EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH

Proposal to the ISOLDE and Neutron Time-of-Flight Committee

Study of the kinetics of complex formation and *in vivo* stability of novel radiometal-chelate conjugates for applications in nuclear medicine.

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Abstract

Targeted radionuclide therapy (TRT) and diagnostics are currently the most intensively developing fields of nuclear medicine as they allow for very precise imaging of tumors (or other targeted tissue), and minimization of healthy tissue damage during medical therapy. TRT relies on the labeling of a radionuclide to a targeting vector – a biomolecule that has high affinity to over-expressed antigens on the surface of tumor cells. It targets tumors, or other diseases, at the cellular level and increases the radiation dose to the target relative to healthy tissue during therapy. However, design and synthesis of radiopharmaceuticals suitable for TRT require a solid understanding of the stability of radionuclide complexes *in vivo*. Conventional methods to characterize thermodynamic stability of complexes often rely on non-radioactive surrogates under biologically irrelevant conditions; moreover, little information on kinetics of formation and kinetic inertness can be drawn. Therefore, in this proposal we request 15 shifts to pursue our work on determining the kinetics of complex formation (and stability) for ^{111}In/^{111}Cd, ^{119}Sb, ^{212}Pb and ^{197m}Hg based ligands and the study of *in vivo* radionuclide generators utilizing pairs of lanthanides with the use of Perturbed Angular Correlation of γ-rays (PAC) spectroscopy.

Requested shifts: 15 shifts (^{111m}Cd, ^{118m}Sb, ^{139m}Nd, ^{140}La, ^{147}Gd, ^{149}Gd, ^{151}Tb, ^{172}Lu, ^{199m}Hg, ^{204m}Pb), split into several runs over 2 years.

I. Motivation and rationale for using PAC spectroscopy

ISOLDE offers a great diversity of pure radioactive beams which are highly demanded for studies of basics mechanisms involved in radionuclide complexation to a targeting vector and the complex thermodynamic stability of radiopharmaceuticals suitable for targeted radionuclide diagnostics and therapy (TRT). Many of the radioisotopes of interest in nuclear medicine are metals, and can be attached to the targeting vector of interest with relative ease via a chelating ligand to form a radionuclide complex (radiopharmaceutical). However, the design and synthesis of such complexes suitable for TRT requires a solid understanding of the targeting vector complexation, radiometal coordination, and overall thermodynamic complex stability and kinetic inertness *in vivo*. Conventional methods, such as NMR, EXAFS, UV, potentiometric titration, and X-ray crystallography, often rely on non-radioactive surrogate probes under biologically irrelevant conditions, i.e. physiologically-relevant concentrations of studied metal ions, and very low concentrations of the studied complexes. Moreover, limited quantitative information on kinetics of complex formation, or transchelation, can be drawn from these experiments. Therefore, in this proposal we want to make use of the radioactive ion beams produced at ISOLDE; we particularly wish to take advantage of those ion beams for isotopes which are suitable for PAC and very hard to produce by other techniques, in order to directly and systematically investigate radiometal-complex structure, kinetics of formation, and stability. In the first set of experiments, we propose to use well established systems based on ^{111}In and DOTA/DTPA followed by novel chelation systems based on –"pa" ligands at TRIUMF to confirm data on complex structure and stability constants. Further we propose to use ^{111m}Cd to confirm our data obtained for ^{111}In as the coordination geometry is very different for these two chemical elements. Based on these results we will establish chelation preferences of several novel therapeutic radionuclides for alpha and Auger electron therapy, namely ^{212}Pb, ^{119}Sb and ^{197m}Hg, based on experiments performed with PAC analogues: ^{204m}Pb, ^{118m}Sb and ^{199m}Hg, respectively. The second set of experiments will aim at establishing the possibility for *in vivo* generators by measuring the release of radiometals from chelates during transition from meta-stable to ground state with the use of PAC. For these experiments we propose to use lanthanide pairs due to their similarity in chelation preferences, including: ^{139m}Nd/^{139}Pr, ^{140}La/^{140}Ce, ^{147}Gd/^{147}Eu, ^{149}Gd/^{149}Eu, ^{151}Tb/^{151}Gd, and ^{172}Lu/^{172}Yb. PAC is a well-established spectroscopic technique in condensed and soft matter fields [Tro00]. Over the past decades, PAC has proven to be invaluable for studies of the ligand type, coordination and position around the metal ion of interest, flexibility of the metal ion binding site, and determination of rate constants for chemical exchanges on the nanosecond time scale [Hem04]. Therefore, due to its sensitivity (many orders higher than other spectroscopic techniques) and information available, PAC appears to be a perfect technique for experiments described in this proposal. The ultimate aim and anticipated future direction of this project is use PAC to measure the in vitro and/or in vivo integrity of a metal-based radiopharmaceutical as a function of time.

