FINAL REPORT

Title: Student Support for Radiochemistry Conference

U.S. Department of Energy
Office of Science (BER)
Award Number: DE-FG01-09ER64740
Report Period: July 1, 2009 – June 30, 2010

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Summary

The objectives of this program were to provide bursaries to assist students and post-doctoral fellows being trained in radiochemistry to actively participate in the 18th International Symposium in Radiopharmaceutical Sciences (ISRS-2009) held in Edmonton, Canada on July 12-19, 2009. The critical shortage of scientists in the U.S. trained radiochemistry and imaging scientists is well documented. Scientific meetings such as ISRS-2009 provide an outstanding opportunity to recruit active researchers and trainees in a venue that can inspire and mentor them to join the next generation of radiochemical scientists. The ISRS-2009 was particularly important in this meeting this objective since it is regarded as the premier international meeting that features investigators from across the globe involved in cutting-edge research to synthesize and characterize radiolabeled biomolecules for molecular imaging in living systems. For example, radiochemistry and radionuclide imaging scientists presented new approaches and technologies for synthesis of novel radiolabeled biomolecules with PET (including, ^{11}C and ^{18}F) and SPECT (including ^{99m}Tc and ^{111}In). The radiochemical and radionuclide imaging research presented at the ISRS-2009 are directly related to and supportive of the biomolecular radioisotope, radiochemistry and imaging programs in the DOE, Office of Science (BER).

There were a total of fifteen students or post-doctoral fellows from a variety of radiochemistry and radionuclide imaging research and educational institutions from across the country (Table 1). Announcements of the SRS/DOE bursary award program were made on the ISRS-2009 meeting web site (www.ISRS18.com), on the SRS website (www.srsweb.org), and *via* SRS email blasts (announcement Figure 1). The applications were reviewed and awardees selected by a committee composed of Dr. Ken Krohn, University of Washington, Seattle, WA, Dr. William Eckelman, Bethesda, MD,Dr. Michael Welch, Washington University, St. Louis, MO and Dr. Wynn Volkert, University of Missouri, Columbia, MO.

The trainees presented results of their work via either an oral or a poster presentation. Abstracts of their papers presented at the ISRS-2009 meeting were published in the Journal of Labelled Compounds and Radiopharmaceuticals, Volume 52, Supplement 1, 2009 (www.interscience.wiley.com/journal/jier), the official Abstract Book for the ISRS-2009 meeting. A copy of the published abstracts presented by each of the fifteen trainees receiving the SRS/DOE Bursary Award is provided on the following pages. The list of the fifteen trainees receiving the 2009 Bursary awards funded by this DOE grant was published in the July 2010 issue of Nuclear Medicine and Biology (Volume 37(5), July 2010) and in the SRS website with appropriate acknowledgement to the U.S. Department [See Appendix 1 for copies of the 15 student/trainee abstracts].

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APPENDIX

1. ISRS Bursary Announcement

2. List of the 15 students and trainees receiving bursaries to participate in the ISRS-2009 meeting funded by this DOE grant.

3. Copies of the abstracts of the research presentations of the 15 trainees at the ISRS-2009 meeting in Edmonton, Canada held July 12 – 17, 2009., These abstracts were published in *Journal of Labelled Compounds and Radiopharmaceuticals* (2009) 52: Supplement 1.

SRS / U.S. Department of Energy Bursary Award Announcement
For U.S. Trainees in Radionuclide Imaging Research for Participation in the ISRS-2009 Meeting.

Students or post doctoral trainees at US institutions who are accepted for a poster or oral presentation at the 18th International Symposium on Radiopharmaceutical Sciences are eligible to apply for a bursary. Bursaries will be provided to each trainee for each person selected for the award; the amount is dependant on travel distance. Successful applicants will require a letter from their mentor committing them to provide the additional funds for the trainee to present their work the meeting (oral or poster presentation).

The applicant should submit their abstract for the meeting, a CV and maximum of a one page summary of their reason for applying and the estimated total cost [including the itinerary] to attend the meeting. It is important that the trainee commit to participating in the entire meeting. All funds will be presented to the successful applicants in Edmonton.

Please email your application to balld@missouri.edu with the Subject Line: SRS DOE Award. The deadline for application is June 15, 2009.

Funding for this award is provided by the US Department of Energy, Office of Science Financial Assistance Program (Funding Opportunity Number DE-PS02-08ER08-01; CFDA 81.049) through a grant to the Society of Radiopharmaceutical Sciences (SRS).

SOCIETY OF
Radiopharmaceutical
Sciences

2009 Student Bursary Recipients

The Mission of the Society of Radiopharmaceutical Sciences (SRS) emphasizes that our Society is an "organization dedicated to the advancement of excellence in education and research in radiopharmaceutical sciences in the study and use of radiopharmaceuticals." An important goal of the SRS is to provide an inclusive and supportive environment for early career trainees and scientists and increase the number of qualified professionals in our field. In this regard, the SRS provides support in the form of bursaries for students and post-doctoral fellows to participate in high-quality national and international meetings and educational programs that are sponsored, co-sponsored or directly related to radiopharmaceutical sciences. These meetings and courses provide an outstanding learning environment to stimulate creative research discussions and provide a powerful educational tool for those new to the field. It is important to acknowledge the students and trainees who were selected to receive partial or full support from the SRS for participation in radiopharmaceutical science meetings and the educational programs. The intent of the SRS is to publish a list of students and post-doctoral fellows receiving SRS bursaries in the *Nuclear Medicine and Biology Journal* each year and post the list on the SRS website to keep our membership informed about the extent SRS is contributing to our educational mission in this manner. The students and trainees receiving SRS support in 2009 are listed below and on the next page. The SRS gratefully acknowledges support provided by the Office of Science (BER), U.S. Department of Energy, Grant No. DE-FG02-09ER64740 for 15 U.S. students and trainees to participate in the ISRS-2009 meeting.

The following students and trainees received support from the Office of Science (BER), U.S. Department of Energy, Grant No. DE-FG02-09ER64740:

- Aaron L. Smith, Emory University
- Ashley L. Fiamengo, Washington University School of Medicine
- Brienne Bottenus, University of Missouri
- Charles Glaus, Washington University School in St. Louis
- Christopher P. Surdock, University of Tennessee Health Science Center
- Hancheng Cai, University of Southern California
- Heather Bigott-Hennkens, University of Missouri
- Jai Woong Seo, UC Davis
- Jonathan Engle, University of Wisconsin
- Michael Pun, University of California, San Francisco
- Shawn Pan, University of California – Berkeley
- Stephanie Lane, University of Missouri-Columbia
- Tapan Nayak, National Cancer Institute/National Institute of Health
- Wone Woo Seo, Emory University
- Yunjun Guo, Washington University in St.Louis

- Abd El-Galiel, The Methodist Hospital Research Institute
- Andrea North, NIBIB\NIH
- Ann-Marie Chacko, Institute for Environmental Medicine
- Aurélie Maisonial, Université d'Auvergne
- Babak Behnam Azad, University of Western Ontario
- Bernd Dörner, University of Vienna
- Bo Yeun Yang, Seoul National University
- Brandon Buckway, University of Utah
- Byung Seok Moon, Inha University
- Carl Jenks, Washington University School of Medicine
- Carsten Burchardt, Johannes-Gutenberg University Mainz
- Cheong A. Park, Sogang University
- Choong Mo Kang, Sungkyunkwan University
- Cui. Mengchao, Beijing Normal University
- Dag Erlend Olberg, University of Tromsø
- Derya ilem, Ege University
- Eftychia Koumarianou, Institute R-RP, NCSR "Demokritos", Athens
- Ethan R. Balkin, University of Missouri

P076 DEVELOPMENT OF A NOVEL PET OXYTOCIN RECEPTOR BIOMARKER

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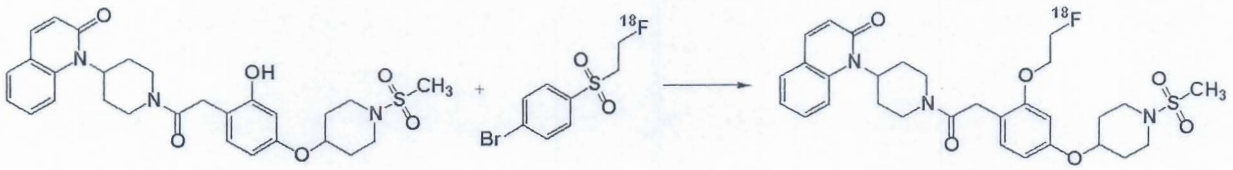
1. Department of Radiology, Emory University, Atlanta, GA; 2. Department of Behavioral Neuroscience, Emory University, Atlanta, GA

Objectives: The development of a PET radioligand to enable pharmacological studies of oxytocin receptors in living human and non-human primates would greatly enhance the ability to understand the neurobiological mechanisms underlying oxytocin behavioral effects. The compound (1-(1-(2-(2,2,2-trifluoroethoxy)-4-(1-methylsulfonyl-4-piperidinyloxy) phenylacetyl)-4-piperidinyl)-3,4-dihydro-2(1H)-quinolinone) has been shown to contain a high affinity for oxytocin receptors in humans. We have developed a fluorinated analog, 1-(1-(2-(2-fluoroethoxy)-4-(1-methylsulfonyl-4-piperidinyloxy) phenylacetyl)-4-piperidinyl)-3,4-dihydro-2(1H)-quinolinone (2), that is a potential radioligand when labeled with fluorine-18 for in vivo PET studies. We report here the synthesis of a precursor to obtain [^{18}F]2 in a one step process and autoradiography evaluation of 2.

Methods: The PET labeling precursor, 1-(1-(2-(hydroxy)-4-(1-methylsulfonyl-4-piperidinyloxy) phenylacetyl)-4-piperidinyl)-3,4-dihydro-2(1H)-quinolinone (1) was synthesized in 11 steps using ethyl vinyl ether, oxalyl chloride, and 2,4-dihydroxyacetophenone as starting materials. The reference standard of 2, and its radioactive derivative, were synthesized via a reaction of compound 1 with fluoroethylbrosylate or [^{18}F] fluoroethylbrosylate. In vitro competition assays were performed with 2 using vole brain tissue known to contain oxytocin and vasopressin receptors.



Results: [^{18}F]2 was obtained in 85 min from the start of synthesis with a radiochemical yield of 13% as measured by radiometric HPLC. Biological evaluation via autoradiography demonstrated an IC_{50} of approximately 10nM for oxytocin receptors and 70nM for vasopressin receptors.

