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Welcome to
UK PET Chemistry 2026
Michael Fairclough, Joseph Ford, Véronique Gouverneur

UK PET Chemistry 2026 – Programme

UK PET Chemistry meeting – Merton College 16th September 2026		
09:00 – 09:45	**Registration & poster set-up** Tea/Coffee	
09:50 – 10:00	**Welcome address** Mike Fairclough/Joseph Ford/Véronique Gouverneur	
10:00 – 10:40	**Keynote 1: Professor Jason Holland – Supramolecular Agents as Radiotheranostic Drugs.** *(35 mins + 5 mins Q&A)*	
10:40 – 11:25	**Oral presentation (Session 1) – Innovations in Fluorine-18 radiochemistry and radiolabelling.** *3 x 12 min talks (+ 3 mins Q&A)*	
	Maddison Lovell (University of Oxford)	A Ni-Mediated Cross-Coupling Approach to Deuterated ^{18}F-Fluoromethylated (Hetero)arenes.
	Gianluca Destro (University of Edinburgh)	Advancing Copper-Mediated Radiofluorination for [^{18}F]SynVesT-1 through Catalyst Optimisation.
	Pawan Mishra (University of Cardiff)	The synthesis of [^{18}F]SynVesT-1 and [^{18}F]SynVesT-2 from enantioenriched boronic esters.
11:25 – 11:45	**Refreshment break & posters**	
11:45 – 12:30	**Oral presentation (Session 2) – Novel Molecular Imaging Agents and Biomarker targeting.** *3 x 12 min talks (+ 3 mins Q&A)*	
	Christina Siakalli (Imperial College London)	Coordination Chemistry of Hydroxyquinoline-Based Macrocyclic Lanthanide Complexes.
	Lennart Mayer (University of Cambridge)	Development of Second-Generaton Difluoromethylated PET Tracers for Huntingtin Aggregate Imaging.
	Shinong Zeng (University of Cambridge)	Synthesis and Evaluation of Fluorine-18 Labelled N-acylethanolamine acid amidase Radiotracers for Neuroinflammation Imaging in Multiple Sclerosis.
12:30 – 12:40	**Positron Pulse/UK PET Chemistry Website**	
12:40 – 13:40	**Lunch** **Posters/Sponsor stands/Networking**	
13:40 -14:20	**Keynote 2: Professor Bart Cornelissen - PET Imaging and radionuclide therapy of DNA damage** *(35 mins + 5 mins Q&A)*	
14:20 – 15:05	**Oral presentation (Session 3) -Theranostics and Clinical Translation of Radiopharmaceuticals.** *3 x 12 min talks (+ 3 mins Q&A)*	
	Fraser Hill-Casey (LabLogic/Medicines Discovery Cataoult)	Earlier Radiochemical Purity Results of Ac-225 Radiopharmaceuticals Using Fr-221 Peak Identification.
	Holly McErlain (University of Glasgow)	The Development of Novel Total-Body PET Theranostics for Minimal Residual Disease.
	James Wood (King's College London)	Novel CXCR4- and ACKR3-targeted theranostic agents for PET/SPECT imaging and radionuclide therapy in cancer.

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<tr><td>15:05 – 15:25</td><td colspan="2">Refreshment break & Posters</td></tr>
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<tr><td>Session A (GMP)
Preparing for MHRA Inspection - Maggie Cooper</td><td>Session B
Radiochemistry and preclinical imaging at Oxford - Mike Fairclough/Gaurav Malviya</td></tr>
<tr><td>16:10 – 16:50</td><td colspan="2">Keynote 3: Dr Victor Pike - ‘PET radiochemistry and tracer development: recent advances at NIH’ (35 min + 5 mins Q&A)</td></tr>
<tr><td>16:50 – 17:00</td><td colspan="2">UK PET Chemistry updates – Sally Pimlott
Prizes & Closing remarks</td></tr>
<tr><td>17:00 – 17:05</td><td colspan="2">UK PET Chemistry – 2027 Announcement</td></tr>
<tr><td>17:05</td><td colspan="2">Meeting close & Drinks Reception</td></tr>
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KEY NOTE SPEAKERS

Professor Jason Holland

Jason Holland is from Yorkshire in the United Kingdom and received a master's degree in Chemistry from the University of York (MChem, 2004) followed by a doctorate from Merton College at the University of Oxford (D.Phil, 2008). He trained as post-doctoral scholar with Jason S. Lewis in radiochemistry and translational molecular imaging at Memorial Sloan-Kettering Cancer Center in New York (2008 – 2010). He was then awarded an ETH Fellowship and worked at ETH Zürich and the Paul Scherrer Institute (2010 – 2012). Following this he was appointed as Assistant in Chemistry in the Division of Nuclear Medicine and Molecular Imaging at Massachusetts General Hospital, Boston, with a joint faculty appointment as an Instructor in Radiology at Harvard Medical School (2012 – 2014; promoted to Assistant Prof.). In 2015, he worked in the Department of Nuclear Medicine at the University Hospital Freiburg as a Visiting Scientist. In April 2016, Jason began his research group as an SNSF Professor in the Department of Chemistry at the University of Zurich, and in October 2022, was appointed as the Chair of Medicinal Radiochemistry.

The group is funded by the European Research Council (Starting Grant 2015 & Consolidator Grant 2020), The European Innovation Council (SMARTdrugs), the Swiss National Science Foundation (SNSF Professorship), the Swiss Cancer Research Foundation, the Swiss Government Excellence Scholarship scheme, and the University of Zurich.

Research activities focus on advancing radiolabelling methods through novel bioconjugation approaches for labelling bioactive molecules with various radionuclides (^{18}F, ^{64}Cu, $^{67/68}$Ga, $^{86/90}$Y, ^{89}Zr, ^{99m}Tc, ^{111}In, ^{161}Tb, ^{177}Lu, ^{188}Re, etc).

