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A Bivalent Inhibitor of Prostate Specific Membrane Antigen Radiolabeled with Copper-64 with High Tumour Uptake and Retention

Nicholas Zia,[a] Carleen Cullinane,*[b],[c] Jessica K. Van Zuylekom,[c] Kelly Waldeck,[c] Lachlan E. McInnes,[a] Gojko Buncic,[a] Mohammad B. Haskali,[c] Peter D. Roselt,[c] Rodney J. Hicks*[b],[c] and Paul S. Donnelly*[a]

Dedication ((optional))

Abstract: *Molecules containing lysine-ureido-glutamic acid functional groups bind to the active site of prostate specific membrane antigen which is overexpressed in prostate cancer. To prepare copper radiopharmaceuticals for the diagnosis and therapy of prostate cancer macrobicyclic sarcophagine ligands tethered to either one or two lysine-ureido-glutamic acid functional groups through an appropriate linker have been prepared. Both ligands can be readily radiolabeled with positron-emitting copper-64 at room temperature. The bivalent agent, where two targeting groups are tethered to a single copper complex, dramatically outperforms the monomeric agent with respect to tumour uptake and retention. The high tumour uptake, low background and prolonged tumour retention, even at 24 hours post injection, suggest the bivalent agent is a promising diagnostic for prostate cancer and could be used for prospective dosimetry for therapy with a copper-67 variant.*

Prostate cancer is the most frequent malignant tumour in men and recurrence after initial therapy is common. Early detection of metastatic or recurrent lesions can guide potential therapeutic intervention. The prostate specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II, N-acetyl-α-linked dipeptidase I or folate hydrolase, is a membrane bound carboxypeptidase that acts as a glutamate carboxypeptidase on the neuropeptide N-acetyl-L-aspartyl-L-glutamate and various other substrates including folate.[1] PSMA is located within the cytosol in normal prostate cells but becomes membrane bound in prostate carcinoma.[2] PSMA expression is especially high in metastatic and hormone-refractory cancers making it an excellent candidate for diagnostic imaging and targeted radiotherapy.[1, 3] Low molecular weight inhibitors of PSMA, based on ureido linked dipeptides with the general formula lysine-ureido- glutamate have proved useful in developing diagnostic imaging and therapeutic agents that bind selectively to PSMA.[4]

Diagnostic imaging by positron emission tomography (PET) relies on tracers that have been labeled with positron-emitting radionuclides and can guide therapy with ionizing particle-emitting radionuclides. Diagnostic PET imaging and radionuclide therapy both require selective targeting of tumour tissue and this can be achieved by tethering the radionuclides to peptides or small molecules that bind selectively to surface receptors expressed in higher density on tumour cell membranes when compared to non-tumour tissue.[5] Ideally, a single molecular agent should be used for both imaging and therapy using a 'matched pair' of isotopes. Substantial research has led to adaption of protocols where PET imaging with positron-emitting gallium-68, [^{68}Ga]Ga-PSMA-11, is used to guide therapy with a different molecule containing β-emitting lutetium-177, PSMA-617.[6] Both agents rely on substituted Lys-ureido-Glu pharmacophores to target PSMA. It is unlikely that different molecules using two different chemical elements (gallium and lutetium) have the same binding and internalization interactions. The use of the same element for both imaging and therapy would represent an important advance.

There are two radionuclides of copper that offer the potential of being used as 'matched pair' with the same molecular 'theranostic' agent. The positron-emitting copper-64 isotope ($t_{1/2}$ = 12.7 h, β^+ = 17.4%, $E_{max}\beta^+$ = 653 keV) can be used as a companion diagnostic to plan therapy with β^--emitting copper-67 ($t_{1/2}$ = 61.9 h, β^- = 100%, $E_{mean}\beta^-$ = 141 keV).[5c, 7] The use of copper radionuclides for diagnostic imaging and therapy requires the use of metal-binding ligands that form complexes that are stable in vivo. The macrobicyclic hexamine cage sarcophagine (sar) ligands form kinetically inert and stable Cu(II) complexes.[8]