Conclusions: The preliminary studies suggest that [^{18}F]2 could be a potential PET agent used for in vivo PET studies.

NEW PHOSPHONIC ACID DERIVATIVES OF CROSS-BRIDGED CYCLAM AS 64Cu CHELATORS

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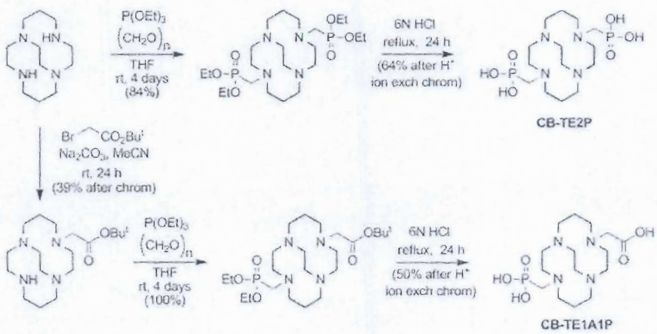
Objectives: ^{64}Cu is a promising radionuclide that is well suited for both PET imaging and therapy and can be produced in high yield and specific activity on a biomedical cyclotron. Azamacrocycles are chelators of choice for complexing ^{64}Cu. When conjugated to a targeting moiety and radiolabeled, these are potentially able to recognize specific targets, accumulate and allow for external, non-invasive detection. Widespread use of ^{64}Cu for imaging and radiotherapy depends on development of optimal chelators. Copper(II) binds to several endogenous proteins; therefore, in order to be of practical use, the macrocycles need to form complexes that are stable under physiological conditions. The cross-bridged macrocycle (CB-TE2A) forms Cu(II) complexes that are much more kinetically inert than the non-bridged DOTA and TETA analogs.[1] Unfortunately, Cu(II)-CB-TE2A has a slow rate of complexation requiring conditions that are harsher than desirable in order to achieve ^{64}Cu labeling in a reasonable time frame. In order to find chelators that complex Cu(II) with faster kinetics while retaining the high stability and the significant inertness observed with CB-TE2A, phosphonic acid (-CH_2-PO_3H_2) donor groups were investigated as pendant arms.[2,3] It has been shown previously that chelators with phosphonic acid pendant arms have higher selectivity as well as increased thermodynamic and kinetic stability compared to their acetic acid analogs.[4]

Methods: The newly synthesized compounds were radiolabeled and compared in vivo to other macrocycles commonly used to complex ^{64}Cu through biodistribution studies using healthy rats.

Results: CB-TE2P and CB-TE1A1P were synthesized, radiolabeled with ^{64}Cu and their in vivo behavior was investigated. While CB-TE2P labeling with ^{64}Cu was complete within 1 hour in buffer at higher temperatures, radiolabeling yields above 90% were observed even at 37° C. Remarkably, CB-TE1A1P had 100% radiolabeling yields at 37° C.



A biodistribution study showed rapid blood clearance and low liver accumulation at 24 h, suggesting that ^{64}Cu-CB-TE2P did not appreciably dissociate in vivo. A higher uptake was observed in the kidney while no significant uptake was detected in lung, spleen, heart or stomach. There was a relatively high uptake in the bone, however, this was not surprising as the methanephosphonic pendant arms are known to have high affinity for the hydroxyapatite in bone. An even better profile was observed for CB-TE1A1P, with lower uptake and faster clearance in kidney and bone.

Conclusions: The biodistribution of ^{64}Cu-CB-TE2P and ^{64}Cu-CB-TE1A1P compared favorably to CB-TE2A, NOTA and DiamSar, with better blood, liver and kidney clearance and lower accumulation in bone marrow than ^{64}Cu-labeled NOTA and DiamSar. The biodistribution of the two new compounds was comparable to ^{64}Cu-CB-TE2A at 24 h post-injection, with the added advantage of more rapid formation kinetics under milder conditions. Research is underway to investigate the conjugation of these chelators with biological targeting molecules.

Research Support: Funding for this research was provided by NIH, grant R01 CA093375.

References: 1. Boswell C. A., Sun X. K., Niu W. J., et al. J. Med. Chem 2004;47(6):1465-1474. 2.Kotek J., Lubal P., Hermann P., et al. Chem. Eur. J. 2003;9(1):233-248. 3.Lukes I., Kotek J., Vojtisek P., Hermann P. Coord. Chem. Rev. 2001;216:287-312. 4.Sun X. K., Wuest M., Kovacs Z., et al. J. Biol. Inorg. Chem. 2003;8(1-2):217-225.

IN VITRO AND IN VIVO EVALUATION OF STRUCTURALLY DIVERSE CU-64-LABELED RGD PEPTIDES FOR PET IMAGING OF αVβ3 EXPRESSION

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Objectives: Integrin $\alpha_v\beta_3$ is upregulated in tumor vasculature, osteoclasts and areas of collateral circulation following ischemic injury. Here, we investigate structurally diverse bifunctional RGD (arginine-glycine-aspartic acid) peptides for $\alpha_v\beta_3$ integrin affinity in vitro and in vivo. Bifunctional ligands allow for targeting with a peptide as well as radiolabeling with ^{64}Cu via a macrocyclic chelator for PET imaging.

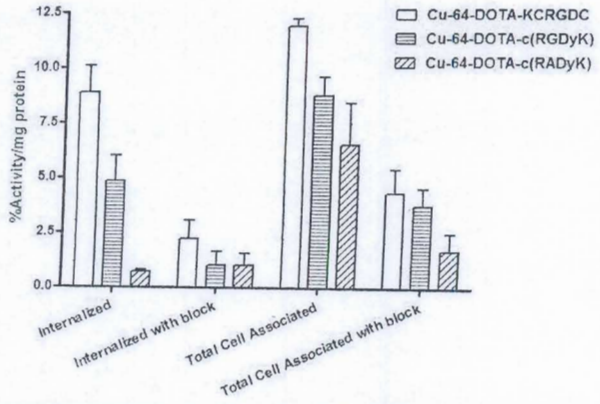
Methods: A series of peptides containing the RGD sequence were synthesized. Affinity to $\alpha_v\beta_3$ and specificity for $\alpha_v\beta_5$ and $\alpha_{IIb}\beta_3$ were determined in an isolated, competitive binding assay. Cellular uptake studies in an $\alpha_v\beta_3$-positive cell line (U87MG human glioblastoma cells) were performed using the ^{64}Cu-DOTA-labeled peptides. In vivo characteristics were examined in biodistribution and microPET studies in U87MG tumor-bearing nu/nu mice.

Results: A lactam-cyclized peptide (c(RGDyK) demonstrated higher affinity for $\alpha_v\beta_3$ than disulfide-cyclized (KCRGDC) or linear peptide (GRGDS) (Table 1). Disulfide-cyclized peptides exhibit the best selectivity of the ligands investigated. A control, lactam-cyclized peptide (c(RADyK)) has low affinity for all three integrins. Conjugation of Cu(II)-containing chelators did not affect the binding affinity or selectivity of the peptides.

Table 1. IC_{50} values for RGD peptides.

	αvβ3 (nM)	αvβ5 (nM)	αIIbβ3 (nM)
c(RGDyK)	3.7	171	0.11
KCRGDC	10.4	921	>5,000
GRGDS	15.9	>5,000	873
c(RADyK)	1,400	>5,000	>5,000

In cell studies the disulfide-cyclized peptide showed higher internalization than the lactam-cyclized peptide (Figure 1).



Uptake of RGD peptides could be blocked by high doses of unlabeled peptide. Internalization of the control peptide was minimal.

Biodistribution studies in the murine tumor model showed rapid uptake and retention of the ^{64}Cu-labeled peptides in tumor with good tumor:blood and tumor:muscle ratios (^{64}Cu-DOTA-KCRGDC, 4h post-injection: 4.23 ± 1.4 and 8.56 ± 2.4 respectively). Uptake can be blocked by co-administration of high doses of unlabeled peptide.

Conclusions: The peptides will be further investigated via microPET imaging of $\alpha_v\beta_3$-expressing animal models, including the U87MG tumor model and hind limb ischemia for imaging angiogenesis following ischemic injury. In addition to evaluating the radiolabeled $\alpha_v\beta_3$-targeted peptides, we are also pursuing the goal of accomplishing higher binding affinity by attaching several peptides onto nanoparticles.

INVESTIGATION OF A NEW BOMBESIN DERIVATIVE FOR THE MOLECULAR IMAGING OF PROSTATE, BREAST, AND PANCREATIC CANCERS

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1. HS Truman VA Hospital, Columbia, MO; 2. University of Missouri, Columbia, MO

Objectives: The Bombesin analogue, DOTA-8-AOC-[(D)W^6]BBN(6-13)NHC$_2$H$_5$, was evaluated as a potential new targeting vector for ^{67}Ga/^{68}Ga molecular imaging of BB2 receptor (BB2r) expression using preclinical xenograft models of human prostate, breast, and pancreatic cancers.

Methods: ^{67}Ga- DOTA-8-AOC-[(D)W^6]BBN(6-13)NHC$_2$H$_5$ was synthesized and purified by HPLC prior to utilization. In vitro competitive binding assays were performed in PC-3 human prostate, T47D human breast, and CF-PAC1 human pancreatic tumor cell lines. In vivo pharmacokinetic studies were performed in SCID mice bearing bi-lateral PC-3, T47D, and CF-PAC1 human cell line flank tumor xenografts at 4-6 weeks post tumor cell inoculation. Tissues were collected at 15 min, 1, 4 and 24 hours P.I. of the ^{67}Ga conjugate. Correlative Micro-SPECT images of ^{67}Ga distribution were obtained at 4 hours P.I. in all three tumor xenograft SCID mice models.

Results: The ^{67}Ga conjugate showed rapid clearance from non-target tissues with tumor retention visualized in PC-3 prostate, T47-D breast, and CF-PAC1 pancreatic tumor xenografts when imaged using Micro-SPECT. Pharmacokinetic results demonstrated uptake in BB2r expressing tumor xenografts and the normal pancreas. The overall tumor to pancreas ratios at 4 hours P.I. remained high ranging from a value of 19:1 observed for the PC-3 prostate cancer xenograft model down to a 4:1 ratio observed in the CF-PAC1 pancreatic cancer xenograft model. Primary clearance of the ^{67}Ga conjugate was via the renal system with very limited renal retention observed. Variation in tumor uptake between cell lines studied corresponded with variations in BB2r expression for the respective cell line.