II. Proposed experiments

1. Complex structure and kinetics for complex formation and stability of several novel radiopharmaceuticals

TRT based on alpha and Auger electron emitting radionuclides can be a very powerful strategy for selective killing of cancer cells. Thanks to high Linear Energy Transfer (LET) of alpha particles and Auger electrons, when their emitters are attached to a selective delivery

system, they can provide a very localized and lethal radiation dose to cancer cells with minimal damage to surrounding healthy tissues. Recent success using alpha emitting radionuclides in clinics suggests its wide application in the near future [Kra16]. For Auger electron emitting radionuclides, the proximity to the DNA is a crucial component of successful therapy. Several studies have shown pre-clinical promise of application of Auger electron emitting radionuclides for therapy (e.g. [Thi16]). In both cases stable attachment of radionuclides to the selective delivery systems (e.g. antibody, peptides, nanotransporters etc.) is a key factor for effective application of radiopharmaceuticals. Bifunctional chelators (BFCs) are typically used to attach radionuclides to biomolecules. As implied by their name, BFCs have two functions, first to bind the radiometal ion in a tight and stable coordination complex, and secondly they incorporate a reactive functionality (point of derivatization) for attachment of a targeting vector (e.g. biomolecule). The reactive functionality affixed to the BFC typically reacts with primary amines on biomolecules to create a covalent linkage between the targeting vector and chelate, without compromising either binding affinity/specificity of the biovector or the metal-complexation performance of the chelator. Choice of an appropriate BFC in governed by the best-fit of the ratiometal governed by preferences in coordination chemistry and donor-ability of the ligand in order to form a stable and inert metal-chelate complex. Each element has specific preference for chelation agents based on its chemistry. Therefore, finding the most suitable chelation agent is a crucial point for each radiopharmaceutical.

In the present project we propose first establishing and validating a PAC measurement system for determination of complex structure and thermodynamic stability constants by measuring these parameters for well-known ^{111}In-DTPA/DOTA complexes and comparing our experimental values with literature values. Further, we will test several alternative chelation systems suitable for ^{111}In designed by Dr. Orvig's group at the Chemistry Department of the University of British Columbia; all these experiments will be performed at TRIUMF. Later, we will use at ISOLDE a ^{111m}Cd beam to confirm that our data obtained with ^{111}In were recorded on In and not its daughter (Cd). The octadentate picolinate acid chelator H_4octapa (N_4O_4) developed by Orvig and co-workers [Pri12, Pri13] has shown promise as a bifunctional chelate for ^{111}In radiopharmaceuticals. H_4octapa boasts the ability to complex $^{111}In^{3+}$ quantitatively at ambient temperature in 10 min with specific activities as high as 2.3 mCi/nmol. Moreover, the resulting $[^{111}In(octapa)]^-$ complex demonstrated improved *in vitro* stability in mouse serum when compared to $[^{111}In(DOTA)]^-$ and $[^{111}In(DTPA)]^{2-}$ over 24 hours. Computational studies using DFT revealed an 8-coordinate structure of $[In(octapa)]^-$ (Figure 1), and potentiometric titrations determined the thermodynamic formation constant of the complex to be log K_{ML} = 26.8, compared to 23.9 for the In-DOTA complex (Table 1) [Pri12].