Professor Bart Cornelissen

Prof. Dr. Bart Cornelissen is a prominent scientist specializing in radiopharmacy, oncology, and molecular imaging. He holds a dual appointment as a Full Professor at the University Medical Center Groningen (UMCG) in the Netherlands and as an Honorary Fellow at the University of Oxford in the UK. He leads the Nuclear Medicine and Biology team at UMCG. His research centers on developing radiolabelled compounds to image tumour biology, with a focus on cancer hallmarks such as DNA damage and repair, novel targeted radionuclide therapies (TRT), and radiobiology of TRT. [1, 2, 3]

Having earned his PhD at the University of Ghent in Belgium and completed postdoctoral work at the University of Toronto, Dr. Cornelissen moved to the Gray Institute for Radiation Oncology at the Department of Oncology Oxford in 2007, and the UMCG's Department of Nuclear Medicine and Molecular Imaging in 2021, authoring over 120 peer-reviewed papers.

Doctor Victor Pike

Victor Pike has worked in PET radiochemistry for almost five decades. He spent 23 years at the MRC Cyclotron Unit at Hammersmith Hospital, later associated with Imperial College London, where he became Head of Chemistry & Engineering. In 2001, he moved to the US National Institutes of Health (NIH) to become Chief of PET Radiopharmaceutical Sciences in the newly created Molecular Imaging Branch of the National Institute of Mental Health (NIMH).

For the past 25 years, his research has focused exclusively on the discovery and development of novel PET radiotracers for molecular imaging, particularly for investigating targets of importance in neuropsychiatric research. His work has encompassed radiotracer design and evaluation, radiochemistry with the short-lived positron-emitting radionuclides carbon-11 and fluorine-18, and the translation of promising radiotracers from animal studies to clinical imaging in humans. This research has resulted in numerous successful PET radiotracers and has been conducted through close collaborations with other chemists, pharmacologists, imaging scientists, and clinicians.

Having spent much of his early PET career in the UK, Victor is especially pleased to return and participate in this UK PET Chemistry Meeting at Merton College.

ORAL PRESENTATIONS

Innovations in Fluorine-18 radiochemistry and radiolabelling

A Ni-Mediated Cross-Coupling Approach to Deuterated ^{18}F-Fluoromethylated (Hetero)arenes

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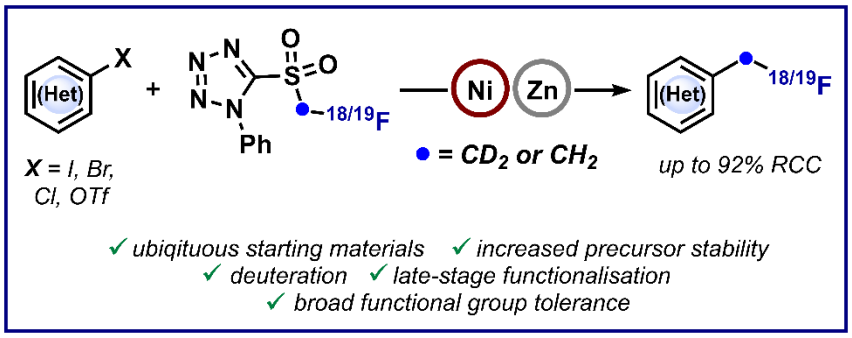
Keywords: ^{18}F-radiochemistry, fluoromethylation, deuteration

Abstract

The (hetero)aryl-^{18}F-fluoromethyl group ([^{18}F]CH_2F) is highly prevalent in ^{18}F-containing PET radiotracers.[1] However, radiotracers bearing a [^{18}F]CH_2F group can be susceptible to *in vivo* degradation by radiodefluorination.[2] Practitioners have therefore exploited deuteration of the fluoroalkyl chain as a tool for increasing stability whilst maintaining biological activity.[3] To date, radiosynthetic strategies to access deuterated ^{18}F-fluoroalkyl compounds demand the multi-step synthesis of bespoke labelling precursors, bearing preinstalled leaving groups, such as (pseudo)halides, that can be displaced with [^{18}F]fluoride. In addition to synthetic challenges arising from the late-stage introduction of reactive groups, careful planning is required to ensure the isotopic integrity of the deuterated precursor is maintained in further synthetic manipulations. Moreover, precursors bearing reactive leaving groups often also suffer from stability issues.[1] Contrastingly, only a single protocol for the direct installation of $CH_2{}^{18}F$ onto aromatic substrates has been disclosed to date, and this was not extended to deuteration.[4]

With these challenges in mind, we have developed a novel platform for $^{18}F,D_2$-fluoromethylation, *via* a cross-electrophile coupling between aryl (pseudo)halides and a suitable deuterated reagent. This approach offers a series of key advantages over traditional methodologies, such as the use of readily available starting materials, obviating the need for lengthy precursor synthesis, and modular installation of [^{18}F]CD_2F, allowing for rapid library generation for PET ligand discovery. The same ^{19}F-fluoromethyl containing reagent is also competent in the analogous non-radioactive reaction, for the preparation of reference standards for quality control and analysis. This technology has been exemplified on a broad substrate scope and has been extended to (semi)automation for the isolation a $^{18}F,D_2$-containing PARP radiotracer.



Acknowledgements: M.L. is grateful to the Centre for Doctoral Training in Synthesis for Biology and Medicine for a studentship. V.G., J.F. and S.O. acknowledge the Biotechnology and Biosciences Research Council (BB/V010999/1) and V.G. and J.F. acknowledge the Engineering and Physical Sciences Research Council (EP/Y001931/1) for financial support.

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[2] Shetty, H. U., et. al., *J. Pharmacol. Exp. Ther.*, 2008, **327**, 727–735; Magata, Y., et. al., *Nucl. Med. and Biol.*, 2000, **27**, 163–168.
[3] Kuchar. M., et. al., *Molecules*, 2015, **20**, 16186–16220.
[4] Doi, H., et. al., *Bull. Chem. Soc. Jpn.*, 2012, **85**, 1233–1238.

