# SYNTHESIS AND IMAGING OF AN 18F-LABELED RGD PEPTIDE FOR DETECTING αvβ3 INTEGRIN EXPRESSION IN VIVO

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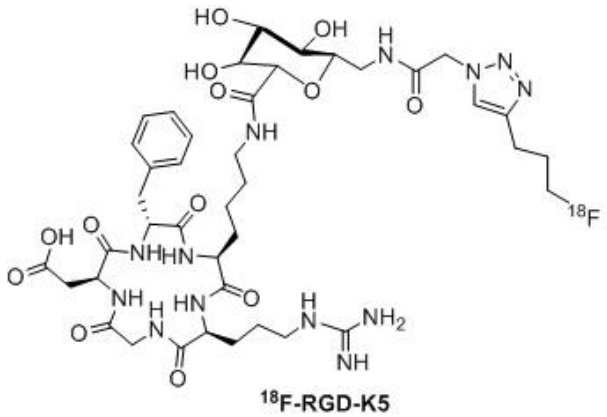
**Objectives:** To prepare and validate $^{18}$F-RGD-K5, a click chemistry-derived RGD-containing tracer for imaging integrin $\alpha_v\beta_3$ expression in vivo.

**Methods:** Synthesis of $^{18}$F-RGD-K5 was accomplished on an Explora RN automated synthesis module with average yields of 10-20% (decay corrected) and with average synthesis times of 90 min (n = 25). The specific activities ranged from 1.3 to 30 Ci/μmol. Briefly, pentyne tosylate was reacted with K$^{18}$F in the presence of K222, $K_2CO_3$ and MeCN at 110˚C followed by distillation and clicking with RGD-K5-$N_3$ in the presence of Cu(I). $^{18}$F-RGD-K5 was purified by RP-HPLC (MeCN:water w/ 0.05% TFA) and reconstituted in 10% EtOH:Water, via C18 trap and release, followed by sterile filtration. RGD-K5 binding affinity was determined by both a Biacore and a cell-binding assay using cRGDfK as the control. Metabolic stability analyses were carried out in athymic nude mice at 30 and 60 min post injection. Biodistribution of $^{18}$F-RGD-K5 was evaluated at several time points in U87MG tumor bearing aythmic mice. MicroPET imaging studies were also carried out in same U87MG mouse model capturing either static or dynamic images. cRGDyK was co-administered for blocking studies.

**Results:** RGD-K5 binds to integrin $\alpha_v\beta_3$ ($K_{d=}$ 7.9 nM) and its selectivity towards integrin $\alpha_v\beta_3$ is 2.3x to 3.4x higher vs related integrins. The pharmacokinetic results show limited uptake of the tracer in various organs after 2 hrs, with renal clearance being the predominant excretion pathway. In vivo metabolism analyses show that the tracer remains 98% intact after 2 hrs. MicroPET imaging results show $^{18}$F-RGD-K5 has preferential tumor uptake in U87MG xenografts with a tumor/muscle (T/M) ratio of >5:1 after 2 hrs. Co-administration of cRGDyK depressed $^{18}$F-RGD-K5 uptake in U87MG tumors. RGD-K5 was non-cytotoxic up to 5 μM in LS174T, A172 and MRC5 cell lines.

**Conclusions:** $^{18}$F-RGD-K5 has favorable imaging qualities: it displays selective renal clearance, is metabolically stable, has a high T/M ratio and has a high specificity for the integrin $\alpha_v\beta_3$ receptor. $^{18}$F-RGD-K5 is a promising tracer for imaging integrin $\alpha_v\beta_3$ expression in vivo.




**$^{18}$F-RGD-K5**

## SYNTHESIS, IN VITRO AND IN VIVO EVALUATION OF A METABOLICALLY STABILIZED GLYCOPEPTOID FOR PET IMAGING OF NEUROTENSIN RECEPTOR EXPRESSION

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**Objectives:** The neurotensin receptor (NTR1) is overexpressed in various colon cancer cell lines, suggesting its pivotal role during colorectal oncogenesis. The aim of this study is the development of a $^{18}$F-labeled bioisosteric NT(8-13)-derivative with high metabolic stability suitable for in-vivo imaging of NTR1 with positron emission tomography (PET). Therefore, we optimized a strategy for concomitant $^{18}$F-labeling and glycosylation based on the $Cu^{1}$-catalyzed Huisgen 1,3-dipolar cycloaddition („click"-chemistry), leading to the FDG-conjugated peptoid derivative [$^{18}$F]FDG-NT58, which was evaluated in vitro and in vivo.