Conclusions: The pharmacokinetic and imaging properties of ^{67}Ga-DOTA-8-AOC-[(D)W^6]BBN(6-13)NHC$_2$H$_5$ demonstrate significant potential of this analog as a SPECT or PET molecular imaging agent to assess in vivo BB2r expression in a variety of cancers.

Research Support: U.S. Department of Veteran's Affairs Merit Review

P255 OPTIMIZATION OF THE BOMBESIN PEPTIDE SEQUENCE FOR IN VIVO PRECLINICAL IMAGING OF GRP RECEPTOR POSITIVE TUMORS

B. BOTTENUS*[1], J. GARRISON[2], B. COOK[2], T. ROLD[1], G. SIECKMAN[1], S. SUBLETT[2], S. FIGUEROA[1], S. S. JURISSON[2] and T. HOFFMAN[1]

1. HS Truman VA Hospital, Columbia, MO; 2. University of Missouri, Columbia, MO

Objectives: The purpose of this study was to determine what effect small changes to the truncated bombesin antagonist sequence would have on tumor uptake and non-tumor clearance rates in hopes of optimizing the target:nontarget ratios for imaging of gastrin releasing peptide receptor (GRPr) positive tumors.

Methods: DOTA-8-AOC-(X) –BBN(7-13)(NHC_2H_5) where BBN(7-13) is W-A-V-G-H-L and X = Q, (D)F-Q, (D)A-Q, (D)S-Q, (D)Y-Q, (D)W-Q, (D)F-N-Q, (D)F-G-N-Q were synthesized using standard Fmoc protected solid phase peptide synthesis and labeled with Ga-nat/67. IC_{50} values were determined for each Ga labeled peptide in the GRPr expressing cell line in PC-3. In vivo biodistributions were performed in SCID mice bearing PC-3 tumor xenografts and tissues evaluated to determine %ID and %ID/g in each organ/tissue for peptides with IC_{50} values< 20 nM. SPECT imaging was also conducted in SCID mice bearing PC-3 tumor xenografts.

Results: Solid phase peptide synthesis yields of the peptides investigated ranged from 2.87% to 24.5%. The highest yields came from the X= (D)W-Q conjugate and the lowest yield came from the longest peptide x=(D)F-G-N-Q, which would be expected. All natural Ga conjugates were purified using RP-HPLC. IC_{50} analysis of the Ga conjugates exhibited increased binding affinity when the unnatural $(D)F^6$ was present (3.34 ±0.39) as compared to the analogue with no unnatural amino acids present (5.44 ± 1.56). When the position of the (D)F was altered from the 6^{th} position to the 4^{th} position a loss of binding affinity was observed, ranging from IC_{50} values of 3.34 to 29.53. The 6^{th} position amino acid was then altered to determine effects of structure in that position on binding affinity. Results showed a two-fold increase in binding affinity with aromatic amino acids (IC_{50}'s ranging from 3.3 to 5.9) when compared to the aliphatic amino acid (IC_{50} of 105). Due to the high binding affinities observed when X=Q, (D)F-Q, (D)W-Q, and (D)Y-Q , biodistribution studies in SCID mice bearing PC-3 tumor xenografts were studied with the Ga-67 labeled peptides at 15 min, 1 h, and 4 h. All peptide derivatives showed high and specific uptake in tumors with varied clearance rates and pathways. Of the analogues studied the X=(D)W-Q analogue showed the highest tumor uptake at 4 hours (7.31 ± 0.81) with the highest tumor: pancreas ratio (19:1) as well. SPECT imaging results showed tumor visualization in all cases.

Conclusions: Modification to the truncated bombesin sequence exhibited highest binding affinity when an unnatural D aromatic amino acid was substituted into the sixth position of the sequence. Based on the current results Ga-DOTA-8-AOC-(D)W-BBN(7-13)(NHC_2H_5) showed the highest uptake in PC-3 tumors and therefore warrants further investigation as a molecular imaging agent for the gastrin releasing peptide receptor.

Research Support: U.S. Department of Veteran's Affairs Merit Review

DUAL-MODALITY NANOPARTICLES FOR PET/MR MOLECULAR IMAGING

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1. Georgia Institute of Technology, Dept. of Biomedical Engineering, Atlanta, GA; 2. Washington University School of Medicine, Mallinckrodt Institute of Radiology, St. Louis, MO

Objectives: Combining PET with the high resolution, contrast-enhanced abilities of MRI would produce a breakthrough in the detection and monitoring of disease. Interest in combining PET with MRI has surged, and structured nanomaterials have emerged as a platform for dual PET/MR imaging agents. To this end, we report the development of nanoparticles for dual PET/MR imaging of αvβ3 integrin expression in a model of angiogenesis.

Methods: Iron oxide cores coated with amine-modified, crosslinked dextran served as the magnetic nanoparticle (MNP) platform. DOTA was conjugated to the MNP coating to allow radiolabeling with ^{64}Cu. DOTA-MNPs were reacted with NHS-polyethylene glycol-maleimide and multiple c(RGDyC) peptides were conjugated to the particles. Labeled nanoparticles (^{64}Cu-MNP-RGD) were characterized by radio-FPLC, TLC, and zeta-DLS. The number of peptides per particle was measured and stability in mouse serum was determined (24h at 37°C). A 1% agar imaging phantom was used for PET and MRI characterization. Cell imaging was performed using U87MG cells (αvβ3 positive) treated with dye-labeled MNP-RGD or MNP, with and without free-peptide blocking. Uptake assays were performed using M21 (αvβ3 positive) and M21L (αvβ3 negative) cell lines treated with ^{64}Cu-MNP-RGD or ^{64}Cu-MNP, with and without blocking. U87MG tumor-bearing mice were injected with ^{64}Cu-MNP-RGD or ^{64}Cu-MNP and PET/CT imaging was performed, followed by organ biodistribution. MRI at 7T was performed before injection and at 24h p.i., tumor contrast was quantified, and colormaps were generated for T2-weighted images.

Results: Radio-FPLC and TLC analysis showed high yield, radiochemical purity, specific activity, and particle monodispersity. The particles had a diameter of 42±6nm, a surface potential of 4mV, contained 43±9 peptides, and were stable in serum. Imaging phantoms confirmed the labeled particles produced both strong PET signal and MRI contrast. Cell imaging and uptake studies verified specific targeting of ^{64}Cu-MNP-RGD to αvβ3. Peptide-functionalized ^{64}Cu-MNP-RGD showed rapid blood clearance and increased uptake by the reticuloendothelial system versus ^{64}Cu-MNP (blood: 1±0.3 vs. 16.7±1.5; liver: 50.4±5.1 vs. 22.4±11.5; spleen: 61.1±14.7 vs. 13.7±7.1%ID/g at 24h p.i., respectively). While both ^{64}Cu-MNP-RGD and ^{64}Cu-MNP was present in tumors, the tumor-to-tissue ratios for ^{64}Cu-MNP-RGD were significantly greater than those of ^{64}Cu-MNP (blood: 3.4±1.6 vs. 0.4±0.1; muscle: 6.4±2.2 vs. 2.9±0.8; fat: 8.9±4.7 vs. 3.4± at 24h p.i., respectively). PET images of ^{64}Cu-MNP-RGD show clear delineation of tumors, while ^{64}Cu-MNP has widespread, diffuse accumulation (Fig. 1). Both RGD-targeted and non-targeted particles produced contrast enhancement in MRIs, however accumulation of non-targeted particles is likely due to EPR effects.

Conclusions: Our studies assess the efficacy of the dual PET/MR nanoparticles for in vivo molecular imaging, and offer insight into opportunities for PET/MR in the detection and monitoring of disease.

Research Support: National Heart Lung and Blood Institute: Programs of Excellence in Nanotechnology (U01HL80711, HL080729)

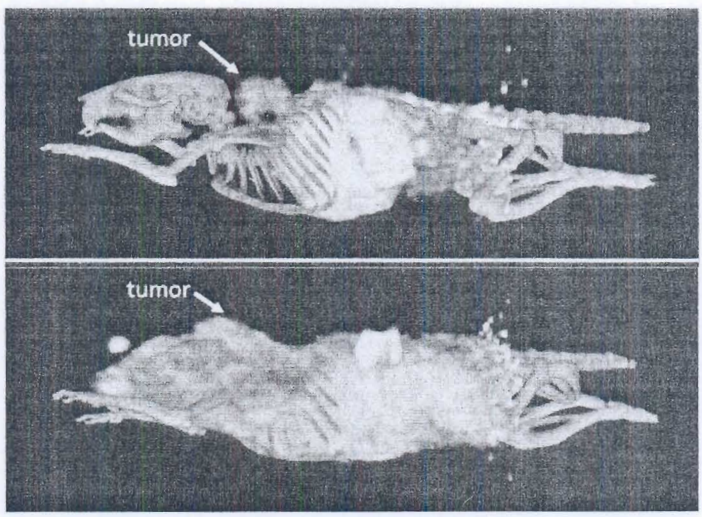

Figure 1: 3D MicroPET/CT imaging ^{64}Cu-MNP-RGD (top) and ^{64}Cu-MNP (bottom) in tumor-bearing mice at 24 hr post-injection. PET/CT images show clear tumor delineation using RGD-targeted nanoparticles (top), while untargeted nanoparticles (bottom) resulted in widespread uptake.

P133 LONG-TERM EVALUATION OF A COMMERCIALLY AVAILABE Ge-68/Ga-68 GENERATOR FOR PET IMAGING

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Objectives: Gallium-68 is an ideal radionuclide for positron emission tomography (PET), because the half-life of ^{68}Ga (68 min) and its positron emission (E_{max}=1.92 MeV, 89%) are suitable characteristics for in vivo imaging. In addition, it can be obtained via a ^{68}Ge/^{68}Ga generator which has the advantage of allowing both clinical and basic studies without an on-site cyclotron. Furthermore, the long half-life of the parent nuclide, ^{68}Ge (270.8 days), provides a long life-span generator. The Isotope Products Laboratories Ionic Gallium Generator (IGG100) is a commercial available ^{68}Ge/^{68}Ga generator. The generator is a closed system consisting of an ion exchange column containing a titanium dioxide bed on ^{68}Ge in a borosilicate glass tube, and PEEK end plugs which are attached using PVC inlet and outlet lines via barbed fittings. The column is mounted in a tungsten/lead shielded assembly. The assembly is secured in a stainless steel outer box with two handles and recessed inlet and outlet ports. In this study, we evaluated the profile of the generator for approximately 200 elutions over a two year time period.