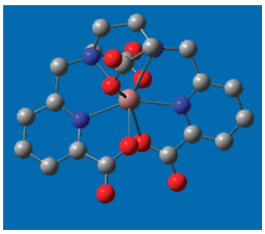

Figure 1. DFT structure of ($[In(octapa)]^-$ (solvent = water) showing 8-coordinate structure [Pri12, Pri13].

The goal of this proposal is to establish a PAC method that can provide invaluable insight into the structure, and stability of metal-based radiopharmaceuticals by first validating the PAC technique with known metal-chelate pairs and comparing to literature thermodynamic stability values. Based on this data we will test chelation systems for other promising therapeutic radionuclides as below. The methods developed within the experiments of this proposal will build the framework for future PAC experiments of metal-based radiopharmaceutcials in an *in vitro* or *in vivo* system; these experiments could provide vital information regarding complex stability and behaviour of the metal ion under truly biologically relevant conditions.

^{204m}Pb for ^{212}Pb based radiopharmaceuticals: ^{212}Pb ($t_{1/2}$ = 10.6 h) is a β^- emitter (100%, 570 keV) widely studied for α-particle therapy because it is the immediate parent radionuclide of the α-emitter ^{212}Bi ($t_{1/2}$ = 60.6 m). Radionuclides of lead are found in their +2 oxidation state, and classified as a borderline acid according to Pearson's hard-soft acid-base theory [Ram13]. TCMC, 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane is the most successful lead(II) chelate in development thus far for ^{212}Pb radiopharmaceuticals. TCMC employs an octadentate ligand set with nitrogen and oxygen donors. The bioconjugate ^{212}Pb-TCMC-Trastuzumab currently completed a Phase I clinical trial for treatment of cancers that express the HER-2 antibody receptor [Yon11]. TCMC will be tested with ^{204m}Pb as a surrogate for ^{212}Pb radiopharmaceuticals.

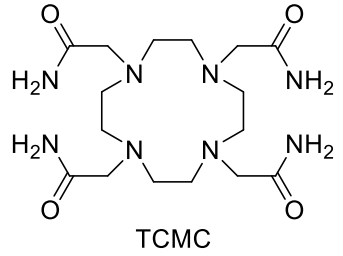

Figure 2. TCMC

***^{118m}Sb for ^{119}Sb based radiopharmaceuticals*:** ^{119}Sb, with half life 38.5 hours, decays by conversion electrons and a cascade of Auger electrons with the absence of long-range radiation, making it an ideal candidate for Auger therapy. Several chelation agents will be tested with ^{118m}Sb, i.e. desferrioxamine shown in Fig 3.

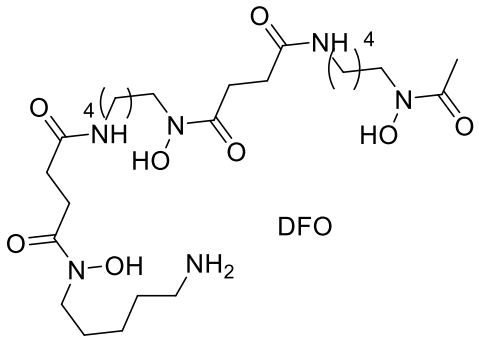

Figure 3. Desferrioxamine (DFO)

^{199m}Hg for ^{197m}Hg based radiopharmaceuticals ^{197m}Hg ($t_{1/2}$ = 23.8 h) decays via an isomeric transition (91.4%) and a small branch of electron capture (8.6%) and could be a promising candidate for Auger therapy. Mercury(I/II) can be classified as a soft acid according to

Pearson's hard-soft acid-base theory, and consequently prefers soft donor atoms such as sulfur. Tri-sulfide $(SR)_3$ systems are among the most prevalent type of chelators used for mercury(II) chelation [Jul15; Fu11].