Advancing Copper-Mediated Radiofluorination for [^{18}F]SynVesT-1 through Catalyst Optimisation

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Keywords: PET, Fluorine-18, Copper Mediated Radiofluorination

Abstract

At the University of Edinburgh, we have routinely synthesised the [^{18}F]SynVesT-1 following the published copper-mediated radiofluorination (CMRF) procedure;[1,2] however, in our hands the process has been difficult to reproduce and has consistently delivered no more than ~3% ± 0.02 activity yield (AY) in all 2025 n= 54, a molar activity (A_m) of 124.3 ± 92.2 and a radiochemical purity (RCP)> 97%. Similar difficulties have been reported by colleagues at other sites, motivating a systematic investigation to improve robustness and yield and to enable reliable routine production. We evaluated the established aryl stannyl and boronic ester precursors, starting with manual radiolabelling to de-risk key variables. Reaction parameters were systematically screened, including precursor loading (2.5 µmol), copper salt identity and loading (10 µmol) and solvent (DMI, DMA, and DMF). Particular emphasis was placed on fluoride processing, implementing neutral elution with $Et_4N^+OTf^-$.[3] In parallel, a set of novel copper catalyst formulations was assessed, including systems incorporating electron-rich heteroarene ligands. Reactions were quantified by HPLC, with radiochemical conversion (RCC) compared against the literature condition. Screening of 18 copper salts under neutral elution identified four salts that exceeded our standard routine RCC benchmark. The most effective system, combining an electron-rich heteroarene ligand with DMA as solvent, delivered reproducible performance without loss of stereochemical integrity (e.r. >99:1). Under these conditions, RCCs of 87.7% (boronic ester) and 91.0% (stannyl) were obtained versus 75% under the standard condition (n=6 for each), using only 2.5 µmol of precursor. Optimised conditions were translated to an RN+ Synthra automated module with semi-preparative HPLC purification and reformulation, affording [^{18}F]SynVesT-1 with AY= 20.3%± 1.10 (n=3), A_m from 40 to 300 GBq/µmol, and RCP>98%, while reducing the reaction time from 76 to 60 minutes (Fig. 1). Further work is ongoing to strengthen automated robustness and progress towards GMP-compatible routine production.

Figures

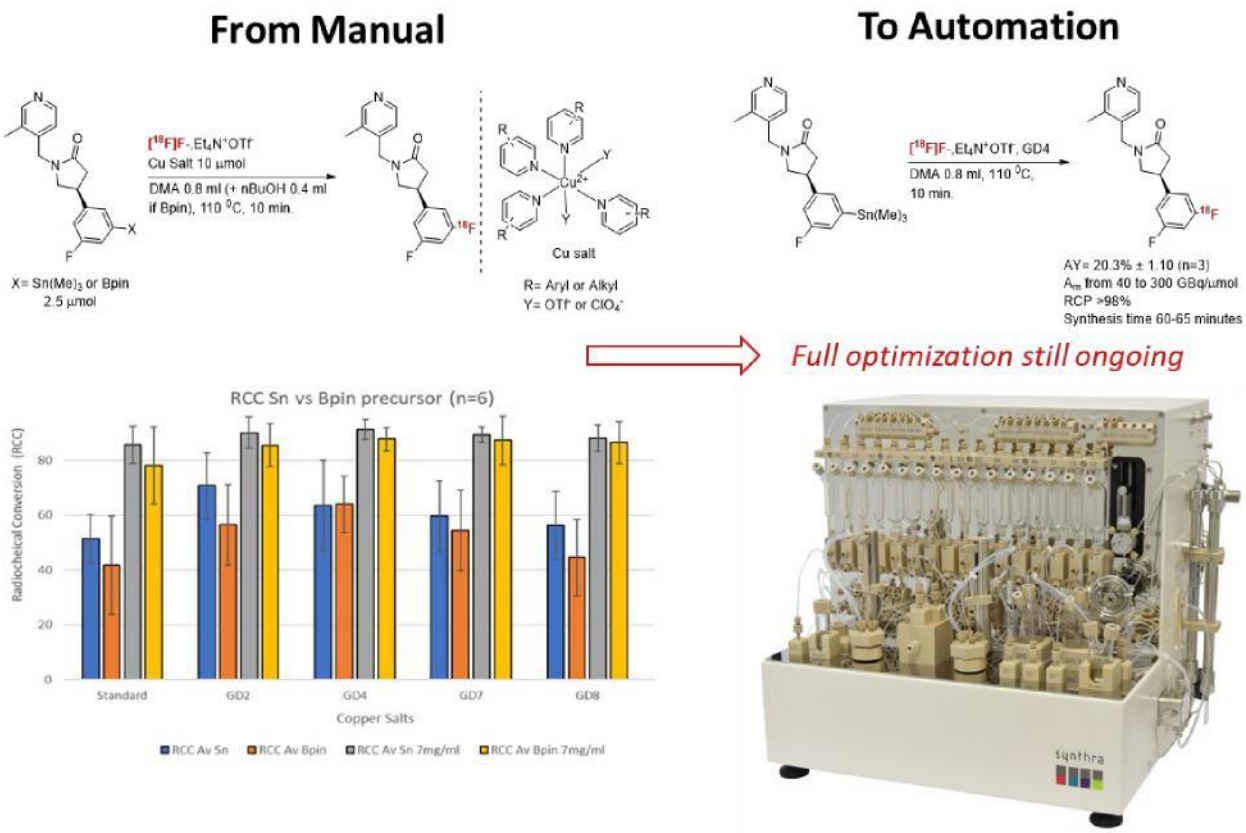

Fig. 1: From the combination of best copper salts with enhanced elution method and precursors to automated radiosynthesis on Synthra Rn plus.

Acknowledgements: This work is supported by Wellcome Trust TDA – grant number 221295/Z/20/Z.

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The synthesis of [^{18}F]SynVesT-1 and [^{18}F]SynVesT-2 from enantioenriched boronic esters

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Wales Research and Diagnostic PET Imaging Centre, Cardiff University, University Hospital of Wales, Heath Park, Cardiff CF14 4XN, U.K.