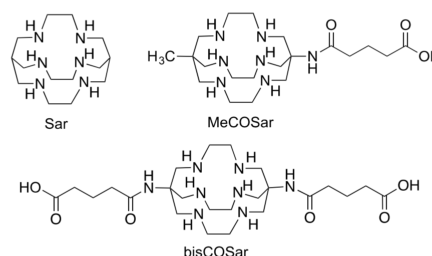

Figure 1. The structures of Sar, MeCOSar and bisCOSar.

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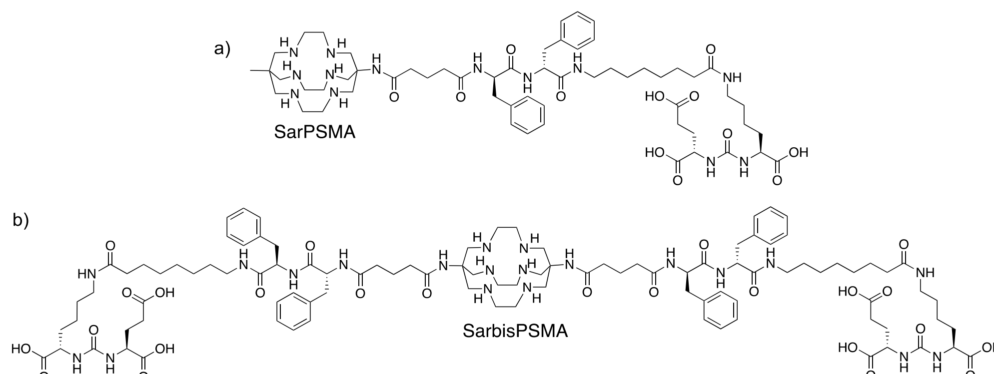

Figure 2. The structures of SarPSMA (a) and SarbisPSMA (b).

The fast complexation kinetics of sarcophagine with Cu(II) even at low concentrations and at room temperature make sar ligands well suited for copper radiopharmaceutical applications.[9] Sarcophagine ligands with pendent carboxylate functional groups can be conjugated to tumour targeting peptides and antibodies.[10] A copper-64 sarcophagine-octreotate conjugate, [^{64}Cu]CuSarTate, performed very well in a first in human trial in neuroendocrine tumour patients.[11] A clinical trial where [^{67}Cu]CuSarTate is being administered to meningioma patients is in progress (ACTRN12618000309280).

The protease active site of PSMA contains two zinc(II) ions that resides within a deep hydrophobic tunnel.[2a] Inhibitors of PSMA based on glutamate-ureido-lysine molecules interact with the active site through the three carboxylate residues. It has also been suggested that the ureido functional group may coordinate to one of the zinc(II) ions.[12] Separation of the radioactive metal complex and the glutamate-ureido-lysine functional group by hydrophobic linkers that are approximately 20 Å long provides the best results.[12-13] In this work, a sarcophagine chelator, MeCOSar (Figure 1),[14] was separated from a glutamate-ureido-lysine dimer by two hydrophobic D-phenylalanine residues and 6-aminooctanoic acid (Aoc). The use of the D-phenylalanine residues was aimed at providing a linkage with improved metabolic stability. The lysine-ureido- glutamate functional group was synthesized by reacting *N*-imidazole-activated and *t*-Boc protected glutamic acid with *N*ε-DDiv protected L-lysine that had been immobilised on Wang resin. The 8-aminooctanoic acid and two D-phenylalanine residues were sequentially incorporated using standard solid phase peptide synthesis followed by addition of the sarcophagine chelator, (t-Boc)$_{4-5}$MeCOSar.[14] Deprotection and cleavage from the resin followed by purification using reversed phase HPLC allowed isolation of SarPSMA (Figure 2).