**Methods:** The peptide-peptoid hybrids were obtained by microwave assisted Fmoc-solid-phase synthesis and analyzed by ESI-MS and LC-MS. Glycosylation of NT58 with 2-deoxy-2-fluoro-glucosyl azide was carried out using standard click-chemistry conditions ($CuSO_4$, sodium ascorbate, phosphate buffered saline). Receptor binding assays were performed using human NTR1 expressing CHO cells with $^{3}$H-neurotensin. The $^{18}$F-labeled glycopeptide ([$^{18}$F]FDG-NT58) was synthesized by $Cu^{1}$-catalyzed cycloaddition with 2-deoxy-2-[$^{18}$F]fluoro-glucosyl azide and isolated by semipreparative radio-HPLC. Saturation and internalization experiments were performed using NTR positive HT29 cells. Biodistribution and $\mu$PET studies were carried out using a HT29 cell xenograft nude mice model.

**Results:** NTR1-binding affinity of the glycosylated NT-derivatives was 0.32 nM (FDG-NT(8-13)) and 16 nM (FDG-NT58). Optimization of the three-step two-pot radiosynthesis of [$^{18}$F]FDG-NT58 led to a decay-uncorrected RCY of 17-20% after 75 min (based on [$^{18}$F]fluoride). After 30 min, 60-80% internalization of [$^{18}$F]FDG-NT58 was determined in HT29 cells. Furthermore, saturation experiments revealed a $K_D$ of 7.2±1.7 nM. [$^{18}$F]FDG-NT58 was stable in vitro (human serum, >98%, 3h, 37°C) and in vivo (blood, >99%, 65 min p.i.). Biodistribution experiments with [$^{18}$F]FDG-NT58 demonstrated a high kidney uptake (51-56 %/g) and negligible liver uptake, whereas tumor uptake was 1.3-2.5 %ID/g (30-65 min p.i). Tumor-to-blood ratios were about 3 (10-65 min p.i.) and coinjection of NT58 decreased the tumor uptake significantly. In $\mu$PET studies specific tumor uptake of [$^{18}$F]FDG-NT58 was observed (SUV=0.18±0.06, n=4), when compared with NT58-coinjected animals (SUV=0.05±0.01, n=3) at 55 min p.i.

**Conclusions:** Applying a novel click chemistry based glycosylation method for $^{18}$F-labeling, we successfully developed [$^{18}$F]FDG-NT58 as a peptoidic tracer with high affinity to NTR1, high metabolic stability and rapid biodistribution, allowing imaging studies of NTR positive tumors by $\mu$PET. Future efforts will aim at the decrease of kidney uptake by varying the glycosyl residue of [$^{18}$F]FDG-NT58.

## SITE-SPECIFIC 11C-LABELING OF PEPTIDES USING [11C]METHYL-TRIFLATE

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**Objectives:** Carbon-11 labeled peptides as potential PET radiopharmaceuticals have often been overlooked or disregarded because of the presumption that the presence of multiple reaction sites will lead to low labeling specificity when $^{11}$C-methylating agents such as [$^{11}$C]methyl iodide ($^{11}CH_3I$), [$^{11}$C]methyl-triflate ($^{11}CH_3Tf$) and [$^{11}$C]methyl-nonaflate ($^{11}CH_3Nf$) are used. From previous studies there is evidence that certain $^{11}$C-labeling precursors such as $^{11}CH_3Tf$ and $^{11}CH_3Nf$ display a strong preference for the most nucleophilic reaction site. This proof of principle study had as objective to confirm the hypothesis that a site-specific labeling of peptides using the highly reactive precursors $^{11}CH_3Tf$ and $^{11}CH_3Nf$ is possible in one step without protecting the other nucleophilic moieties present.