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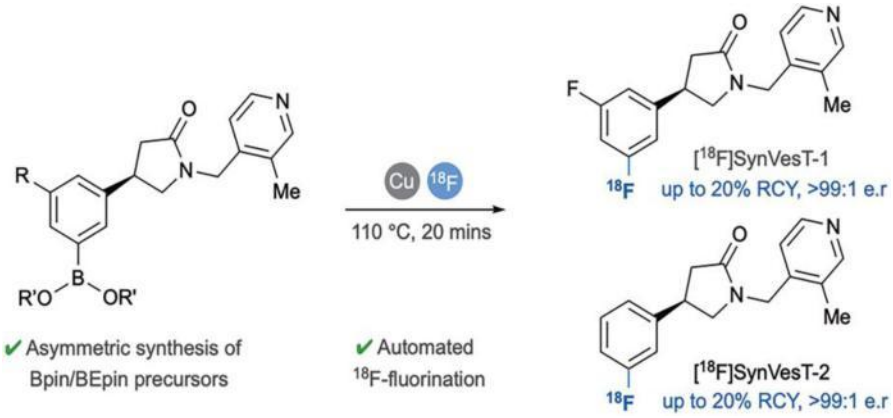
Relevant Keywords: 18-Fluorine, PET imaging, synaptic vesicle glycoprotein (SV2A) **Abstract:**

^{18}F-labelled radiotracers targeting synaptic vesicle glycoprotein 2A (SV2A) enable the noninvasive assessment of synaptic density by positron emission tomography (PET) and have important applications in the diagnosis and study of neurological disorders. However, asymmetric syntheses of the clinically relevant radiotracer [^{18}F]SynVesT-1 remain limited.

We report the asymmetric synthesis of the boronic ester precursors of both SynVesT-1 and SynVesT-2 with excellent enantiomeric purity (e.r. 99:1). Automated copper-mediated ^{18}F-fluorination of the corresponding aryl Bpin precursors afforded enantiopure [^{18}F]SynVesT-1 and [^{18}F]SynVesT-2 in activity yields sufficient for preclinical and clinical PET imaging. Although purification of the aryl Bpin precursors proved challenging, the corresponding aryl BEpin analogues were readily purified and delivered comparable radiochemical yields under the optimised automated ^{18}F-fluorination conditions. These results identify aryl BEpin precursors as practical alternatives to conventional organostannane precursors, offering a robust and efficient route to enantiopure SV2A PET radiotracers compatible with automated production for imaging applications.



Acknowledgements

Financial support for this was provided by the EPSRC (EP/T031220/1 and EP/T517951/

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2. Mishra, P.**;** Hind, J.; Ian Fallis, I.; Treadwell, M. Radiochemical Synthesis of Alkyl Geminal 18F-Difluoroalkyl Motifs Mediated by Silver(I) Oxide**.** *Org. Lett*. **2025**, 27, 1724–1728

ORAL PRESENTATIONS

Novel Molecular Imaging Agents and Biomarker Targeting

Coordination Chemistry of Hydroxyquinoline-Based Macrocyclic Lanthanide Complexes

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Keywords: (up to 3 max) e.g. Terbium-161, Macrocyclic Chelators, Lanthanide

Coordination **Abstract**

Heavier radionuclides such as [$^{149/161}Tb^{3+}$], [$^{177}Lu^{3+}$] and [$^{225}Ac^{3+}$] are increasingly important in nuclear medicine, particularly for theranostic applications enabling simultaneous diagnosis, monitoring, and treatment of disease.[1-2] The design and synthesis of novel radiopharmaceuticals relies on the stable complexation of the desired radionuclide within a bifunctional chelator, attached to suitable bioconjugate moieties for specific disease targeting and cell accumulation *in vivo*.[2] The coordination chemistry of state-of-the-art macrocyclic chelators, such as macropa, has been explored thoroughly and next-generation chelators developed to improve thermodynamic stability and radiochemical yield.[3,4]

This work explores the effect of replacing the picolinic acid pendant arms on macropa with 8-hydroxyquinoline moieties, yielding a series of novel aza-crown macrocycles (H_2KHQ, MHQ, PyMHQ). Their coordination with key lanthanide ions was investigated. H_2KHQ has demonstrated preferential binding to the larger lanthanide ions, supported by stability constants, forming two-fold symmetric complexes in solution and solid states. H_2KHQ was successfully radiolabelled with [^{161}Tb]$TbCl_3$ in 92% radiochemical yield under mild conditions.[5]

Second generation chelators (MHQ, PyMHQ) aim to improve thermodynamic stability and enable dual-size selectivity. Coordination studies with La^{3+}, Tb^{3+}, and Lu^{3+} reveal a conformational toggle, enabling adaptation between coordination numbers 10 and 8 to accommodate both large and small lanthanide ions. By comparing the solution- and solid-state structures of the early *vs* late lanthanide complexes, we aim to delineate systematic trends in coordination number and thermodynamic stability arising from both the progressive ionic contraction of the series and the structural ligand changes. These results contribute to the broader understanding of lanthanide coordination chemistry and support future design efforts of theranostic radiopharmaceuticals.

Acknowledgements:

The research was supported by the EPSRC Centre for Doctoral Training in Smart Medical Imaging (EP/S022104/1), and as part of the PRISMAP project supported by the European Union's Horizon 2020 research and innovation program under grant agreement no. 101008571.

