7=16.3 min; MALDI m/z-3852.1, calculated in 3852.2) and CB-TE1A1P-1 (HPLC R_t = 15.9 min; MALDI m/z=3826.1, calculated in 3825.2) were radiolabeled with /geq 95% yield. ^64Cu-DOTA-1 and ^64Cu-CB-TE1A1P-1 showed hgh binding (61.0+/1 1.1% and 65.3 +/- 1.8%, respectively) and internalization (46.2 +/- 1.7% and 47.4 +/- 0.6%, respectively) to alpha_nuBeta_6-positive cells, compared to <5% bindning to the alpha_nuBeta_6-negative control (See PDF of Figure 1B]. Biodistribution showed both conjugates had little demetalation (<3.5% ID/g) but ^64 Cu-DOTA-1 demonstrated faster clearance from the kidneys. HOwever, ^64Cu-CB-TE1A1P-1 showed a higher positive/negative tumor uptake ratio at 4 hours p.i. compared to ^64Cu-DOTA-1, 3.8:1 vs 2.5:1, respectively (n=3). Both conjugates were radiolabeled in good yield under mild conditions. Both conjugates showed similar bindin gto Dx3puroBeta_6 cells/tumors but CB=TE1A1P-1 demonstrated higher specificity for the alpha_nuBeta_6 target. (See PDF Attached for figures) Fig. 1A) Structures of the two radiolabeled conjugates: DOTA -PEG_28-A20FMDV2 and CB-TE1A1P-PEG_28-A20FMDV2 Fig. 1B) Cell binding results for each peptide conjugate and its internalization relative to total amount bound 9n=4)

32 - Imaging Biomarkers

Imaging - Friday 14 June 2013 13:30

Presenter: LEWIS, Jason

For good reason, discovering biomarkers that can be assayed from biological fluids has long been regarded as a “holy grail” for medical diagnostics. Indeed, several decades of systematic research have identified many secreted molecules differentially regulated in the context of malignant cancers that are now routinely measured in man to screen for disease onset, develop prognoses, and monitor tumor response or recurrence. Their rapid commercialization, favorable economics, and simple experimental outputs (lending itself to standardization for multi-center trials) have engendered the widespread use of many analytical platforms to measure serum biomarker levels (e.g. ELISAs). The resulting vast body of epidemiological data has consistently reinforced the notion that, while exciting progress has been made, we have yet to find a single, “smoking-gun” serum biomarker that can be effectively applied to address all of the above-mentioned clinical issues for a given cancer. However, despite their considerable advantages, many circulating biomarkers have well documented limitations. One prominent shortcoming in oncology is a high frequency of false positive indications for malignant disease in upfront diagnosis. Because one common cause of false positivism is biomarker production from benign disorders in unrelated host tissues, we hypothesized that probing the site(s) of biomarker secretion with an imaging tool could be a broadly useful strategy to deconvolute the meaning of foreboding but inconclusive circulating biomarker levels. In preparation to address this hypothesis clinically, we have developed a series of 89Zr-radiolabeled antibodies that specially target serum biomarkers, and as a result overcome the documented limitations of these tests.

33 - 99Mo/99mTc Supply - Current Status, Update and Path Forward

Tc - Saturday 15 June 2013 10:58

Presenter: SCHAFFER, Paul

A team of four Canadian institutions have combined expertise and infrastructure to demonstrate multi-Curie-level production of 99mTc via high current (80 – 240 μA), medium energy (16.5 – 18 MeV) proton irradiation of enriched 100Mo targets. The approach taken is built on a process that saw new technology implemented for a robust high-current solid target design, 100Mo target manufacture, solid target transfer to and from the cyclotron beam port to a hotcell and target dissolution providing purified sodium pertechnetate Na[99mTcO4] acceptable for radiopharmaceutical formulation. This seminar will include a summary of the work underway, including steps associated with scale-up, regulatory affairs and clinical validation with a goal of having a cost-effective process in place for the 2016 Chalk River reactor shutdown. A summary of the current status of various 99Mo and 99mTc production alternatives will also be discussed.