**Methods:** Three model peptides, one 10-mere and two 6-mere peptides and their corresponding mono-methylated derivatives (standards) were synthesized by solid phase peptide synthesis (SPPS) to serve as $^{11}$C radio-labeling precursors and their non-radioactive standard compounds. To render peptides susceptible to the labeling with [$^{11}$C]methyliodide and $^{11}CH_3Tf$, the radio-labeling precursors containing many protonated moieties (from acidic preparative HPLC workup) were treated with various equivalents of NaOH and then lyophilized to produce peptides in solid deprotonated form. $^{11}CH_3Tf$ (at room temperature) and [$^{11}$C]methyliodide (at elevated temperatures) were reacted with these deprotonated peptides in acetonitrile/water mixtures (12:1). After various time points, aliquots were taken and injected onto HPLC. For this purpose, an HPLC method was developed capable of differentiating between all methylated peptidic standard compounds. Retention times of the radioactive peaks were compared to the known retention times of the methylated standards to identify the $^{11}$C-labeled proteins.

**Results:** [$^{11}$C]Methyliodide exhibits almost no reactivity towards the investigated peptides. $^{11}$C-Methylation did occur though not at significant levels (<5%). In stark contrast, $^{11}CH_3Tf$ reacted with even low amounts of peptide (0.09-0.12 $\mu$mol) at room temperature and led to the exclusive formation of only one $^{11}$C-methylated peptide. In the case of peptide A and C, the reaction site was identified to be the cystein residue which reacts in good RCYs (50-65%) with the $^{11}CH_3Tf$. When peptide B was used, $^{11}CH_3Tf$ reacted with the N-terminus only (90-95% RCY) and left the lysine side chain un-methylated. Experiments using $^{11}CH_3Nf$ are currently under way.

**Conclusions:** In case of the investigated peptides A and C, $^{11}CH_3Tf$ demonstrated high selectivity towards the Cysteine side-chain, and no affinity towards any other amino acid residues. When peptide B which lacked a cystein residue was used, the $^{11}$C-methylation occurred exclusively at the N-terminus of the peptide and not at the lysine side chain. We demonstrated that $^{11}CH_3Tf$ is a highly selective labeling agent and can effectively distinguish between different chemical groups despite its extraordinary reactivity. It is anticipated that the use of $^{11}CH_3Nf$ will result in even higher RCYs. A complete systematic study of the reactivity of various peptidic side chains towards $^{11}$C-methylation is currently under way.

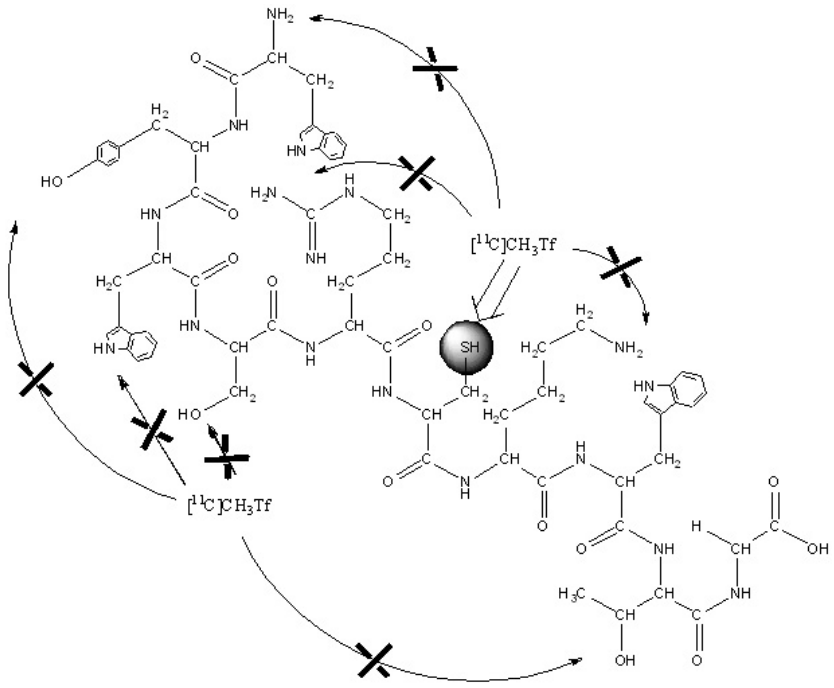


Fig. Site-specific $^{11}$C-methylation of a 10-mere peptide at the cystein-residue using [$^{11}$C]methyltriflate