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Development of Second-Generation Difluoromethylated PET Tracers for Huntingtin Aggregate Imaging

L. K. Mayer,1, [2] C. G. F. Dickmann,[1] S. Milicevic Sephton,[1] F. I. Aigbirhio[1]

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Background: The development of PET radiotracers for imaging mutant huntingtin protein aggregates remains an important objective in Huntington's disease research. [^{18}F]difluoromethylation is an attractive strategy in radiotracer design due to its favourable effects on physicochemical and pharmacokinetic properties, and recent development of a practical [^{18}F]difluorocarbene reagent by Sap and co-workers [1] has significantly expanded access to such tracers. Previous work within our group established an automated [^{18}F]difluoromethylation methodology [2], [3] for a series of huntingtin-targeted ligands derived from structures reported through the CHDI Foundation.[4] While the resulting compounds demonstrated promising characteristics, instability of precursor molecules under radiolabelling conditions resulted in low radiochemical yields, limiting further biological evaluation.

Aims: To address these challenges, a second generation of ligands has been designed based on the previously identified binding scaffold. In the new series, the linker connecting key pharmacophoric fragments is systematically varied with the aim of improving precursor stability during radiolabelling while maintaining favourable molecular properties.

Methods and Results: A total of 28 ligand designs incorporating ether, thioether and amine linkers were evaluated using CNS MPO scoring. An isoindoline-based scaffold identified from recent CHDI studies was selected for synthesis due to its reported high affinity for mutant huntingtin aggregates and consistently favourable CNS MPO scores across the linker series. A modular synthetic strategy employing common intermediates and Buchwald-type cross-coupling reactions has been developed to facilitate rapid analogue preparation. Initial synthetic studies have yielded the first precursor compounds and established routes for the preparation of the linker-diversified ligand series. Ongoing work is focused on completion of the compound library, radiolabelling using automated [^{18}F]difluoromethylation methods, and evaluation of tracer performance. This approach will enable investigation of the influence of linker composition on radiochemical stability and may provide improved candidates for future preclinical imaging studies in Huntington's disease.

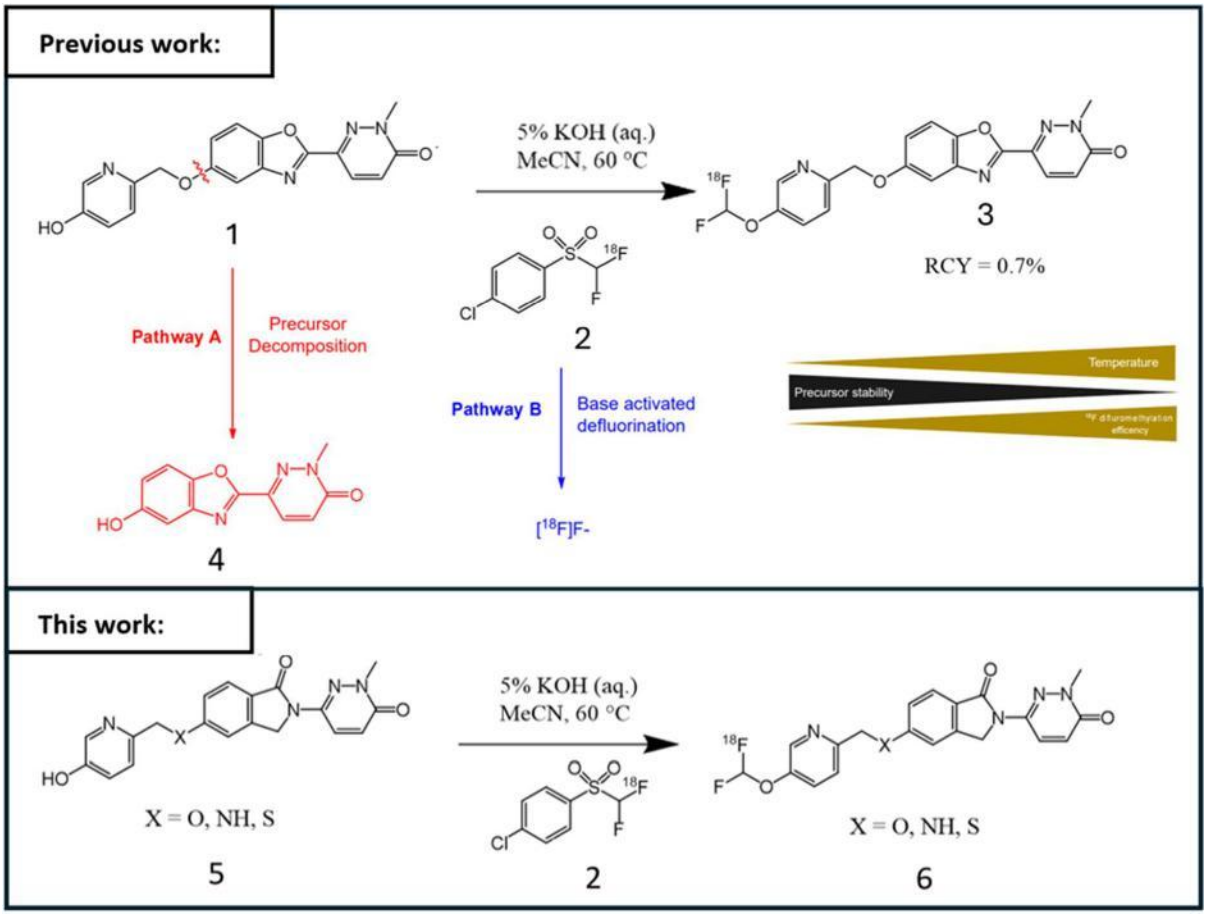

Figure 1. Previous and current work on difluoromethylated PET Tracers for Huntingtin Aggregate Imaging

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Synthesis and Evaluation of Fluorine-18 Labelled N-acylethanolamine acid amidase Radiotracers for Neuroinflammation Imaging in Multiple Sclerosis

Shinong Zeng[1], Simon Zientek[1], Hannah Unsworth[1], Stephen Thompson[1], Franklin I. Aigbirhio[1], Luca Gobbi[2], Maude Giroud[2], Philipp Schmid[2], Martin Ritter[2], Chiara Brändli[2], Emma Acker[2], Louise Enzensdorfer[2], Bernd Kuhn[2], Jörg Benz[2], Ludovic Collin[2], Anto Pavlovic[2], Matthias Wittwer[2], Julie Blaising[2], Uwe Grether[2]and Selena Milicevic Sephton[1]*

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Keywords: (up to 3 max) e.g. Fluorine-18, Radiochemistry, Multiple Sclerosis.