The high tumour retention of antibodies is attributed to multivalent interactions provided by the presence of two antigen binding domains per antibody. The multivalency of antibodies has inspired studies on bivalent peptides that have reduced k_{off} rates leading to better tumour retention.[15] To investigate the potential advantages of bivalent interactions with PSMA a bivalent sarcophagine conjugate was prepared a derivative of sarcophagine with two aliphatic carboxylate groups (bisCOSar, Figure 1).[10b] The synthesis of SarbisPSMA was achieved by reacting dPhe-dPhe-Aoc-t-BocLys-ureido-(t-Boc)$_2$Glu prepared using standard peptide coupling techniques with the t-Boc protected N-hydroxysuccinimidyl ester of bisCOSar.[10b] Both SarPSMA and SarbisPSMA can be readily labelled with copper-64 in 20 minutes in aqueous solutions at room temperature to give radiochemical purities of >97%.

The cell surface binding and internalization was measured in PSMA positive LNCaP (human prostate adenocarcinoma) cells. Cells were incubated with either [^{64}Cu]CuSarPSMA or [^{64}Cu]CuSarbisPSMA (5 nM final concentration) at 37°C for either 15, 30 or 60 minutes. The cell medium was then removed and the cells washed with phosphate buffered saline. The surface bound fraction was determined by washing the cells with 0.5 M glycine, pH 2.5. The internalized fraction was determined by lysing the cells with NaOH (1 M). Both cell surface and internalized fraction were normalized to total protein concentrations in the fractions (%IA/mg protein). [^{64}Cu]CuSarPSMA showed reasonable cell surface binding at all time points (2.4 ± 0.3 %IA/mg at 30 minutes, Figure 3).

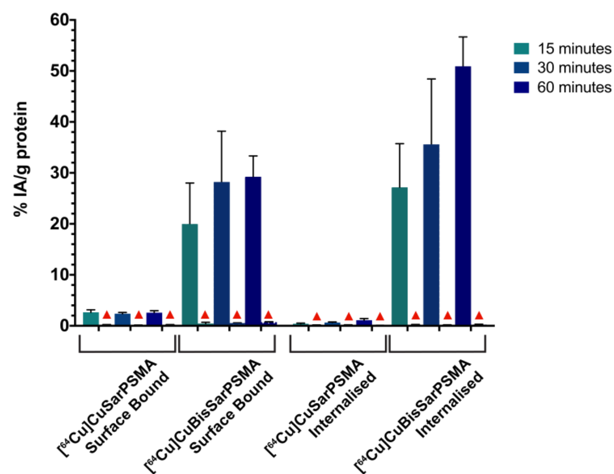

Figure 3. Binding to cell surface and internalization of [^{64}Cu]CuSarPSMA and [^{64}Cu]CuSarbisPSMA in PSMA positive LNCaP cells expressed as % injected activity per mg of protein (%IA/mg ± SEM). Red triangles highlight the extent of cell binding and internalization under the same conditions except in the presence of a 100-fold excess of non-radioactive 'blocking' peptide.

The bivalent agent, [^{64}Cu]CuSarbisPSMA, displayed higher cell surface binding (28 ± 10 %IA/mg at 30 minutes) and internalization (36 ± 13 %IA/mg at 30 minutes). Cell surface binding and internalization could be inhibited for both agents by

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the addition of excess non-radioactive agent, consistent with receptor mediated binding and uptake (Figure 3). It is possible that the higher surface binding and internalization of the bivalent agent is caused by reduced dissociation rates (k_{off}) when compared to the monomer as has been suggested for a bivalent PSMA targeting gallium-68 complex.[15c] Although it is acknowledged that PSMA is an internalizing membrane protein and further experiments are needed to investigate the origins of the increased uptake.