## DOTA-SIB, A TRIFUNCTIONAL PROSTHETIC GROUP FOR MULTI-MODAL LABELING

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**Objectives:** To counter the tumor heterogeneity in targeted radionuclide therapy, it would be helpful if the same molecule could be utilized to attach different radionuclides to an antibody (mAb) or peptide. Our long term objective is to be able to develop a reagent that can be utilized to label a rapidly internalizing mAb targeting the epidermal growth factor receptor variant III (EGFRvIII) with the α-particle emitter $^{211}$At and the low energy β-emitter $^{177}$Lu. Our approach is based on the fact that tumor retention of radioactivity from internalizing mAbs labeled with radiometals often is higher than that from their conventionally radioiodinated analogues, which has been attributed in part to the highly hydrophilic nature of the chelating function. To exploit this, we have designed a prosthetic moiety that encompasses the structural elements of DOTA and that of N-succinimidyl 3-iodobenzoate (SIB), the archetypal conjugation radioiodination agent.

**Methods:** A standard of DOTA-SIB (Fig. 1), and a tin precursor with the COOH functions protected were synthesized in multiple steps. The tin precursor was radioiodinated and the product, protected DOTA-[$^{131}$I]SIB, was isolated by reversed-phase HPLC, extracted into ethyl acetate, and the dried activity was treated with TFA to yield DOTA-[$^{131}$I]SIB. An anti-EGFRvIII antibody, L8A4 was conjugated with DOTA-[$^{131}$I]SIB and, for comparison, with [$^{125}$I]SGMIB, a residualizing radioiodination agent developed by us.[1] Paired-label internalization assay in vitro and biodistribution in vivo of the two labeled mAbs were performed using EGFRvIII expressing U87MGΔEGFR glioma cells and mice bearing U87MGΔEGFR glioma xenografts, respectively.

**Results:** The tin precursor was radioiodinated in 82±11% (n=4) radiochemical yield and after deprotection, DOTA-[$^{131}$I]SIB was conjugated with L8A4 in 30±7% (n = 3) yield. Protein-associated radioactivity (TCA precipitation), and immunoreactivity determined by the Lindmo assay were 97-98% and 80-100%, respectively, and was comparable to that of L8A4 labeled using [$^{125}$I]SGMIB. In U87MGΔEGFR cells, the intracellularly trapped radioactivity from the DOTA-[$^{131}$I]SIB-L8A4 at 8, 16, and 24 h of incubation was 12.3 ± 2.0%, 21.4 ± 0.5%, and 26.2 ± 1.1%, respectively of the initially bound activity compared to 12.5 ± 1.8%, 16.7 ± 0.5%, and 14.9 ± 1.1%, respectively for [$^{125}$I]SGMIB-L8A4. From a paired-label biodistribution, the in vivo tumor uptake values (%ID/g) at 6 h, 1, 2, and 6 d were 14.0 ± 4.3, 23.1 ± 4.0, 25.7 ± 2.1 and 8.2 ± 5.6 for DOTA-[$^{131}$I]SIB-L8A4 and 15.5 ± 4.4, 22.5 ± 3.6, and 20.6 ± 2.1 and 4.3 ± 2.4 for [$^{125}$I]SGMIB-L8A4, respectively.

**Conclusions:** These results suggest that DOTA-SIB can be a valuable agent for the radioiodination of internalizing mAbs. Experiments are underway to label DOTA SIB-L8A4 with $^{177}$Lu and evaluate its internalization and biodistribution in EGFRvIII-expressing tumor models.