Abstract

N-acylethanolamine acid amidase (NAAA) is a lysosomal N-terminal hydrolase that regulates levels of palmitoylethanolamide (PEA) and plays an important role in inflammatory and pain pathways by terminating PEA-mediated anti-inflammatory signaling.[1] Through modulation of PEA signaling, NAAA has emerged as a promising target for investigating neuroinflammation, including in multiple sclerosis (MS). Moreover, non-invasive imaging of neuroinflammation is important for understanding disease progression and evaluating therapeutic interventions in MS.[2] However, no PET radiotracer has yet been reported for imaging NAAA in either peripheral tissues or the central nervous system. To address this unmet need, we aimed to develop a PET radiotracer targeting NAAA, using ARN1972, a potent and selective NAAA inhibitor, as the lead structure.[3]

A comprehensive structure–activity relationship (SAR) study was conducted using a fragment-based approach guided by the available crystal structure of NAAA. Selected candidates were radiolabelled with tritium and evaluated in a human NAAA cell pellet binding assay, leading to the identification of a lead scaffold. Based on this scaffold, a library of 96 fluorinated analogues was designed and assessed in silico using CNS PET MPO scoring. Three leading candidates were synthesized via 6-, 6-, and 4-step routes, with overall yields of 2%, 5%, and 15%, respectively. Their in vitro binding affinities toward human NAAA gave IC_{50} values of 0.67, 3.57, and 17.04 μM. The compound with the highest affinity was radiolabelled with fluorine-18, affording an RCP of 100% and a DCRCY of 0.2%. The tracer demonstrated good biostability in rat plasma over 30 min. It has been advanced as a PET radiotracer candidate and efforts towards its evaluation will be presented.

Images*/Figures/Tables

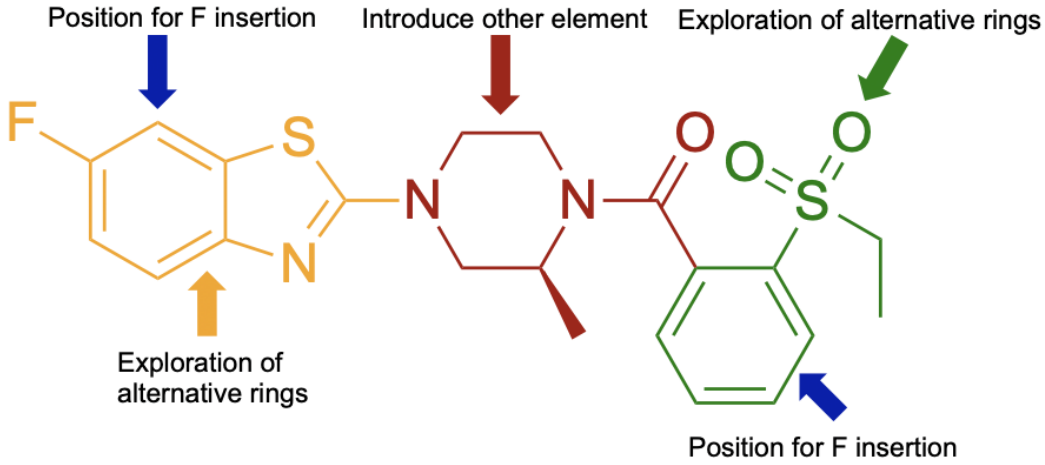

Figure Structure of NAAA lead compound ARN1972, developed through SAR studies by Roche showing areas of possible modification and incorporation of fluorine.

Acknowledgements: (add if necessary)

This work is supported by Multiple Sclerosis Society Catalyst Award (Grant Number 159) which partly covered studentship for Simon Zientek. Cambridge China Studentship Council is acknowledged for providing PhD studentship for Shinong Zeng. Department of Chemistry University of Cambridge is acknowledged for running mass spectrometry and X-ray crystal analysis.

References: (Maximum of 5)

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ORAL PRESENTATIONS

Theranostics and Clinical Translation of Radiopharmaceuticals

Earlier Radiochemical Purity Results of Ac-225 Radiopharmaceuticals Using Fr-221 Peak Identification

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Keywords: Ac-225, Radiochemical purity, Quality Control

Abstract

Actinium-225 (Ac-225) is an alpha-emitting radionuclide with a 9.9-day half-life and decay chain comprising four daughter alpha emissions, making it highly attractive for targeted alpha therapy. Efficient and immediate quality control (QC) methods are essential to support radiopharmaceutical development and clinical translation.

As a challenge to QC method development, Ac-225 suffers from few notable gamma emissions, whilst its decay daughters, francium-221 (Fr-221) and bismuth-213 (Bi-213), emit more intense gamma rays at 218 keV (11% yield) and 440 keV (26%), respectively. Consequently, the radiochemical purity (RCP) of Ac-225-labelled compounds is assessed by radio-HPLC fraction collections and delayed gamma measurements using sodium-iodide (NaI(Tl)) scintillator- based gamma counters after secular equilibrium is re-established between Ac-225 and its daughters (30 mins for Fr-221 or 5 hours for Bi-213).

However, gamma emissions from Bi-213 spill down into the Fr-221 energy window through scattering, causing an overestimation of Fr-221 counts [2]. Consequently, traditional techniques for estimating the RCP require waiting over 5 hours for Ac-225 – Bi-213 to have reached secular equilibrium.

This spill-down effect can be compensated for via energy window corrections through acquisition of Bi-213 gamma spectra [1], although this requires regular calibrations, requiring precious Ac-225 resource.

We have shown that through Fr-221 peak identification from gamma spectra of each fraction acquired via gamma counter, the Fr-221 signal is isolated above background and avoids the detection of Bi-213 gammas. This approach delivers earlier QC results (Figure 1), without the need for additional calibrations.