Methods: The IGG100 generator produced by Eckert & Ziegler Isotope Products GmbH (Berlin, Germany) was loaded with 1,850 MBq of ^{68}Ge. The ^{68}Ga was eluted with 0.1M ultrapure hydrochloric acid according to the manufacturer instructions. Elutions were carried out at 2 mL/min for 3 min using an infusion pump, and the ^{68}Ga activity was collected every 0.5 min. The elution profile was determined by measuring the ^{68}Ga activity in the six 1 mL fractions. The ^{68}Ge breakthrough was calculated as a percentage of ^{68}Ge per ^{68}Ga in the fractions.

Results: The ^{68}Ga elution yield based on loaded ^{68}Ge was 61.0 ± 3.5 % (n=195), and 80% of the ^{68}Ga was recovered in fractions 3 and 4. These trends were the same through the two year testing period. The breakthrough of ^{68}Ge in all six fractions was <0.005% of eluted ^{68}Ga at 450 days after ^{68}Ge loaded (115th elution), and increased to 0.02% in another 200 days. The breakthrough in fractions 3 and 4 was ~0.008% at 650 days.

Conclusions: The results indicate that the IGG100 generator produced ^{68}Ga with high elution yields over a two year time period. The percentage of Germanium-68 breakthrough increased slowly over the 650 day time period but was remained acceptable limits.

Research Support: This work was supported by NIH/NCI Grant R24 CA086307 "Radionuclide Resource for Cancer Applications."

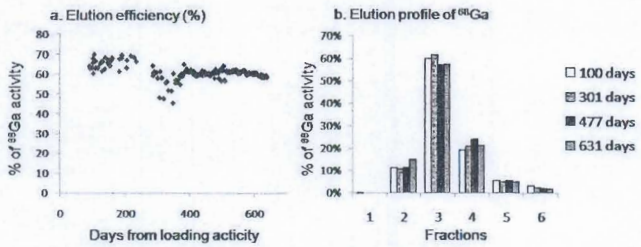

Figure 1. (a) The percentage of eluted ^{68}Ga based on the activity of loaded ^{68}Ge. Day 0 is the day of ^{68}Ge loading on the ^{68}Ge/^{68}Ga generator. (b) Elution profile of ^{68}Ga in fraction 1 to 6. The activity in 1 mL per fraction is expressed as percentage of the total ^{68}Ga activity.

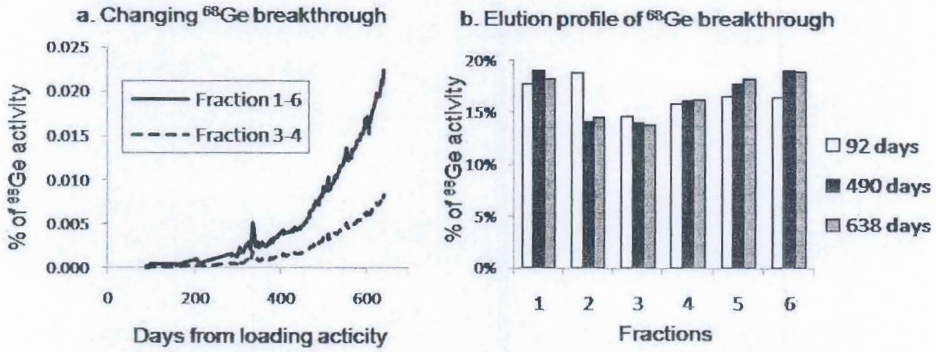

Figure 2. (a) ^{68}Ge breakthrough is expressed as percentage of ^{68}Ge/ ^{68}Ga in total fractions (solid line), and the fraction 3 and 4 (dashed line). (b) Elution profile of ^{68}Ge breakthrough in fraction 1 to 6. The activity in 1 mL per fraction is expressed as percentage of the total ^{68}Ge activity.

P070 FLUORINE-18 LABELING OF SUBSTITUTED BENZILS FOR IMAGING CARBOXYLESTERASE

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Objectives: Irinotecan is a potent chemotherapeutic used in the treatment of several cancers, including neuroblastoma. Irinotecan itself is a non-toxic prodrug which is converted in vivo to the cytotoxic form, camptothecin, via metabolism by carboxylesterase (CE) enzymes (Yoon, Mol Cancer Ther 2003,2:1171-81). Researchers at St. Jude Children's Research Hospital are taking advantage of CE isoform diversity to design a two-pronged protocol of tumor specific chemotherapy. These complementary approaches combine specific inhibition of human CE activity in normal tissues in an effort to increase drug delivery to the tumor (Wadkins, J Med Chem 2005,48:2906-15), and tumor-specific activation of prodrugs by using neural progenitor cells transfected with a carboxylesterase cDNA (Danks, Cancer Res 2007, 67:22-5). The tumor-selective trafficking of neural progenitor cells allows over expression of CE within the tumor. Both lines of investigation would benefit from in vivo quantification of CE activity in tumors and normal tissues, allowing titration of drug dosing for CE inhibitors and measurement of CE increases selectively at tumor foci in progenitor cell studies. Our laboratory is developing PET radiotracers based on CE inhibitors developed here at St Jude, many of which contain a benzil (diphenylethane-1,2-dione) core structure. To determine whether the benzil structure was sufficiently activated for direct labeling with ^{18}F, we performed the 4-nitro to 4-fluorobenzil conversion as proof of concept.

Methods: Aqueous [^{18}F]fluoride was captured on a Waters QMA anion exchange resin and eluted with a mixture of 5 mg Kryptofix and 0.5 mg K_2CO_3 in 2:1 acetonitrile/water. The resulting acetonitrile/water azeotrope was evaporated at 85 C yielding the anhydrous Kryptofix-K-^{18}F complex which was then heated at 130 C for 45 minutes with 4-nitrobenzil (5 mg) in anhydrous DMSO. HPLC separation of the 4-[^{18}F]fluorobenzil and the unlabelled nitro- and fluorobenzil standards was achieved on ZORBAX Eclipse DBX-C18 column (Agilent, 4.6 x 250 mm, 5μm) eluted with 3:1 MeCN/water at 0.5 mL/min.

Results: Nucleophilic aromatic fluorination of 4-nitrobenzil gave 50-65% conversion to the 4-[^{18}F]fluorobenzil, as determined by TLC (silica gel, ethyl acetate/hexanes, 3/7) with radiation detection. HPLC analysis of the crude ^{18}F product under the stated conditions also showed a radiation peak corresponding to 4-[^{18}F]fluorobenzil and good separation from 4-nitrobenzil precursor on the UV chromatogram.

Conclusions: These results verify that benzil compounds are adequate precursors for nucleophilic fluorination reactions, although the nitro leaving group requires long reaction times and high temperatures. The ability to directly label such relatively unactivated benzils greatly simplifies the goal of preparing a diverse library of radiotracers with differing CE isoform selectivity. Our lab is currently synthesizing new radiolabeled compounds based on the structure activity relationship scaffold of the benzil compounds, with intentions to design a series of radiotracers with low nanomolar affinity for CE.

Research Support: Supported in part by NCI grants CA113446 and CA108775.

References: Wadkins, RM; Hyatt, JL; Wei, X; Yoon, KJ; Wierdl, M; Edwards, CC; Morton, CL; Obenauer, JC; Damodaran, K; Beroza, P; Danks, MK; and Potter, PM. Identification and characterization of novel benzil (diphenylethane-1,2-dione) analogues as inhibitors of mammalian carboylesterases. J. Med. Chem. 2005, 48, 2906-2915 Hicks, LD; Hyatt, JL; Moak, T; Edwards, CC; Tsurkan, L; Wierdl, M; Ferreira, AM; Wadkins, RM; and Potter, PM.Analysis of the inhibition of mammalian carbosylesterases by novel fluorobenzoins and fluorobenzils. Bioorg. Med. Chem. 2007, 15, 3801-3817 Yoon, KJ; Krull, EJ; Morton, CL; Bornmann, WG; Lee, RE; Potter, PM; and Danks, MK.Activation of a camptothecin prodrug by specific carobylesterases as predicted by quantitative structure-activity relationship and molecular docking studies. Molecular Cancer Therapeutics. 2003, 2, 1171-1181 Hyatt, JL; Wadkins, RM; Tsurkan, L; Hicks, LD; Hatfield, MJ; Edwards, CC; Ross, CR; Cantalupo, SA; Crundwell, G; Danks, MK; Guy, RK; and Potter, PM. Planarity and constraint of the carbonyl groups in 1,2-diones are determinants for selective inhibition of human carboxylesterase 1. J. Med. Chem. 2007,50, 5727-5734 Danks, MK; Yoon, KJ; Bush, RA; Remack, JS; Wierdl, M; Tsurkan, L; Kim, SU; Garcia, E; Metz, MZ; Najbauer, J; Potter, PM; and Aboody, KS.Tumor-targeted enzyme/prodrug therapy mediates long-term disease-free survival of mice bearing disseminated neuroblastoma. Cancer Res. 2007,67, 1, 22-25 Snyder, SE; Kume, A; Jung, YW; Conner, SE; Sherman, PS; Albin, RL; Wieland, DM; Kilbourn, MR.Synthesis of carbon-11-, fluorine-18-, and iodine-125-labeled GABAA-gated chloride ion channel blockers: Substituted 5-tert-butyl-2-phenyl-1,3-dithianes and dithiane oxides. J. Med. Chem. 1995, 38, 2663-2671 Haka, MS; Kilbourn, MR; Watkins, GL; and Toorongian, SA.Aryltrimethylammonium trifluoromethanesulfonates as precursors to aryl [18F]fluorides;Improved synthesis of [18F]GBR-13119. J. Labelled Compd. Radiopharm. 1989, 27, 7, 823-833