34 - DIRECTED DISCUSSIONS

Tc - Saturday 15 June 2013 11:16
Presenter:

36 - Tales from the Crypt - Adventures with Sarcophagine Chelators

CHELATES - Sunday 16 June 2013 09:51
Presenter: Dr. PACKARD, Alan (Boston Children's Hospital/Harvard Medical School)

Retention of the radiometal is recurring challenge in the development of radiometal-labeled proteins. It is a particular challenge in the case of radiolabeled antibodies that have circulation times of 3-4 days and are used in combination with longer lived radionuclides such as 64Cu and 89Zr, where this imposes significant constraints on the metal-bifunctional chelator complex. The limitations of existing, albeit widely used, bifunctional chelators such as DOTA in this application has generated significant interest in the development of a new generation of bifunctional chelators that retain the metal over prolonged periods of time in vivo. Sarcophagine-based bifunctional chelators are particularly attractive for this application because of they form extraordinarily stable complexes with 64Cu(II) under mild conditions. Previous studies showed that 64Cu forms an extremely stable complex with SarAr, a derivative of the prototypical sarcophagine ligand diamsar that incorporates a p-aminobenzyl moiety to facilitate conjugation to proteins. Evaluation of the biodistribution of a series of 64Cu-labeled SarAr conjugates of derivatives of the ch14.18, an antibody that binds to the GD2 receptor expressed by neuroblastoma and melanoma, confirmed that the metal was, in fact, tightly retained in the complex with little loss of metal up to 48 h post-injection. Contrary to expectations, however, we observed very high renal uptake of 64Cu-labeled ch14.18.ΔCH2 (MW 100 kDa) at 48 h post-injection (PI). We hypothesized that this high renal uptake was a consequence of the interaction of the high positive charge associated with the Cu-SarAr complex and the negatively charged basal cells of the glomerulus. To test this hypothesis we prepared a series of Sar derivatives with progressively lower net positive charges. A series of three Sar bifunctional chelators were synthesized, conjugated to ch14.18.ΔCH2 using EDC (1-ethyl-3-[3-dimethylaminopropyl]carbodiimide), and the immune-conjugates purified by semi-preparative HPLC using a size exclusion column. The antibody-Sar conjugates were labeled with 64Cu and injected into mice via the lateral tail vein. Small animal PET scans were obtained at 1, 24, and 48 h post-injection. Following the 48 h PET scan, a CT scan was obtained and the animals were sacrificed, dissected, and selected tissues were weighed and assayed for 64Cu. PET and CT scans were analyzed using AMIDE. The biodistribution data showed that the bifunctional chelator charge significantly alters the renal uptake of the labelled protein, decreasing it from approximately 40% ID/g for SarAr, which has a net charge of +4, to 28% ID/g for CO2H-Sar-CH3 (net charge +1), and 5% to 6% for CO2H-Sar-NH2 and CO2H-Sar-Sulphonate (net charge +2 and 0, respectively). In contrast, uptake by other tissues, such as liver, is relatively unaffected by the large change in the charge of the bifunctional chelator (e.g,. 12.8% ID/g for SarAr and 10.2% ID/g for CO2H-Sar-Sulphonate). In summary, decreasing the net charge of on the bifunctional chelator decreased the renal uptake of the 64Cu-labeled antibody approximately 8-fold, from 40% ID/g to 5% ID/g suggesting that the high Cu affinity of these chelators might be exploited without producing unacceptably high renal retention. Acknowledgement: Children's Hospital Radiology Foundation.

37 - Connecting Pathology, Fluorescence Microscopy and Molecular Imaging and Therapy Through Advances in Coordination Chemistry

Tc - Saturday 15 June 2013 09:00
Presenter: VALLIANT, John

The ability to visualize specific biochemical targets is a fundamental component of both nuclear medicine and pathology. Through advances in coordination chemistry of radiometals it is possible to create new constructs that can better link these fields and in vitro and in vivo imaging. This requires the development and evaluation of new chelates and the associated coordination complexes and the creation of new bioconjugation strategies. A review of strategies for the preparation of targeted molecular imaging probes that can be visualized using fluorescence based techniques and SPECT/PET will be presented. This will include the development of a new generation of isostructural luminescent and radio-imaging probes derived from organometallic complexes of 99mTc(I) and Re(I). The ability to tune pharmacokinetics, multivalency and optical properties through simple modifications of the coordination sphere will be presented along with strategies for converting these constructs into radiotherapy and bioactive constructs. The application of similar strategies to other emerging metals and to fields outside of oncology will also be discussed.