Our method isolates the Fr-221 peak via a “enhanced” valley-to-valley integration (Figure 2), eliminating contributions from Bi-213. The method was benchmarked against conventional Bi-213 spill-down correction techniques and the valley-to-valley approach validated through comparison with Monte Carlo simulations. We demonstrate that rapid and reliable assessment of Ac-225 radiochemical purity can be achieved without reliance on extended secular equilibrium or repeated calibrations.

Images*/Figures/Tables

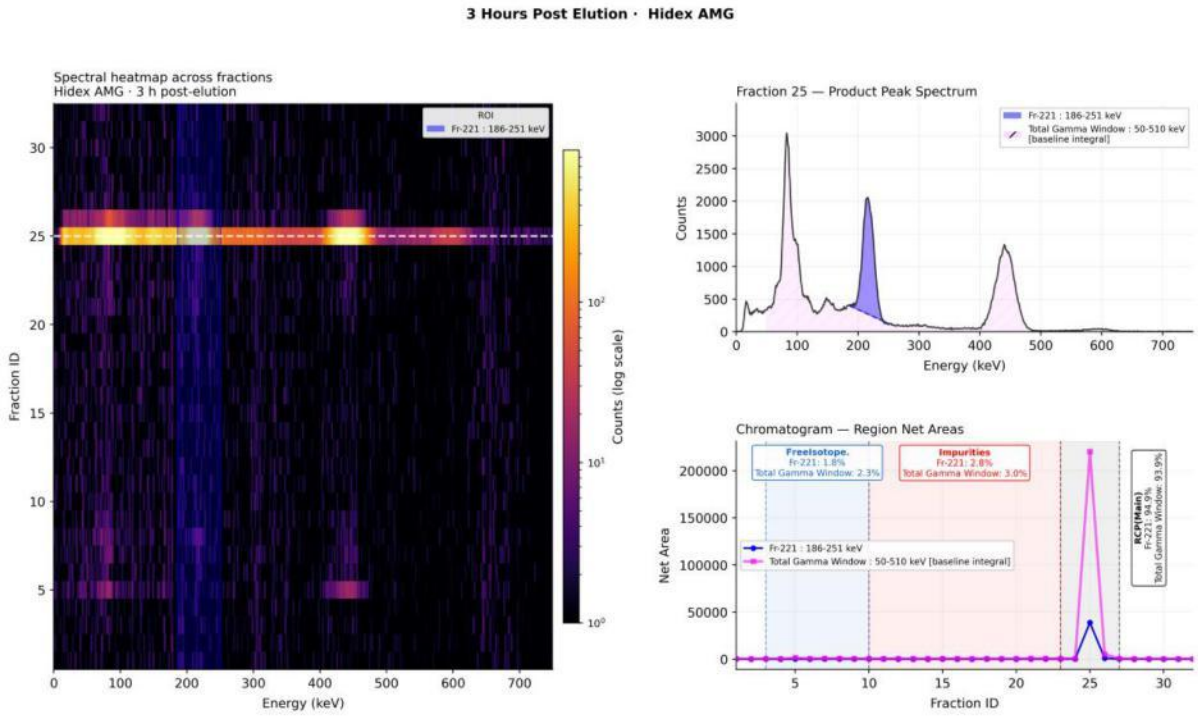

Figure 1 – Determination of RCP during the Fr-221 window (a) Heat map of energy channel as a function of fraction number and integration bounds (b) Indicating the Spectrum of the product peak
(c) The radio-chromatogram of both the Fr-221 and the total gamma spectrum including RCP values.

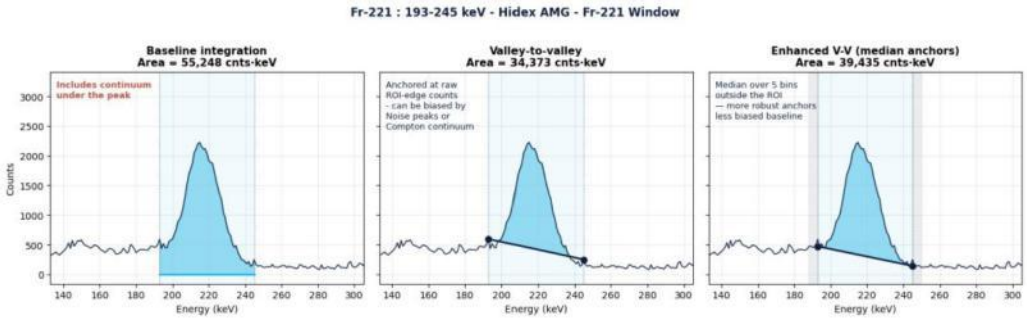

Figure 2 – Examples of the effect of different integration methods on peak quantification.

Acknowledgements:

This work is supported by Innovate UK Knowledge Transfer Partnership #14019 (KSM).
It is also supported by Medicines Discovery Catapult/Innovate UK as a core innovation project (MDCP-0769)

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The Development of Novel Total-Body PET Theranostics for Minimal Residual Disease

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Keywords: Total-body PET, Oncology, Theranostics

Abstract

Following curative-intent cancer treatment, patients must be monitored for minimal residual disease (MRD), which remains a significant challenge in oncology. Standard PET imaging frequently fails to detect metastatic seeding which without intervention will progress into metastatic lesions. Total-body PET imaging is significantly more sensitive by an order of magnitude and consequently, can be utilised to reduce scan acquisition times and administered doses.[1] We propose that the increased field-of-view and sensitivity of total-body PET could be leveraged to detect, locate, and treat MRD in patients during remission when combined with novel theranostics. Our aim is to develop paired radiometal-labelled immunoconjugates for immunoPET imaging (Zirconium-89) and radiotherapy (Lutetium-177).[2] These will target validated biomarkers for cells with high relapse potential, delta-like ligand 3 (DLL3) and leucine-rich repeat-containing G-protein coupled receptor (LGR5), for small cell lung cancer and colorectal cancer respectively (Figure 1).[3,4]