**References:** 1. Vaidyanathan et al. Bioconjugate Chem. 2001;12: 428-38.

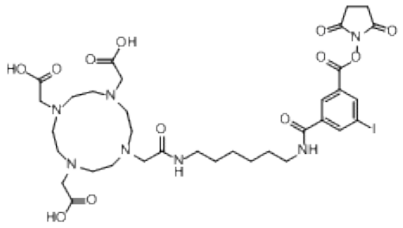

Figure 1. DOTA-SIB

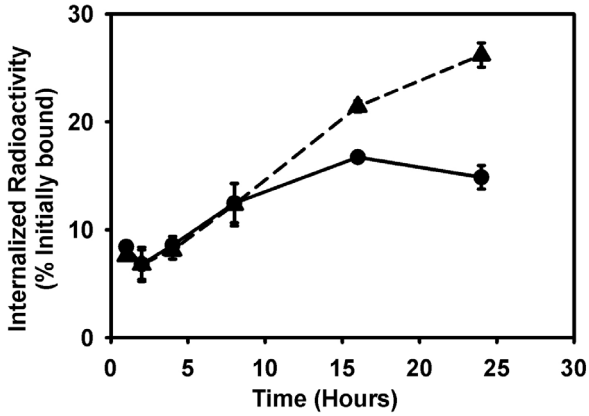


Figure. 2. Paired-label internalization of DOTA-[$^{131}$I]SIB-L8A4 (dashed line, triangle) and [$^{125}$I]SGMIB-L8A4 (solid line, circle) by U87MGΔEGFR cells

## TECHNETIUM-99M LABELLED MACROCYCLIC PEPTIDES AS INTEGRATED RADIOPHARMACEUTICALS

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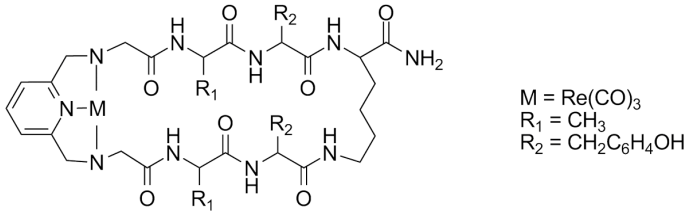
**Objectives:** G-protein coupled receptors (GPCR) are among the most heavily investigated drug targets in the pharmaceutical industry and are the target of over 40% of modern medicinal drugs. It has been hypothesized that ligands which bind and mediate bioactivity through these receptors adopt a general "turn" conformation. Many peptidomimetics intended to mimic these turn regions have been described. In contrast to these peptidomimetics, we have designed a macrocyclic peptide containing a tridentate chelation core, which will replace the turn region of the ligand with a non-peptidic rigid scaffold. This integrated radiopharmaceutical design incorporates Re(I)/Tc(I) directly into the peptide backbone, making the radionuclide a critical component for conformational control and thus influencing receptor binding.

**Methods:** The macrocyclic peptide was synthesized using solid phase Fmoc-based peptide chemistry. Fmoc-Lys(Fmoc)-OH was added as the first amino acid, with peptide chain elongation occurring from both the alpha and epsilon amine of the lysine. The branching five amino-acid peptide was extended by coupling of bromoacetic acid, followed by cyclization with a pyridyl tridentate chelation core through a substitution reaction resulting in an uncoordinated macrocyclic peptide. This macrocycle was then coordinated using $[Re(CO)_3(H_2O)_3]^+$. Both the uncoordinated as well as the coordinated peptide were purified by HPLC and analyzed by ESI-MS. Variable temperature NMR studies were performed to determine if intramolecular hydrogen-bonding was present between the two sides of the macrocyclic scaffold both before and after metal coordination.




**Results:** 2D gCOSY NMR was performed as a means of identifying the chemical shift of NH amide hydrogens present in the two macrocyclic peptides. Evidence of interstrand hydrogen-bonding was determined by analysis of the temperature dependence of the amide proton chemical shifts through variable temperature NMR studies in $d_6$-DMSO. For both macrocyclic peptides, two amide protons had low $\Delta\delta/\Delta T$ values of: -1.3 and -1.5 ppb/K for the uncoordinated species and -0.3 and -0.6 ppb/K for the rhenium coordinated cyclic peptide. These values fall in the $0 < \Delta\delta/\Delta T < -3$ ppb/K range, demonstrating participation in strong intramolecular hydrogen-bonding interactions. Based on these calculations, and with help from the gCOSY spectra, it was determined that alanine and tyrosine are the two amino acid residues involved in intramolecular hydrogen bonds for both the uncoordinated and the rhenium coordinated macrocycle.

**Conclusions:** We now have evidence that a metal complex can be incorporated into the core of a cyclic peptide without disrupting the inherent secondary structure. We are expanding these studies to develop turn-based peptidomimetics containing Re(I)/Tc(I) organometallic species with the intention of developing GPCR-binding radiopharmaceuticals that have improved pharmacokinetic properties.