38 - Metal Building Blocks for Target-Specific Delivery of Radiation

CHELATES - Sunday 16 June 2013 08:30

Presenter: SANTOS, Isabel (Radiopharmaceutical Sciences, Centro Tecnologico e Nuclear, Instituto Superior Tecnico, Universidade Tecnica de Lisboa)

Radiopharmaceutical chemistry is an important topic in Life Sciences, aiming to design radiopharmaceuticals for Molecular Imaging (SPECT and PET) and Targeted Therapy. For both, Molecular Imaging and Targeted Therapy, the radiopharmaceuticals in clinical use are predominantly metal-based complexes and the overwhelming majority corresponds to 99mTc, which still is the workhorse of nuclear medicine, due to its ideal nuclear properties, rich chemistry, low-cost and convenient availability from commercial generators. The design of these drugs is a multidisciplinary area fuelled by the convergence of biology, medicine, chemistry, physics and engineering. Chemists, in particular, play a critical role in this effort, as they are continuously challenged to use innovative chemical strategies to develop “smart drugs”. The introduction of new metals and/or metal-building blocks and generators opened new and innovative routes in radiopharmaceutical chemistry. [1] In this presentation, I will review some of our most relevant results on metal-based chemistry fuelled by in vivo Molecular Imaging and Targeted Therapy. The importance of the chemistry on the modulation of the biological behavior of such complexes will be also discussed.[2-6] [1] Radiopharmaceuticals for imaging and therapy, Dalton Trans. 2011, 40, 6057 – 6300. [2] R. Garcia, et al. J. Am. Chem. Soc., 2000, 122, 11240. [3] M. Morais, et al. Mol. Pharmaceutics, 2011, 8, 609. [4] M. P. C. Campello, et al. Chem. Eur. Journal, 2010, 16, 8446. [5] L. R. Goethals et al. Contrast Media Mol. Imaging, 2011, 6, 178. [6] M. Morais, et al. J. Med. Chem, 2013, DOI: 10.1021/jm301647t.

39 - Production and Applications of High-Specific Activity Sn-117m Labelled Compounds

NEW APPROACHES - Sunday 16 June 2013 12:20

Presenter: STEVENSON, Nigel

Objectives: Sn-117m is a 14 day half-life gamma (~159 keV) and conversion electron (~130 keV) isotope that has been used for bone pain palliation studies. Recently this unique theranostic isotope has found application in investigative efforts to image and treat vulnerable plaque in cardiovascular diseases. Biological labeling demands high specific activity (>1000 Ci/g) that can only be produced with accelerators. We selected the Cd-116(α,3n)Sn-117m reaction and a novel chemical purification method to produce the radioisotope. Other applications that employ Sn-117m are being explored in oncology, rheumatology and neurology. Methods: We employed the Cd-116(α,3n)Sn-117m production reaction with a 47 MeV alpha beam. Resulting yields were confirmed to be high (~0.15 mCi/μAh) with minimal undesirable by-products. An ion exchange column method was used to isolate the Sn-117m resulting in a very pure high specific activity (~20,000 Ci/g) product. The Sn-117m was attached to aminobenzyl-DOTA using a microwave reactor at elevated temperatures and then purified using HPLC. Conjugation of the chelate to annexin V-128 was accomplished by preparing the isothiocyanate version of the chelate and then reacting it with lysine residues on the annexin for 90 mins at 37°C. Results: Several analytical methods (cell binding, electrophoresis, gel permeation chromatography) were used to evaluate the cGMP [Sn-117m]-DOTA-annexin that was produced. PAGE determined that the product was >95% monomer; cell binding results were typically pK=20-24. Overall chelation yields were ~95% and ~40% for conjugation to the annexin. This product was injected in ApoE mice and a therapeutic effect observed at very low doses (~1.7 μCi - equivalent to 3-5 mCi in humans). Early human studies also indicate that imaging of vulnerable plaque in-vivo with as low as 3 mCi is possible. New exploratory studies in surgery, oncology, rheumatology and in treating Alzheimer’s are underway using other Sn-117m compounds and medical devices. For example, studies employing a tin colloid are being used in a rodent rheumatoid arthritis model to explore the possible application of Sn-117m in radiosynovectomy.