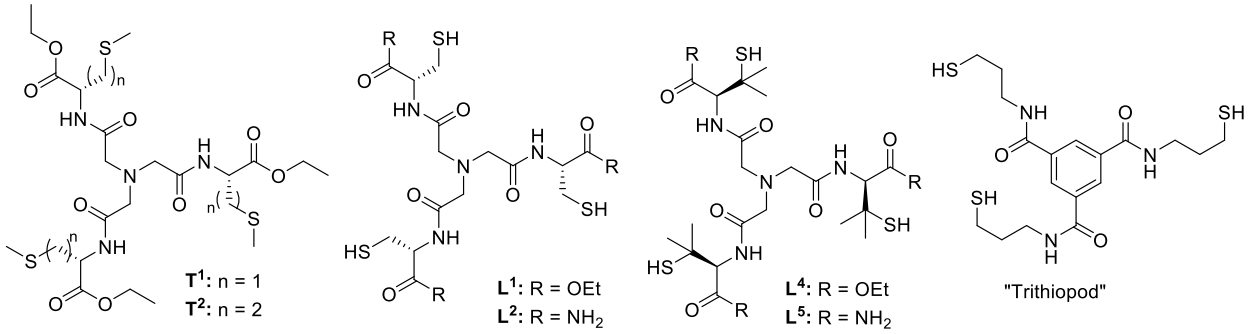

Figure 4. Selected tri-sulfide $(SR)_3$ ligand systems previously investigated for Mg(II) chelation [Jul 15;Fu11]

2. *In vivo* generator systems and their potential for nuclear medicine

In vivo generators are systems where the mother radionuclide is incorporated into a radiopharmaceutical and decays to the daughter radionuclide which in turn is suitable for imaging or therapy. An example of an attractive *in vivo* generator for PET imaging is $^{44m}/^{44g}$Sc, where the meta-stable state has a 58.6 h half-life and the daughter, ^{44g}Sc, is suitable for PET imaging with a half-life of 3.97 h. This type of *in vivo* generator can be suitable for imaging long term biological processes such as diagnostics with antibodies. On the other hand, ^{44g}Sc itself can be suitable for imaging of relatively short biological processes, e.g. diagnostics with peptides. Several other possible *in vivo* generators are ^{140}Nd/^{140}Pr, ^{134}Ce/^{134}La, ^{52}Fe/^{52m}Mn, ^{62}Zn/^{62}Cu for imaging and ^{212}Pb/^{212}Bi, ^{166}Dy/^{166}Ho, ^{225}Ac/^{213}Bi for therapy. It remains unknown, however, whether or not the daughter radionuclide remains attached to the targeting vector during the decay, or during the transition between the meta-stable and ground state. This is difficult to study in detail by other spectroscopic techniques. Therefore, in this proposal we wish to apply several lanthanide-based systems to study the stability of metal-chelate complexes during the decay/transition with PAC spectroscopy: ^{139m}Nd/^{139}Pr, ^{140}La/^{140}Ce, ^{147}Gd/^{147}Eu, ^{149}Gd/^{149}Eu, ^{151}Tb/^{151}Gd, and ^{172}Lu/^{172}Yb. Here it is of particular interest to compare β^- decays (i.e. La>Ce) with EC decays (i.e. Lu>Yb) where the nuclear charge of the daughter nuclide increases or decreases, respectively. The first step towards such experiments would be to study basic geometries of different compounds to establish a small PAC database of reference signals. We propose the following systems:

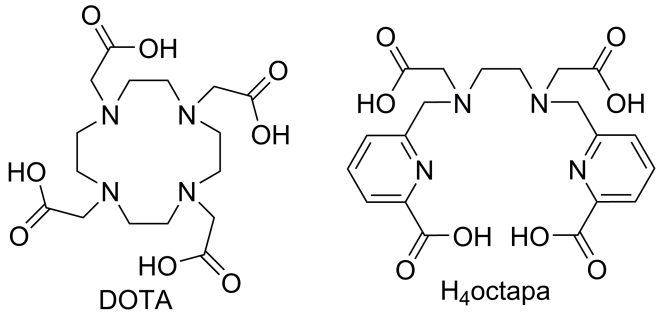

Figure 5. Proposed ligands for use in this study.

The ligands suggested in this study are both octadentate systems that vary in their donor atom type, geometry, and connectivity and consequently can show preferential binding to one metal over another. The closed-chain (macrocyclic) ligand DOTA (N_4O_4) is by far the

most promiscuous chelate in radiopharmaceutical design, and has shown to form thermodynamically stable complexes with many transition metals and lanthanides, albeit at the sacrifice of sluggish labelling kinetics which often require heating samples for extended periods of time to achieve quantitative incorporation of the metal [Pri14, Ram13, Wad10]. The picolinate acid-based chelator H_4octapa (N_4O_4) developed in the Orvig lab [Pri12, Pri13, Ram15] is part of a new class of chelating ligands that feature the ability to complex radiometals such as ^{111}In and ^{177}Lu quantitatively at ambient temperature in 10 minutes, resulting in thermodynamically stable and kinetically inert complexes.

Table 1. Formation constants (log K_{ML}) and pM^a values for selected relevant metal complexes

M =	**In^{3+}**		**Lu^{3+}**		**Gd^{3+}**		**Yb^{3+}**		**Eu^{3+}**	
Chelator	**logK_{ML}**	**pM^a**	**logK_{ML}**	**pM^a**	**logK_{ML}**	**pM^a**	**logK_{ML}**	**pM^a**	**logK_{ML}**	**pM^a**
DOTA[c]	23.9	18.8	25.4	17.1	24.7		25.0		23.5	
octapa^{4-} [d]	26.8	26.5	20.1	19.8	ND[b]		ND[b]		ND[b]	

[a] Calculated for 10 μM total ligand and 1 μM total metal at pH 7.4 and 25 °C. [b]ND = not determined. [c][Cla91; Bye99; Cac87]. [d][Pri12].

III. Methodology

Over the past decades, ^{111}In (2.8 d) has often been used in biological applications of PAC spectroscopy, see for example [Hem04] and references therein. However, ^{111}In decays to ^{111}Cd by electron-capture (EC) leaving the ^{111}Cd ion in a highly charged state. This may lead to so-called "after effects" that can influence PAC spectra and make the data interpretation harder. To resolve any possible doubts, we would like to carry out PAC measurements on the same complexes with ^{111m}Cd (48 min), which decays from its isomeric metastable state by emission of only γ-rays, hence, removing the uncertainty related to the element change. PAC experiments with ^{111}In will be carried out at the University of Copenhagen and TRIUMF because this isotope is available commercially. All other PAC experiments using ^{111m}Cd, ^{118m}Sb, ^{139m}Nd, ^{140}La, ^{147}Gd, ^{149}Gd, ^{151}Tb, ^{172}Lu, ^{199m}Hg, and ^{204m}Pb, will be carried out at ISOLDE (due to its long life-time, we might also consider shipping ^{149}Gd to Copenhagen if required). The radioactive sample will be prepared as follows: the selected PAC isotope will be implanted into a target (ice, Zn foil, a layer of salt, etc.) in either a so-called "biophysics chamber" which is usually mounted behind the SSP-GLM chamber (implantation into ice), or in the GLM chamber if implantation is done into foils. For the target preparation and operation (before and after implantation) we will follow the same procedures as the one developed by the biophysics group from Copenhagen [Hem04]. After the implantation, the radioactive sample will be transported to the chemistry laboratory located in bld. 508. The following steps will be taken for sample preparation (given example illustrates the steps for the collections in ice):