[^{18}F]FBTA2 AS A POTENTIAL RADIOLIGAND FOR IMAGING BRAIN BETA-AMYLOID

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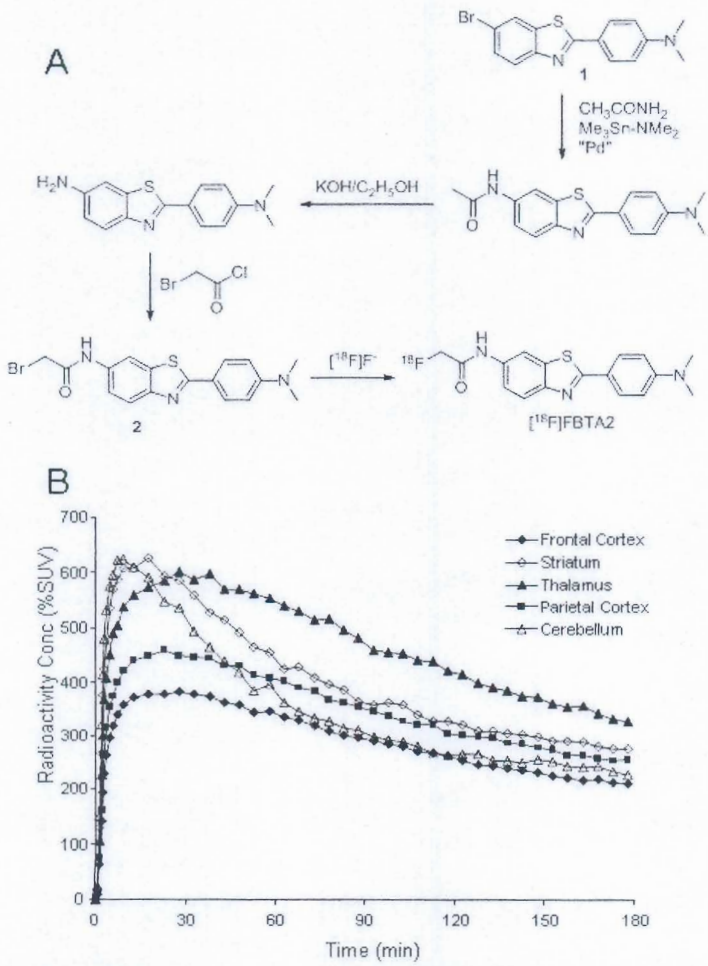
Objectives: [^{11}C]PIB ([methyl-^{11}C]2-(4-(methylamino)phenyl)benzo[d]thiazol-6-ol) is a leading radiotracer for the molecular imaging of A-beta amyloid aggregates in Alzheimer's Disease (AD), and shows rapid and high uptake into brain followed by a quick washout [Mathis C.A. et al. J. Med. Chem., 2003, 46, 2740]. Similarly effective radioligands labeled with longer-lived ^{18}F ($t_{1/2}$ = 109.7 min) are desirable to enable more widespread clinical application. With a view to evaluate more derivatives of PIB, we have exploited an "isoelectronic effect" in the design of PIB analogs [Cai L. et al. J. Med. Chem., 2007, 50, 4746]. These analogs have amido substitutents in place of the hydroxy group. Here we report FBTA2, its labeling with ^{18}F in its fluoroacetamido group, and a kinetic study of this radioligand in monkey with PET.

Methods: Precursor synthesis: The bromoacetamido compound (2) was synthesized in three steps from a known bromo compound (1), itself synthesized in six steps by a known method [Tao X. et al. Chin. J. Chem., 2009, 27, 1] (Scheme). Radiolabeling: [^{18}F]FBTA2 was prepared from 2 with [^{18}F]fluoride ion through an efficient nucleophilic substitution reaction [Briard E. and Pike V.W. J. Label. Compd. Radiopharm., 2004, 47, 217]. Tissue preparation: Human AD brain tissue was homogenized in 500 volumes of phosphate-buffered saline, and aliquots of this suspension (0.100 mL) were used in each tube for in vitro binding assay. PET imaging: A monkey (11.2 kg) was injected with [^{18}F]FBTA2 (6.59 mCi; 3 Ci/μmol). Brain uptake of radioactivity was monitored for 3 h with an HRRT PET camera.

Results: Decay-corrected radiochemical yields of purified and isolated [^{18}F]FBTA2 were about 5%. FBTA2 was found to have high affinity (K_i = 4.6 nM) for AD brain homogenates in vitro (c.f. K_D = 7.2 nM for PIB). The uptake of radioactivity into monkey brain after i.v. injection of [^{18}F]FBTA2 was high (4.00–6.50 SUV at 5–10 min), and more than that of [^{11}C]PIB (2.00–3.00 SUV at 4–6 min). The ratio of radioactivity at its maximum to that at 180 min was 2–3, and comparable to that for [^{11}C]PIB at its maximum compared to that at 60 min [Mathis C.A. et al. J. Med. Chem., 2003, 46, 2740].

Conclusions: FBTA2 showed slightly higher binding affinity than PIB in vitro, and was easily labeled with fluorine-18. The brain kinetics of [^{18}F]FBTA2 has slower washout than that of [^{11}C]PIB in monkeys. Further evaluation of [^{18}F]FBTA2 in AD patients is planned.



Panel A. Synthesis of [^{18}F]FBTA2. Panel B. Time course of radioactivity uptake into brain regions after i.v. injection of [^{18}F]FBTA2 into rhesus monkey.

P237 [^{11}C]GO6976 AS A POTENTIAL RADIOLIGAND FOR IMAGING PROTEIN KINASE C WITH PET

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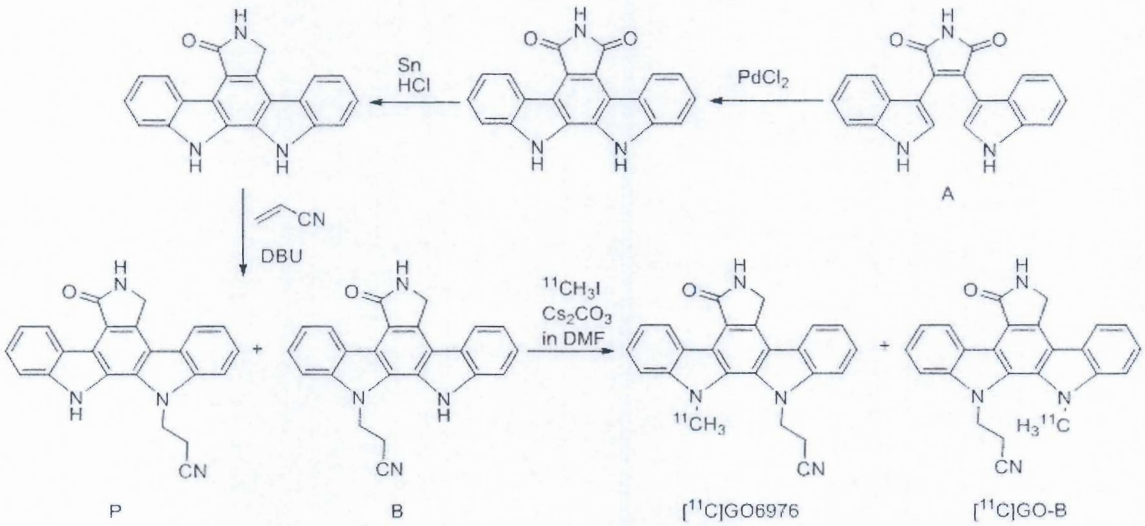
Objectives: Inhibition of protein kinase C (PKC) may become a new strategy for the treatment of bipolar disorder [Zarate C.A. et al., Bipolar Disord. 2007, 9, 561]. PET imaging of brain PKC may also prove useful for the investigation and diagnosis of bipolar disorder and the development of new therapeutics. GO6976 is a potent and selective PKC inhibitor [Martiny-Baron G. et al., J. Biol. Chem. 1993, 268, 9194]. Here we aimed to prepare [^{11}C]GO6976 (Scheme) for evaluation as a potential PET radioligand for imaging brain PKC.

Methods: An N-desmethyl precursor (P) was synthesized in three steps from a commercially available starting material (A, Scheme). P, also containing its unseparated isomer B, was treated with [^{11}C]CH_3I and Cs_2CO_3 in DMF at room temperature for 5 min, and the generated [^{11}C]GO6976 and its unseparated isomer ([^{11}C]GO-B, Scheme) were isolated with reverse phase HPLC. A rat (295 g) was injected with [^{11}C]GO6976/[^{11}C]GO-B (1.08 mCi; 3 Ci/μmol). Brain uptake of radioactivity was monitored for 70 min with an HRRT PET camera. A solution (0.30 mL, 2 mg/mL) of GO6976 in DMSO/PEG 400 (1: 2 v/v) was administered at 1 mg/kg body weight at 30 min after radioligand injection.

Results: Conditions for the preparative separation of the precursor (P) from its isomer (B) remain to be established. Analytical HPLC showed that the obtained mixture contained P and B in 2: 1 ratio. A variety of bases were evaluated for the radiolabeling of this mixture. However, only dry Cs_2CO_3 gave [^{11}C]GO6976 consistently. Low temperature was critical for successful radiolabeling. At 80 °C, acrylonitrile was eliminated from the obtained N-[^{11}C]methyl labeled product. Decay-corrected radiochemical yields of [^{11}C]GO6976/[^{11}C]GO-B were very low (~ 1%). The uptake of radioactivity in brain after i.v. injection of [^{11}C]GO6976 into rat was modest (1.0 SUV at ~ 9 min, n = 1). Administration of GO6976 displaced about 50% of the brain radioactivity.

Conclusions: The radioactivity in rat brain displaceable by carrier after administration of [^{11}C]GO6976/[^{11}C]GO-B may represent specific binding to PKC. Our initial PET findings warrant further improvement to precursor synthesis and [^{11}C]GO6976 radiosynthesis to allow further investigation of this radioligand behavior. This work is in progress.