The PET imaging potential of both tracers was evaluated in PSMA positive LNCaP tumour bearing NSG mice. Following administration of [^{64}Cu]CuSarPSMA via tail vein injection PET images were acquired at 0.5, 2 and 22 hours post injection (p.i) (Figure 4). Significant tumour uptake is evident at all time points (0.5 h SUV_{max} 0.96 ± 0.1, 1.5 h SUV_{max} 0.89 ± 0.1, 22 h SUV_{max} 0.25 ± 0.02). The high uptake in the kidney and bladder reflects both the expected renal clearance of peptides and the relatively high expression of PSMA in murine kidneys.[6a, 16]

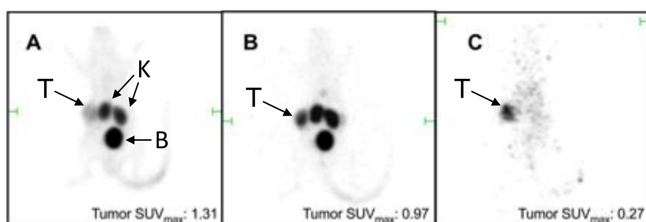

Figure 4. Representative PET images (maximum intensity projection) of LNCaP tumour bearing NSG mice following administration of [^{64}Cu]CuSarPSMA (17 MBq) at 0.5 h (A), 1.5 h (B) and 22 h (C) p.i. Tumour uptake (T) is evident at all times points. Kidney (K) and bladder (B) uptake at 0.5 and 1.5 hours reflects renal metabolism and PSMA expression in murine kidney.

The *in vivo* biodistribution of [^{64}Cu]CuSarPSMA was assessed in the same model. The tumour uptake and organ biodistribution was assessed at 1 h, 6 h, and 22 h (Figure S1). The tumour uptake at 1 h post injection (p.i.) was very high at 9 ± 1 %IA/g. After 6 h the uptake in the tumour reduces to 4.2 ± 0.5 %IA/g and further reduces to 1.0 ± 0.1 IA/g at 24 h p.i. (Figure 5a). The high degree of tumour uptake is similar to the tumour uptake of [^{68}Ga]GaPSMA-11 (5. ± 1 IA/g at 1 h p.i.) in the same model.[15c] The short radioactive half-life of gallium-68 ($t_{1/2}$ = 68 minutes) does not allow the acquisition of data at longer times points.

The *in vivo* biodistribution of bivalent [^{64}Cu]CuSarbisPSMA in the same LNCaP tumor-bearing NSG mouse model revealed significantly higher tumour uptake and retention, 22 ±1 %IA/g at 1 h p.i, 26 ± 4 at 24 h p.i) when compared to the monomer (Figure 5a). The high expression of PSMA in murine kidney once again resulted in high initial kidney uptake (120 ± 7 %IA/g at 1 h p.i) but this reduced to 20 ± 14 %IA/g after 24 h (Figure S2).

The high tumour uptake was confirmed by PET imaging in LNCap tumour bearing male NSG mice. The PET images show high uptake and retention of the tracer over the 24 h imaging period (Figure 5b). The average tumour SUV_{max} at 1 hr was 11.4 ± 1.0 and this increased to 12.9 ± 0.6 at 24 hr (n = 3). The specificity of the PSMA mediated uptake in both the tumour and the kidneys was confirmed by experiments where [^{64}Cu]CuSarbisPSMA was co-injected with the known PSMA specific inhibitor, 2-(phosphonomethyl)pentanedioic acid (PMPA). The co-administration of the PMPA dramatically reduced the uptake of tracer in both the kidney and tumour and led to rapid clearance (Figure 5b).