a) The frozen solution will be left until thawed in the fume hood (about 10 min).
b) The activity will be then added to the complex of interest and left for incubation.
c) Shortly before the PAC measurements sucrose will be added to the sample to slow down the rotational diffusion of molecules, in analogy to experiments described in [Hem04].
d) Due to their rather short half-life, PAC experiments with ^{111m}Cd, ^{118m}Sb,^{139m}Nd, ^{199m}Hg and ^{204m}Pb will be carried out immediately after sample preparation. Due to the longer half-lives of the other isotopes, however, the experiments can be carried out hours or even days after the activity is available.

^{139m}Nd, ^{147}Gd, ^{149}Gd, and ^{151}Tb have unknown nuclear moments and therefore we will have to measure them prior to any PAC experiments. Also, if possible, the proponents would like to ask for access to PAC spectrometers during winter shut down of the facility to perform experiments with ^{111}In. Commercially available $^{111}InCl_3$ solution will be used for these experiments. The reasons for carrying out PAC experiments with ^{111}In and in the SSP laboratory at ISOLDE are as follows: 1) the opportunity to perform ^{111m}Cd and ^{111}In experiments under exactly the same experimental conditions (the same PAC instruments, measurement conditions, etc.) which will make the data analysis and comparison much easier, and 2) access to the SSP lab equipped with 4 6-detector PAC instruments which allows for multiple experiments at the same time. The synthesis and purification of the compounds used in the experiments will be performed at the laboratory at TRIUMF.

Table 2. PAC candidates to be used in this proposal [Nag13]

Decay			Intermediate State						A_{22}
Daughter	Parent	Half-life	γ_1 (keV)	γ_2 (keV)	Half-life (ns)	Spin	Q (eb)	μ (μ_N)	
^{111}Cd	^{111m}Cd	48.5 min	245.5	151	84.5	5/2+	0.77(12)	-0.765(2)	0.1786
^{118}Sn	^{118m}Sb	5 h	253	1091	21.7	5-	±0.16(2)	-0.30(2)	-0.07143
^{139}Pr	^{139m}Nd	5.5 h	708	114	2.6	7/2+	?	±1.19(21)	-0.007
^{140}Ce	^{140}La	40.3 h	329	487	3.47	4+	±0.35(7)	4.35(10)	-0.099(5)
^{147}Eu	^{147}Gd	38 h	929	396	765	11/2-	?	7.05(3)	-0.171
^{149}Eu	^{149}Gd	9 d	299	347	2450	11/2-	?	7.0(3)	-0.181
^{151}Gd	^{151}Tb	17 h	287	108	2.8	5/2-	?	-1.08(13)	-0.345(14)
^{172}Yb	^{172}Lu	6.7 d	91	1094	8.33	3+	±2.9(4)	0.65(4)	-0.212(23)
^{199}Hg	^{199m}Hg	42.6 min	374	158	2.47	5/2-	0.95(7)	0.88(3)	0.2519(4)
^{204}Pb	^{204m}Pb	66.9 min	912	375	265	4+	±0.44(2)	0.224(3)	0.2473

IV. Beam Time Request

We ask for a total of 15 shifts within 2 years to be used as follows:

Collected isotope	Beam	Target	Yield (ions/uC)	Ion source	# shifts
^{111m}Cd	^{111m}Cd	Sn	$8{\cdot}10^8$	VADIS or MK5	3
^{118m}Sb	^{118m}Sb	LaC_x or CeO_2 or UC_x	$>10^8$	Sb RILIS	1
^{139m}Nd	^{139m}Nd	Ta	$3{\cdot}10^7$	Surface ionizer	1
^{140}Ba/^{140}La	^{140}Cs	UC_x	$>10^9$	Surface ionizer	0.5
^{147}Gd	^{147}Gd	Ta	10^9	Surface ionizer	0.5
^{149}Gd	^{149}Gd	Ta	$3{\cdot}10^9$	Surface ionizer	0.5
^{151}Tb	^{151}Dy	Ta	10^{10}	Dy RILIS	0.5
^{172}Lu	^{172}Lu	Ta	$5{\cdot}10^8$	Surface ionizer	2
^{199m}Hg	^{199m}Hg	Pb	$2{\cdot}10^8$	HP	3
^{204m}Pb	^{204m}Pb	UC_X	$2{\cdot}10^8$	Pb RILIS	3

* Yields of the lanthanide ions are averages from recent beam times at ISOLDE PSB. Sb and Te yields are estimated from measured Sn yields.

If there are other users interested in the above beams, we can share the beam time and perform implantations in the alternated manner.

Summary of requested shifts:

In summary, we ask for 15 shifts for collection of the above isotopes, to be split in several runs over 2 years. Number of shifts required for each isotope was estimated based on the

implantations previously carried out either for biophysics PAC experiments or medical isotope collections.

References:

[Bye99] J. G. Byegård *et al.*, J. Radioanaly. Nucl. Chem. 1999, 241(2), 281-290.
[Cac87] W. P. Cacheris *et al.*, Inorg. Chem. 1987, 26(6), 958-960.
[Cla91] E. T. Clarke and A. E. Martell, Inorg. Chim. Acta, 1991, 190(1), 37-46.
[Fu11] J. Fu *et al.*, J. Biol. Inorg. Chem. 2011, 16(1), 15-24.
[Hem04] L. Hemmingsen *et al.*, Chem. Rev. 2004, 104(9), 4027-4061.
[Jul15] A. S. Jullien *et al.*, Eur. J. Inorg. Chem. 2015, 2015(22), 3674-3680.
[Kra16] C. Kratochwil *et al*., J. Nucl. Med. 2016, doi: 2967/jnumed.116.178673.
[Nag13] M.A. Nagl *et al*., NIM A 2013, 726, 17-30
[Pri12] E.W. Price *et al*., J. Am. Chem. Soc. 2012, 134(20), 8670-8683.
[Pri13] E.W. Price *et al*., J. Am. Chem. Soc. 2013, 135(34), 12707-12721.
[Pri14] E. W. Price and C. Orvig, Chem. Soc. Rev. 2014, 43(10), 260-290.
[Ram13] C. F. Ramogida and C. Orvig, Chem. Commun. (Camb). 2013, 49(42), 4720-4739.
[Ram15] C. F. Ramogida *et al*., Inorg. Chem. 2015, 54(4), 2017-2031.
[Thi16] H. Thisgaard *et al.* Theranostics 2016, 6(12), 2278.
[Tro00] W. Troger and T. Butz, Hyperf. Interact. 2000, 129, 511-527.
[Wad10] T.J. Wadas *et al*., Chem. Rev. 2010, 110(5), 2858-2902.
[Yon11] K. Yong and M. W. Brechbiel, Dalt. Trans. 2011, 40(23), 6068-6076.

Appendix

DESCRIPTION OF THE PROPOSED EXPERIMENT

The experimental setup comprises: *(name the fixed-ISOLDE installations, as well as flexible elements of the experiment)*

Part of the Choose an item.	Availability	Design and manufacturing
Part 1: SSP-GLM and biophysics chamber	☒ Existing	☒ To be used without any modification
Part 2: Chemical Laboratory (508/R-002)	☒ Existing	☒ To be used without any modification
Part 3: Experimental PAC zone (508/R-008)	☒ Existing	☒ Various PAC spectrometers

HAZARDS GENERATED BY THE EXPERIMENT

Hazards named in the document relevant for the fixed SSP-GLM and biophysics implantation installations.