Scheme. Synthesis of [^{11}C]GO6976

P261 RADIOSYNTHESIS OF [11C]A000571499, A NOVEL SELECTIVE CB1 ANTAGONIST

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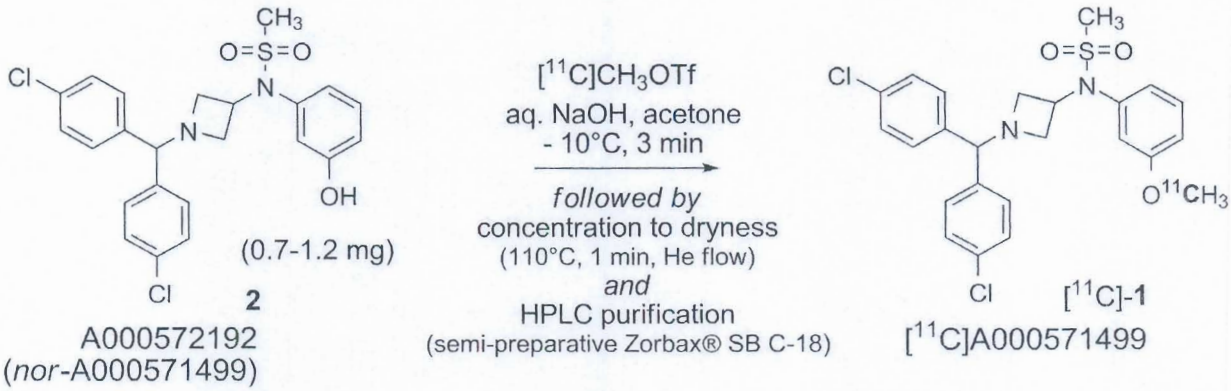
Objectives: Cannabinoid receptors type 1 (CB_1) are found in the brain, where they are thought to be the most widely expressed G-protein coupled receptors, but also in many peripheral tissues (such as heart, lung, prostate, testis and spleen). Within the brain, the highest densities of CB_1 are found in the globus pallidus, the substania nigra, the cerebellum, the cerebral cortex, the striatum and the hippocampus whereas the pons, thalamus and brain stem are almost devoid of CB_1 receptor expression. Abnormalities in regional brain CB_1 receptor densities or function may be involved in an array of neuropsychiatric and/or neurodegenerative disorders. Noninvasive and quantitative molecular imaging of these receptors with positron emission tomography (PET) could not only play a significant role in clinical research on neuropsychiatric conditions but clearly affect ongoing drug discovery and development processes. Within a novel series of N-[1-[bis(4-chlorophenyl)methyl]-3-azetidinyl]methanesulfonamides, developed by Sanofi-Aventis laboratories as highly selective CB_1-antagonists [1,2], A000571499 (1) was selected based on its pharmacological characteristics as a potent candidate for PET imaging and was labeled with carbon-11 ($t_{1/2}$: 20.38 min).

Methods: A000571499 (1) was labelled at its methoxy group from the corresponding nor-derivative 2 (A000572192) and the highly efficient methylation reagent [^{11}C]methyl triflate. Optimized conditions for the preparation of [^{11}C]-1 were the following: (1) trapping at -10°C of [^{11}C]methyl triflate in 300 µL of acetone containing 0.7 to 1.2 mg of precursor 2 (1.4 to 2.5 µmol) and 5 µL of a 3M solution of NaOH in water (15 µmol, about 6-10 eq.) ; (2) concentration to dryness of the reaction mixture (at 110°C, using a helium stream for 1 minute) ; (3) taking up the residue with 0.5 mL of HPLC mobile phase and (4) purification using semi-preparative HPLC (semi-preparative Zorbax® SB C-18, Hewlett-Packard (250 x 9.4 mm)). Formulation of [^{11}C]A000571499 ([^{11}C]-1) for i.v. injection includes a Waters SepPak®Plus C-18 cartridge-based removal of the HPLC solvents followed by a simple dilution with aq. 0.9% NaCl (physiological saline) to an ethanol concentration below 10%.

Results: Typically, starting from 55 GBq of a [^{11}C]CO_2 production batch, 9.5-10.0 GBq of [^{11}C]A000571499 ([^{11}C]-1, 55-148 GBq/µmol) were obtained within a total synthesis time of 25 to 30 minutes (non-decay-corrected radiochemical yields : 17-18%). No attempts were made to further optimise the process, the yields producing sufficient material for further evaluation.

Conclusions: [^{11}C]A000571499 ([^{11}C]-1) was labeled with carbon-11. Dynamic PET studies in baboons are currently underway to evaluate the potential of this radioligand to image CB_1-receptors in vivo.

References: [1] Black et al. WO2007067617. [2] Achard et al. WO2001064634.



COPPER-64 LABELING OF LIPOSOMES: POST-LABELING METHOD USING BIFUNCTIONAL LIGAND (BFL)

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Objectives: Non-invasive liposomal studies have been intensively exploited with SPECT. However, PET has rarely been applied in such studies although PET has advantages for pharmacokinetics and dynamics. We have developed a surface chelation labeling method, using Cu-64 (half life = 12.7 h) by simply adding Cu-64 to preformed liposomes which contain benzylTETA-lipids. Although this method provides fast and simple labeling of Cu-64, several limitations, such as limited buffer choice, prescribed pH during liposome formation, and lower labeling yield for targeted liposomal formulations, are disadvantages. In order to overcome these limitations, we designed and synthesized a bifunctional ligand (BFL), which could be conjugated to preformed liposomes at room temperature (Figure).

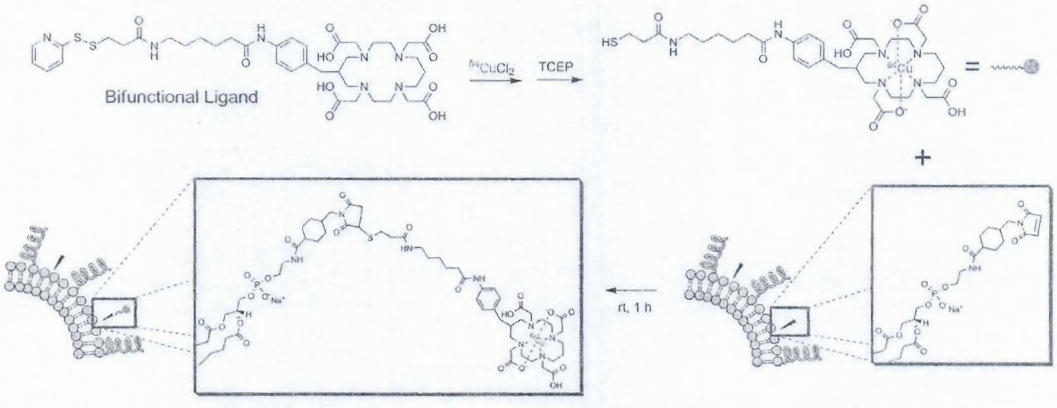

Figure. Post-labeling of liposome with BFL

Methods: Synthesis of bifunctional ligand: In brief, bifunctional ligand was synthesized from 4-nitrobenzyl bromide within six steps, which resulted in 12% overall yield. Liposomal formulation: Liposomes (10 mg) were formulated with HSPC (56 mol%), cholesterol (39 mol%), DSPE-PEG2K (5 mol%), and maleimide lipids of different molar ratios (0.1, 0.5, 1, and 5 mol%) at 60 °C within 10 min by a mini-extruder (100 nm membrane filter) in 0.12 M phosphate buffer (pH 7.0). Labeling: Cu-64 (0.75 mCi) was added to a solution of bifunctional ligands (6 nmol, 60 μL of 0.1 mM in 0.1 M ammonium citrate buffer, pH 5.5). After incubation for 30 min at 30 °C, freshly prepared 1.0 mM tris(2-carboxyethyl)phosphine hydrochloride (TCEP) solution (60 nmol, 60 μL) in 0.12 M phosphate buffer (pH 7.0) was added to bifunctional ligand solution. The mixture was incubated for 10 min at room temperature. Finally, the mixture was added to a liposome (5 mg, 0.2 mL) solution and incubated for 1 h. Labeled liposomes and free ligands were separated by a size exclusion column.

Results: Titration assay of Cu-64 (S.A. = 0.64 mCi/nmol) with BFL showed that 6 nmol of BFL ligand incorporated 99% of 0.75 mCi. Excess of TCEP (> 5 times vs BFL) reduces the pyridyldithio group required to generate free thiols within 10 min. Liposomes containing varied mol percent of maleimide (0.1%, 0.5%, 1.0%, and 5.0%) reacted with activated BFL, which resulted in 3%, 19%, 28%, and 83% labeling yield, respectively. Mole ratios of maleimide lipid vs BFL ligand (mol of maleimide lipid/mol of BFL ligand) were 0.55, 2.83, 5.83, and 28.5.

Conclusions: We have obtained 84% labeling yield when 5 mol% of maleimide (172 nmol) liposomes were reacted with Cu-64 chelated BFL (6 nmol). A key parameter is the molar ratio of maleimide lipids and bifunctional ligands. In vivo stability will be tested with mice to compare the stability of liposomes.

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

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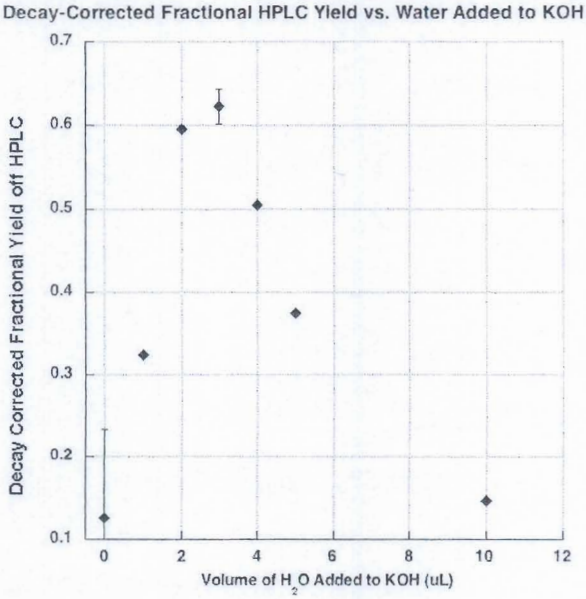
Objectives: In the preparation of (R)-[^{11}C]PK 11195, a ligand of the peripheral benzodiazepine receptor used in PET imaging of activated macrophages and microglia, we have noted sporadic chemical yields after replacing the ultra-dry DMSO (Baker Scientific) with a fresh vial (Fisher Scientific). We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

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

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



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

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

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

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

P073 INVESTIGATION OF META-SUBSTITUTED [18F]FLUOROBENZENE REACTIONS

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Objectives: The ability to reliably produce radiotracers by nucleophilic [^{18}F]fluorination in the meta position, relative to an electron withdrawing group, on a benzene ring remains a chemical challenge. Previous studies focused on [^{18}F]fluoro-for-nitro exchange on substituted 3-nitrobenzenes in a glassy carbon vessel (Constantinou et al., 2001] or under "instant fluorination conditions" [Windhorst et al., 2001]. During our recent investigation of methods to produce high yields of [^{18}F]fluoromethane, we found that reacting [^{18}F]fluoride ion ($K^{18}F/ K_{2.2.2}$) with meta-substituted N,N,N-trimethylanilinium triflates in 2,4,6 collidine/ acetonitrile containing 5-10 μL of water gave up to 50% 3-substituted-[^{18}F]fluorobenzenes (fluorine incorporation for m-toluene 5%; m-acetophenone 11%, m-benzophenone 10%; m-nitrobenzene 50%). When the fluoride was fully dried the yield for the m-nitro reaction increased to greater than 70%. Thus, we explored the ability to exchange label a variety of m-substituted N,N,N-trimethylanilinium triflates under the same conditions that gave consistent high yields for the nitro substituted precursor.