In summary, we have designed and synthesized two new sarcophagine ligands tethered to either one or two PSMA targeting Lys-ureido-Glu pharmacophores through an appropriate linker. Both ligands can be readily radiolabeled with positron-emitting copper-64 and both complexes bind selectively to PSMA positive cells. The high stability of the copper(II) sarcophagine complexes allow acquisition of high quality PET images in PSMA positive tumour bearing mice. The monomeric agent, [^{64}Cu]CuPSMA, has good tumour uptake that is similar to a clinically used gallium-68 PSMA imaging agent (Ga-PSMA-11) at 1 h p.i. The longer half-life of copper-64 when compared to gallium-68 (68 minutes) permits acquisition of images at later time points where clearance of non-bound tracer can lead to better images as well as facilitating centralized manufacturer, and distribution of the tracer. The bivalent agent, [^{64}Cu]CuSarbisPSMA, where two targeting groups are tethered to a single copper complex, dramatically outperforms the monomeric agent with respect to tumour uptake and retention. The high tumour uptake, low background and prolonged tumour retention, even at 24 h post injection, suggest [^{64}Cu]CuSarbisPSMA is a promising diagnostic for prostate cancer and could be used for prospective dosimetry for therapeutic use of a copper-67 variant of this agent.

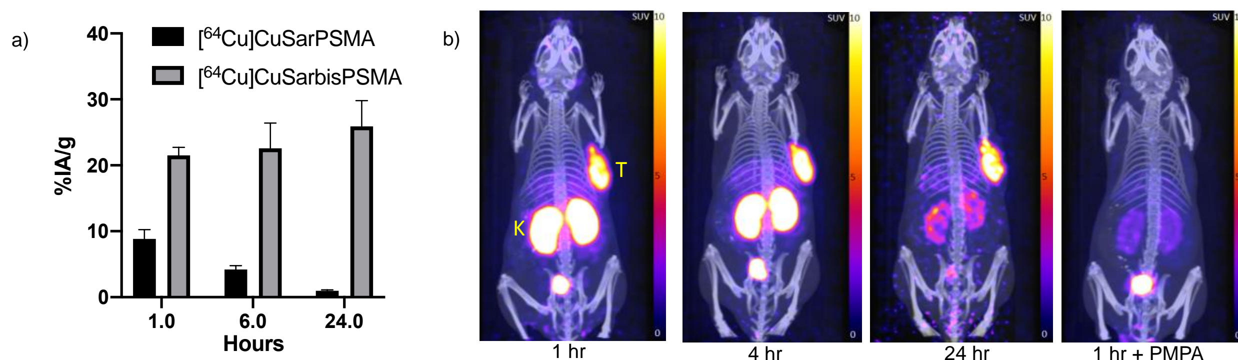

Figure 5. a) *Ex-vivo* tumour uptake expressed as percent injected activity/gram tissue (% IA/g) (mean ± SEM, n = 3/group) in LNCap bearing NSG mice following injection of either [^{64}Cu]CuSarPSMA (2 MBq, 0.9 nmol of peptide) or [^{64}Cu]CuSarbisPSMA (2 MBq, 0.2 nmol of peptide). b) PET/CT images (MIP) of LNCap

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tumour bearing NSG mice following injection of [^{64}Cu]CuSarbisPSMA (2-3 MBq). Tumour (T) and kidney (K) uptake could be blocked by co-administration of PMPA.

Experimental Section

See supporting information for experimental details.

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Keywords: bioinorganic chemistry • copper • macrocyclic ligands • imaging agents • radiopharmaceuticals

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

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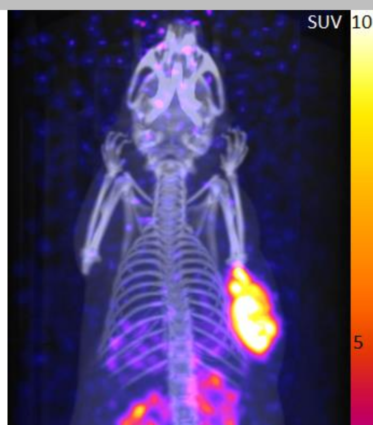
A new potential imaging and therapeutic agent for prostate cancer with high tumour uptake and retention has been prepared by tethering two peptides that bind to prostate specific membrane antigen to a single copper complex.



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Page No. – Page No.

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