**Research Support:** NSERC, CIHR-STP, Lawson Internal Research Fund.

# RADIOSYNTHESIS OF [64CU((S)-P-MALEIMIDO-BENZYL-NOTA)]- AND PREPARATION OF HIGH EFFECTIVE SPECIFIC ACTIVITY [64CU]-MAN-EXENDIN-4(9-39) VIA SITE-SPECIFIC PRELABELING

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**Objectives:** The kinetic stability of a $^{64}$Cu complex is a significant parameter for the design of a $^{64}$Cu-labeled radiotracer. A suitable chelator for $^{64}$Cu is 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA) (1). We describe the radiosynthesis of a [$^{64}$Cu]-NOTA-based maleimide reagent suitable for mild and site-specific radiolabeling of peptides bearing a thiol group. The synthesis procedure of [$^{64}$Cu((S)-p-maleimido-benzyl-NOTA)] [$^{64}$Cu]2 was optimized in terms of high specific activity (SA) of [$^{64}$Cu]2. The maleimide reagent [$^{64}$Cu]2 was used for the radiolabeling of the exendin-4 peptide fragment [Cys$_{40}$(NH$_2$)]exendin-4(9-39), which shows promise for PET imaging of beta cells in vivo.

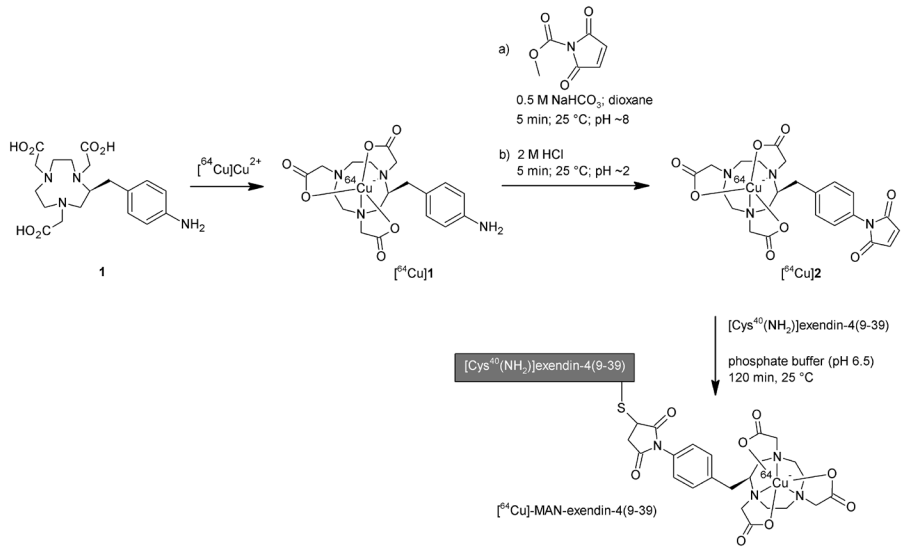
**Methods:** [$^{64}$Cu]2 was synthesized in two steps. Complexation of [$^{64}$Cu]Cu$^{2+}$ with (S)-p-NH$_2$-Bn-NOTA 1 at 90 °C resulted in the formation of two complex isomers. The major isomer [$^{64}$Cu]1 was obtained radiochemically pure after HPLC separation in 64% radiochemical yield (RCY). Maleimide formation was performed using N-methoxycarbonylmaleimide (2). A mixture of N-methoxycarbonylmaleimide (4 mg) and [$^{64}$Cu]1 in (300 $\mu$L) 0.5 M NaHCO$_3$/dioxane (1:1 v/v) were incubated at 25 °C for 5 min and subsequently treated with (50 $\mu$L) 2 M HCl for 5 min. The product [$^{64}$Cu]2 (91% RCY) was isolated by SPE-purification and finally used to radiolabel [Cys$^{40}$(NH$_2$)]exendin-4(9-39) at 25 °C (92% RCY).