Methods: Aqueous [^{18}F]fluoride ion was azeotroped with acetonitrile in a thin walled glass vial, in the presence of base ($KHCO_3$: 1.6 mg or K_2CO_3: 1 mg) and kryptofix (6.2 mg), at 100°C under a vacuum and a stream of nitrogen. The m-substituted N,N,N-trimethylanilinium triflates (5 mg) dissolved in either 2,4,6-collidine: acetonitrile (4:3 v/v; 0.7mL) or DMSO (0.2 mL) was added to the dried [^{18}F]fluoride ion. The reactions were heated at 160°C for 10 minutes. The reactions were analyzed by radio-thin layer chromatography. The chromatograph results were corrected for the amount of [^{18}F]fluoromethane produced in the reaction.

Results: The results are shown in Table 1. The effect of the solvent and the base on the preparation of 3-[^{18}F]fluoro-nitrobenzene is noted. In DMSO the bicarbonate gave a lower yield of the labeled product versus the carbonate. In collidine/acetonitrile the base did not have any effect on the yield. For both bases 3-[^{18}F]fluoro-nitrobenzene yield increased significantly upon changing the solvent from DMSO to collidine/acetonitrile. The only other precursor that produced any [^{18}F]fluorobenzene product under non-aqueous reaction conditions was the 3-methylketo-N,N,N-trimethylanilinium triflate. Reaction of 1,3 dinitrobenzene in collidine/ acetonitrile gave <5% 3-[^{18}F]fluoro-nitrobenzene. Increasing the amount of carbonate from 1-1.5 equivalents reduced the 3-[^{18}F] fluoro-nitrobenzene yield to ~54% with a concomitant rise in [^{18}F]fluoromethane production from 7 to 23%.

Table 1: Reaction yields for the nucleophilic fluornation reactions

NMe_3 OTf Precursor (base)	2,4,6-Collidine: CH_3CN (4:3)	DMSO
m-NO2 (K_2CO_3)	70.9 ± 3.3%	50.2 ± 4.0%
m-NO2 ($KHCO_3$)	69.2 ± 6.7	36.2 ± 1.1%
m-$COCH_3$ (K_2CO_3)	<2%	
m-CN (K_2CO_3)	0%	
m-CH_3 (K_2CO_3)	0%	
m-OH (K_2CO_3)	0%	

Conclusions: No special reaction conditions or vessels were needed to reliably produce high yields of 3-[^{18}F]fluoro-nitrobenzene from 3-nitro-N,N,N-trimethylanilinium triflate in collidine/acetonitrile. These yields were achieved using standard resolubilization conditions. These same non-aqueous reaction conditions did not produce any meta-[^{18}F]fluoro for precursors with either electron-withdrawing (CN, $COCH_3$) or electron-donating substituents (OH, CH_3).

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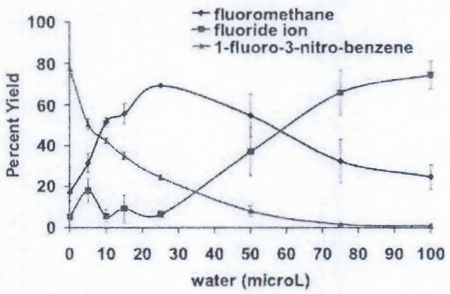

Reaction of [^{18}F]fluoride ion with 3-nitro-NNN-trimethylanilinium triflate in 4:3 collidine: acetonitrile, K_2CO_3 and $K_{2.2.2}$ with increasing amounts of water. The yield of 3-[^{18}F]fluoro-nitrobenzene steadily decreased with increasing amounts of water.

P413 PREPARATION AND BIODISTRIBUTION OF NEW 32P-CP-PLLA MICROPARTICLE

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Objectives: L-Polylactide (PLLA) is a good biocompatibility and biodegradable polymer. ^{32}P-chromic phosphate-L-polylactide (^{32}P-CP-PLLA) microparticle is a new control release preparation of the therapy radionuclide ^{32}P. The objective of the study is on preparation and biodistribution of ^{32}P-CP-PLLA.

Methods: ^{32}P-CP-PLLA microparticles were prepared by an SED process. Nude mice with 1.42±0.43 cm^3 pancreatic cancer xenograft were used to study the biodistribution of ^{32}P-CP-PLLA. The brain, heart, liver, spleen, kidney, lung, thyroid, muscle, bone and tumor were counted for radioactivity in the Liquid Scintillator at 1d, 3d, 7d ,14d and 28d post implantation. Six mice bearing tumor was also imaged by SKYLIGHT SPECT at 10min, 2h, 8h, 1d, 3d, 7d, 14d and 28d after implantation.

Results: The microparticle exhibits as a cylinder, the diameter length, height and mass were 0.85~0.9 mm, 2.2~2.5mm and 0.9~1.1mg, respectively. The radioactivity in the ^{32}P-CP-PLLA microparticles were restrained fully in the tumor(>98%). The microparticle disintegrated seldom at 28d.

Conclusions: The new microparticle is a successful dosage form. It could restrain diffusion of colloidal ^{32}P from tumor tissue to the other outer-tumor organs and deposit colloidal ^{32}P in the tumors for longer time.

Research Support: National 863 Program: 2007AA02Z471

P357 IN VITRO AND IN VIVO EVALUATION OF [64Cu-NO2A-(X)-BBN(7-14)NH2] RADIOPHARMACEUTICALS FOR POTENTIAL PET IMAGING OF HUMAN PROSTATE CANCER

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Objectives: Gastrin-releasing peptide receptors (GRPr) are expressed in high numbers on human prostate cancer. The bombesin peptide derivative, BBN(7-14)NH_2, has high affinity and selectivity to GRPr. Therefore, Cu-64 radiolabeled BBN(7-14)NH_2 conjugates could have potential in positron-emission tomography (PET) of human prostate cancer. Our aim was to produce ^{64}Cu-NO2A-(X)-BBN(7-14)NH_2 conjugates via the bifunctional chelate approach, where X = pharmacokinetic modifier (Beta-alanine, 5-aminovaleric acid, 6-aminohexanoic acid, 8-aminooactanoic acid, 9-aminonanoic acid, or para-aminobenzoic acid), and NO2A = 1,4,7-triazacyclononane-1,4-diacetic acid.

Methods: Solid-phase peptide synthesis was used to produce (X)-BBN(7-14)NH_2 conjugates, after which the bifunctional chelating ligand, NO2A, was added via manual conjugation. Radiolabeling was performed by incubating $^{64}CuCl_2$ with NO2A-(X)-BBN(7-14)NH_2 in buffered, aqueous solution (pH ~ 7). In vitro assays of the conjugates and non-radioactive ^{63}Cu conjugates were performed in human PC-3 cells. In vivo pharmacokinetic studies of the radiolabeled conjugates were performed in normal CF-1 and PC-3 tumor-bearing SCID mice. In vivo, multimodal, molecular images were obtained of the radiolabeled conjugates in PC-3 tumor-bearing SCID mice via microPET/CT and microMRI.

Results: In vitro studies indicated idea uptake of the NO2A conjugates (1.99-6.24 nM), and ^{63}Cu-NO2A conjugates (3.16-51.81 nM) in PC-3 cells. In vivo results of the ^{64}Cu-NO2A-(X)-BBN(7-14)NH_2 conjugates at 1, 4, and 24 h p.i. showed affinity towards GRPr-positive tissue and effective clearance properties. Due to the favorable in vivo pharmacokinetic properties of ^{64}Cu-NO2A-(X)-BBN(7-14)NH_2, high-resolution multimodal, molecular imaging was performed via microPET/CT and microMRI in a PC-3 tumor-bearing SCID mouse model. High-quality target to non-target images were obtained, with the tumors clearly visible.

Conclusions: The NO2A chelator effectively stabilized Cu(II) under in vivo conditions. ^{64}Cu-NO2A-(X)-BBN(7-14)NH_2 conjugates showed affinity and specificity towards GRPr-positive tissues. High quality microPET images of PC-3 xenografted tumors in SCID mouse model were obtained, demonstrating the potential for PET imaging of GRPr-positive human prostate cancer tumors.

P225 PREPARATION, BIOLOGICAL EVALUATION AND PHARMACOKINETICS OF 86Y-CHX-A''-DTPA-PANITUMUMAB FOR QUANTITATIVE PET IMAGING OF HER1-EXPRESSING CANCER

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Objectives: Panitumumab was conjugated to the bifunctional chelating agent, CHX-A''-DTPA and radiolabeled with 86Y (half-life= 14.7 h). Immunoreactivity was evaluated to determine the in vitro specificity of the radioimmunoconjugate (RIC). In vivo biodistribution, blood clearance, area under the curve (AUC), area under the moment curve (AUMC) and mean residence time (MRT) were determined on mice bearing HER-1 over-expressing human colorectal (LS174T), human prostate (PC-3) and human epidermoid (A431) xenografts. Receptor-specificity was demonstrated by co-injection of 0.1 mg panitumumab with the RIC. Longitudinal PET imaging was also performed to determine target-specific uptake.

Methods: Panitumumab was conjugated to the bifunctional chelating agent, CHX-A''-DTPA and radiolabeled with ^{86}Y (half-life= 14.7 h). Immunoreactivity was evaluated to determine the in vitro specificity of the radioimmunoconjugate (RIC). In vivo biodistribution, blood clearance, area under the curve (AUC), area under the moment curve (AUMC) and mean residence time (MRT) were determined on mice bearing HER-1 over-expressing human colorectal (LS174T), human prostate (PC-3) and human epidermoid (A431) xenografts. Receptor-specificity was demonstrated by co-injection of 0.1 mg panitumumab with the RIC. Longitudinal PET imaging was also performed to determine target-specific uptake.

Results: ^{86}Y-CHX-A''-DTPA-Panitumumab was successfully prepared with specific activity exceeding 2 GBq/mg and yields over 70%. The immunoreactivity ranged from 68-78%. Biodistribution and PET imaging studies demonstrated high specific tumor uptake of the RIC. In mice bearing LS174T, PC-3 or A431 tumors, the tumor uptake at 3d pi were 34.65, 22.1 and 22.74 % ID/g, respectively. The corresponding tumor uptake in mice coinjected with 0.1 mg cold panitumumab were 9.28, 8.80 and 10.04 % ID/g, respectively at the same time point, demonstrating specific blockage of the receptor. The LS174T, A431 and PC-3 tumors were clearly visualized by PET imaging after injecting 1.8-2.0 MBq ^{86}Y-CHX-A''-DTPA-panitumumab. Organ uptakes quantified by PET were closely related (r^2= 0.95, P= 0.87, n=30) to values determined by ex vivo biodistribution studies. From non-compartmental pharmacokinetic analysis in tumor bearing mice, the alpha-half life of blood clearance ranged from 2.9-3.8 h and the beta-half life was 76-81 h. LS174T tumor had the highest AUC (96.8 %ID·d·g^{-1}) and AUMC (262.5 %ID·d^2·g^{-1}), however the tumor MRT were identical for all three tumors (2.7-2.8 d). The LS174T tumor AUC: blood AUC ratio of 3.1 was greater than the PC-3 and A431 tumor: blood AUC ratios of 2.0.