Additional hazards:

Hazards			
	Part 1	*Part 2*	*Part 3*
Thermodynamic and fluidic			
Pressure			
Vacuum	8·10-6 - 2·10-5 mbar	Atmospheric pressure	Atmospheric pressure
Temperature	77 K	253K	293
Heat transfer			
Thermal properties of materials			
Cryogenic fluid	LN2 for SSP-GLM biophysics chamber (20l) and sample holder cooling (0.1l)		LN2
Electrical and electromagnetic			
Electricity	230V, max. 10A single phase	230V, max. 10A single phase	230V, max. 10A single phase
Static electricity			
Magnetic field			
Batteries			
Capacitors			
Ionizing radiation			
Target material	Ice or implantation foils		
Beam particle type (e, p, ions, etc)	ions		
Beam intensity			
Beam energy	30-60 keV		
Cooling liquids	LN2		LN2
Gases			
Calibration sources:			
• Open source			
• Sealed source			

• Isotope			
• Activity			
Use of activated material:			
• Description	Described in the proposal. Removal from the chamber, transport to chemical lab 508/R-002 in a standard Pb castle shielding	Chemical preparation in 508/R-002	Samples placed in the PAC spectrometers in 508/R-008 for measurements.
• Dose rate on contact and in 10 cm distance	max. 0.3 µSv/h (Nucleonica gamma dose rate)	max. 0.3 µSv/h (Nucleonica gamma dose rate)	max. 0.3 µSv/h (Nucleonica gamma dose rate)
• Isotope	^{111}Cd or ^{199}Hg	^{111}Cd or ^{199}Hg	^{111}Cd or ^{199}Hg
• Activity	Max 6 MBq per sample	Max 6 MBq per sample	Max 6 MBq per sample
• Isotope	^{118m}Sn or ^{139m}Nd	^{118m}Sn or ^{139m}Nd	^{118m}Sn or ^{139m}Nd
• Activity	Max 0.4 MBq per sample	Max 0.4 MBq per sample	Max 0.4 MBq per sample
• Isotope	^{140}La and ^{147}Gd	^{140}La and ^{147}Gd	^{140}La and ^{147}Gd
• Activity	Max 50 kBq per sample	Max 50 kBq per sample	Max 50 kBq per sample
• Isotope	^{149}Gd	^{149}Gd	^{149}Gd
• Activity	Max 10 kBq per sample	Max 10 kBq per sample	Max 10 kBq per sample
• Isotope	^{151}Gd	^{151}Gd	^{151}Gd
• Activity	Max 0.7 kBq per sample	Max 0.7 kBq per sample	Max 0.7 kBq per sample
• Isotope	^{172}Lu	^{172}Lu	^{172}Lu
• Activity	Max 20 kBq per sample	Max 20 kBq per sample	Max 20 kBq per sample
• Isotope	^{204m}Pb	^{204m}Pb	^{204m}Pb
• Activity	Max 2 MBq per sample	Max 2 MBq per sample	Max 2 MBq per sample
Non-ionizing radiation			
Laser			
UV light			
Microwaves (300MHz-30 GHz)			
Radiofrequency (1-300MHz)			
Chemical			
Toxic			
Harmful	ethanol		
CMR (carcinogens, mutagens and substances toxic to reproduction)			
Corrosive			
Irritant			
Flammable	ethanol		
Oxidizing			
Explosiveness			
Asphyxiant			
Dangerous for the environment			
Mechanical			
Physical impact or mechanical energy (moving parts)			
Mechanical properties (Sharp, rough, slippery)			
Vibration			
Vehicles and Means of Transport			
Noise			
Frequency			
Intensity			
Physical			

Confined spaces			
High workplaces			
Access to high workplaces			
Obstructions in passageways			
Manual handling	SSP protocol	ISOLDE Chemistry Lab protocol and material safety data sheet	SSP protocol
Poor ergonomics			

0.1 Hazard identification

The dominant hazard would be (if present) half-life and possible short-lived contaminations (if present) of the collected sample.