**Results:** Starting with 500 MBq $^{64}$Cu (330 GBq/$\mu$mol at EOB), 125 MBq of the maleimide reagent [$^{64}$Cu]2 was isolated in a synthesis time of 110 min. High effective SA of [$^{64}$Cu]-MAN-exendin-4(9-39) (124 GBq/$\mu$mol at EOB) was obtained by HPLC separation of non-labeled [Cys$^{40}$(NH$_2$)]exendin-4(9-39). [$^{64}$Cu]-MAN-exendin-4(9-39) was finally tested in first preclinical studies, showing uptake of [$^{64}$Cu]-MAN-exendin-4(9-39) in islet cells of rat pancreatic tissue sections.

**Conclusions:** [$^{64}$Cu]2 was successfully used as a prelabeling reagent for radiolabeling of peptides. High RCYs and high effective SAs for [$^{64}$Cu]-MAN-exendin-4(9-39) were obtained using [$^{64}$Cu]2.

**Research Support:** This work was supported by the EU-FP7 integrated project BetaImage contract no.: 222980.

**References:** (1) Prasanphanich, A. et al. (2007) PNAS 104, 12462-12467. (2) de Bruin, B. et al. (2005) Bioconjug. Chem. 16, 406-420.



## IMAGING SEROTONIN TRANSPORTER WITH [C-11]DASB AND [C-11]AFM: A COMPARATIVE STUDY IN HUMANS

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**Objectives:** The new serotonin transporter (SERT) ligand [C-11]AFM was demonstrated to have higher binding affinity in vitro and displayed higher regional specific binding signals in the baboon brain than the current standard ligand [C-11]DASB (1). A PET imaging study in humans was conducted to compare the imaging qualities of these two tracers.

**Methods:** PET imaging was performed on the HRRT scanner. Four healthy human subjects (2 males and 2 females) were each scanned with [C-11]AFM and [C-11]DASB on the same day. Among the subjects, scanning order was counterbalanced between the two tracers. Scan duration was 120 min each. Metabolism of the tracers was analyzed by HPLC. Free fraction in the plasma was measured by ultrafiltration. Imaging data were analyzed using the Simplified Reference Tissue Model (SRTM2).

**Results:** Both [C-11]AFM and [C-11]DASB were prepared in high radiochemical yield and high specific activity. Specific activity at the time of injection was 6.8 ± 5.1 Ci/μmol for [C-11]AFM and 3.5 ± 1.3 Ci/μmol for [C-11]DASB. Injected mass was 2.3 ± 3.4 μg and 1.8 ± 0.6 μg, respectively, for [C-11]AFM and [C-11]DASB. In the blood, [C-11]AFM was metabolized faster than [C-11]DASB. At 30 min post-injection, parent fraction was ~20% for [C-11]AFM and ~40% for [C-11]DASB. Free fraction was lower for [C-11]AFM (8.5 ± 2.3%) than for [C-11]DASB (14.2 ± 4.0%). In the brain [C-11]DASB displayed higher uptake and faster kinetics. Peak uptake in the thalamus was ~60 min for [C-11]AFM and ~40 min for [C-11]DASB. On the other hand, [C-11]AFM displayed higher specific binding signals. For [C-11]AFM, the mean binding potentials ($BP_{ND}$) from all four subjects were 4.18, 2.09, 2.04, 1.84, 1.44, 0.79, respectively, in the raphe, amygdala, putamen, thalamus, caudate, and hippocampus, whereas [C-11]DASB $BP_{ND}$ values were 3.41, 1.49, 1.46, 1.55, 1.02, and 0.59, respectively, in the same regions. In the cortex [C-11]AFM $BP_{ND}$ values were 0.87, 0.57, 0.49, and 0.48 in the anterior cingulate, occipital, temporal, and frontal areas, compared with 0.64, 0.41, 0.38, and 0.38 for [C-11]DASB. Across all brain regions and all subjects, [C-11]AFM specific binding was ~31% higher than that of [C-11]DASB (range of 19 to 42%), a finding consistent with that from imaging study in baboons (1).

**Conclusions:** In humans [C-11]AFM provides higher specific binding signals than [C-11]DASB. This study suggests that [C-11]AFM may be a superior tracer for PET imaging of the SERT.

**Research Support:** Supported by a research grant from NIMH/NIDA (MH066624-05).

**References:** 1. Huang et al. J Cereb Blood Flow Metab 2002; 22:1377-1398