Conclusions: This preclinical study of ^{86}Y-CHX-A''-DTPA-panitumumab demonstrates the potential of the radioimmunoconjugate for non-invasive assessment of the HER-1 status of tumors. It represents the first step towards clinical translation of ^{86}Y PET imaging of HER-1 using the full human monoclonal antibody, panitumumab.

Research Support: Intramural NIH

P235 PET IMAGING OF VEGF-A TUMOR ANGIOGENESIS WITH 86Y-CHX-A''-DTPA-BEVACIZUMAB

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Objectives: The vascular endothelia growth factor (VEGF) is an important angiogenesis target for the development of cancer therapeutics. Bevacizumab, a humanized mAb binds to tumor-secreted VEGF-A and therefore inhibits tumor angiogenesis. In 2004, Bevacizumab was approved by the FDA for the treatment of metastatic colorectal carcinoma in combination with chemotherapy. In this report, we describe the preclinical evaluation of ^{86}Y-CHX-A''-DTPA-bevacizumab for potential use in quantitative PET imaging of VEGF-A tumor angiogenesis.

Methods: Bevacizumab was conjugated to the bifunctional chelating agent, CHX-A''-DTPA and radiolabeled with ^{86}Y (half-life= 14.7 h). Immunoreactivity was evaluated to determine the in vitro specificity of the radioimmunoconjugate (RIC). In vivo biodistribution and PET imaging studies were performed on mice bearing VEGF-A positive human colorectal (LS174T), human ovarian (SKOV3) and VEGF-A negative human mesothelioma (MSTO-211H) xenografts. Receptor-specificity was demonstrated by co-injection of 0.05 mg bevacizumab with the RIC.

Results: ^{86}Y-CHX-A''-DTPA-bevacizumab was successfully prepared with specific activity exceeding 2 GBq/mg and yields over 70%. Biodistribution and PET imaging studies demonstrated high specific tumor uptake of the RIC. In mice bearing VEGF-A +ve LS174T, SKOV3 and VEGF-A –ve MSTO-211H tumors, the tumor uptake at 3d pi were 13.6, 17.4 and 6.8 % ID/g, respectively. The corresponding tumor uptake in mice coinjected with 0.05 mg cold bevacizumab were 5.8, 8.9 and 7.4 % ID/g, respectively at the same time point, demonstrating specific blockage of the target in VEGF-A +ve tumors. The LS174T, SKOV3 were clearly visualized by PET imaging after injecting 1.8-2.0 MBq ^{86}Y-CHX-A''-DTPA-bevacizumab. Organ uptakes quantified by PET were closely related (r^2= 0.87, P= 0.64, n=18) to values determined by ex vivo biodistribution studies.

Conclusions: This preclinical study demonstrates the potential of the 86Y-CHX-A''-DTPA-bevacizumab radioimmunoconjugate for non-invasive assessment of the VEGF-A tumor angiogenesis status.

Research Support: Intramural NIH

P091 SYNTHESIS AND EVALUATION OF FLUORINE-18 LABELED 2-FLUOROETHYL-6-PHENYLIMIDAZO[2,1-B] THIAZOLE AS A POTENTIAL MITOCHONDRIAL COMPLEX 1 INHIBITOR

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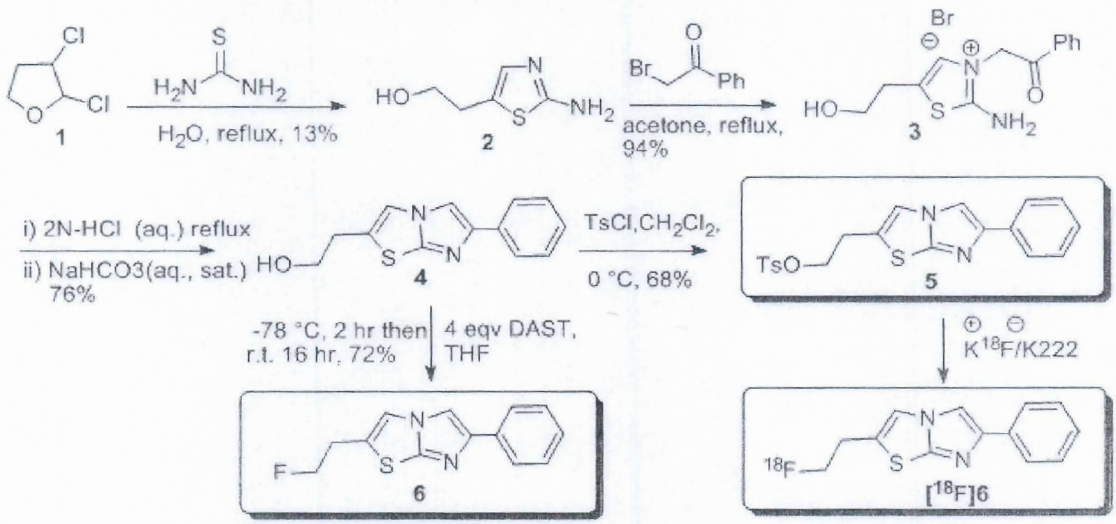
Objectives: The 2-alkyl substituted 6-phenylimidazo[2,1-b]thiazoles are potent inhibitors of the mitochondrial electron carrier enzyme, complex 1 (MC1) which is enriched in tissues consuming large amount of energy such as the heart. We developed a synthesis for fluorine-18 labeled 2-fluoroethyl-6-phenylimidazo[2,1-b]thiazole as a candidate fluorine-18 labeled potent inhibitor of MC1 for the assessment of myocardial perfusion using positron emission tomography (PET).

Methods: Compound 6 was synthesized from commercially available 2, 3-dichlorotetrahydrofuran as shown in scheme and ^{18}F labeling was performed from tosylate precursor 5 by 18F/K222 reaction.



Results: Radiochemical yield and with radiochemical purity over 99% as measured by radiometric HPLC. Biological evaluation in Sprague Dawley rats showed low heart uptake and defluorination.

Conclusions: A novel potential MC1 inhibitor has been prepared and radiolabeled with fluorine-18, but it did not show pharmacological requirements as a cardio-PET tracer.

P316 RELATIONSHIP BETWEEN CISPLATIN, COPPER-64 RADIOPHARMACEUTICALS AND p53 IN THE TRAFFICKING OF 64Cu TO THE NUCLEI OF TUMOR CELLS

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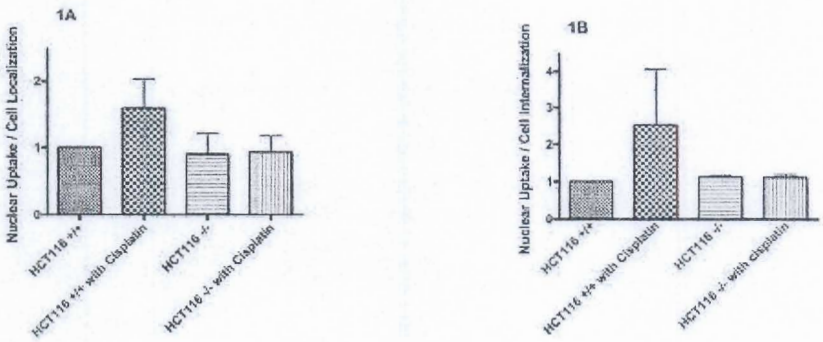
Objectives: Copper-64 ($T_{1/2}$ =12.7 h) emits β^+ and β^- particles for applications in both PET imaging and cancer therapy. Cisplatin is an effective antineoplastic agent that is used for the treatment of cancer. Its cytotoxicity is mediated mainly through interaction with DNA and inhibition of DNA synthesis and replication. We previously reported that the tumor suppressor protein p53 was involved in copper trafficking to tumor cell nuclei, as ^{64}Cu was delivered to nuclei in a p53 positive HCT116 colorectal cancer cells in significantly greater amounts than in p53 negative HCT116 cells.[1] Recently it was demonstrated that p53 may be a functional link of the differential effect of copper on cisplatin mediated cell death.[2] We are investigating the mechanism(s) of how ^{64}Cu and cisplatin may affect each other's trafficking to tumor cell nuclei, and their effects on cancer therapy.

Methods: Two human colorectal HCT116 cell lines that are positive and negative for p53 were used to compare internalization and nuclear localization of ^{64}Cu-acetate under the influence of cisplatin. HCT116 cells were incubated with or without cisplatin for a 16 h time course. Two different time points for the addition of ^{64}Cu were applied: 1) ^{64}Cu was added 1 h before cisplatin; and 2) ^{64}Cu was added 12 h after cisplatin.

Results: In HCT116+/+ cell line, cisplatin enhanced ^{64}Cu nuclear localization (HCT116+/+ w/ cisplatin versus wo/ cisplatin = 1.60±0.45 in Figure 1A, 2.53±1.55, in Figure 1B). However, cisplatin did not affect ^{64}Cu nuclear uptake in p53 negative cells (HCT116-/- w/ C-DDP versus wo/ C-DDP = 1.06±0.15 in Figure 1A, 0.99±0.07 in Figure 1B). Western blot showed that the expression of p53 was notably up-regulated by cisplatin, and the accumulation of p53 was more prevalent in the nucleus rather than in the cytosol.



Conclusions: These data demonstrate that p53 plays an important role in ^{64}Cu trafficking to cell nucleus as the upregulation of p53 expression enhances the nuclear uptake of ^{64}Cu. The data suggest that a synergistic therapeutic effect will result in combining cisplatin chemotherapy with targeted radiotherapy using ^{64}Cu radiopharmaceuticals in p53 positive tumors, in part due to the delivery of a higher radiation dose to the cell nucleus.

References: 1.Eiblmaier et al., Cancer Biol Ther. 2008; 7: 63-69.2.Kabolizadeh et al., Biochem Pharmacol. 2007; 73: 1270 1279.