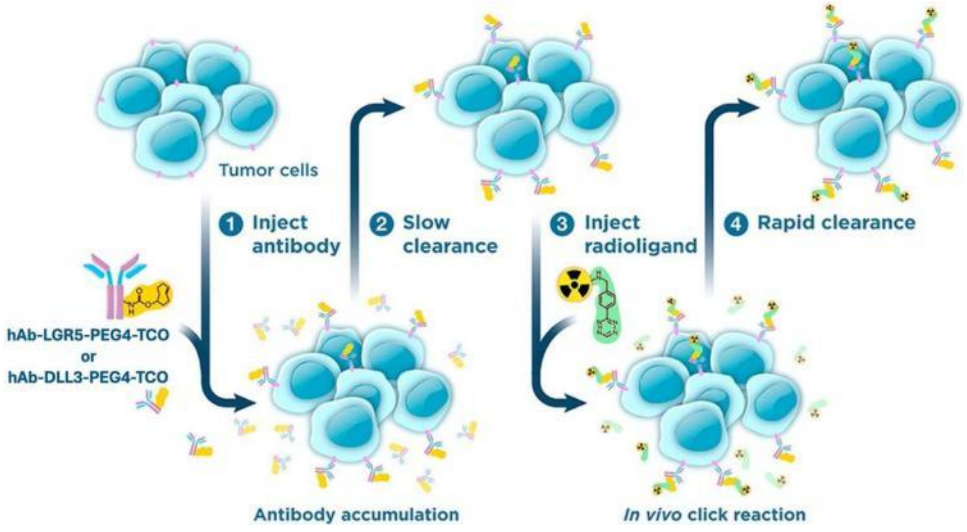
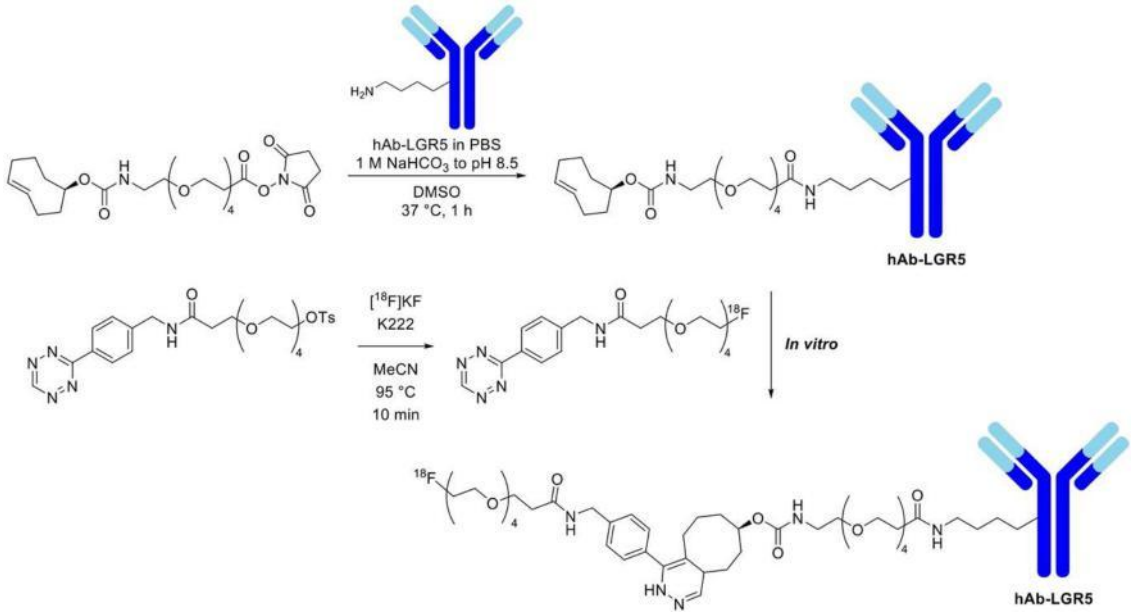


Figure 1. ImmunoPET strategy for imaging of DLL3 and LGR5. Adapted from Zeglis, B. M., *et al*., *Optimization of a Pretargeted Strategy for the PET Imaging of Colorectal Carcinoma via the Modulation of Radioligand Pharmacokinetics*. Molecular Pharmaceutics, 2015. 12: p. 3575–3587.[2]

To facilitate proof-of-concept studies, we have designed and optimised a synthetic route to a tetrazine-Peg4-tosylate precursor for radiofluorination to afford [^{18}F]tetrazine-Peg4-F (Scheme 1). Additionally, a complimentary synthetic route was developed to produce the equivalent fluorine-19 compound which enabled efficient optimisation of the radiolabelling procedure. These synthetic routes will be discussed in detail during this presentation. Following conjugation of commercially available *trans*-cyclooctene-Peg4-NHS ester with hAb-LGR5, the resultant *trans*-cyclooctene-antibody conjugate underwent an *in vitro* click reaction with [^{18}F]tetrazine-Peg4-F *via* inverse electron-demand Diels-Alder cycloaddition (IEDDA) and retro Diels-Alder reaction. *In vitro* studies with this LGR5 immunoconjugate labelled with fluorine-18 are ongoing. Future work will include *in vitro* and *in vivo* preclinical studies with this LGR5 immunoconjugate labelled with fluorine-18 prepared *via in vivo* click reactions.



Scheme 1. Synthesis of LGR5 immunoconjugate labelled with fluorine-18

Acknowledgements:

This work is supported by the Medical Research Council via the Total Body PET Infrastructure Project (MR/Y008944/1) and the Cancer Research UK Scotland Institute (A25006). Attendance at this meeting was supported by a SINAPSE Travel Award.

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Novel CXCR4- and ACKR3-targeted theranostic agents for PET/SPECT imaging and radionuclide therapy in cancer

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Relevant Keywords: Chemokine, Bicyclam, Copper

The chemokine receptors CXCR4 and ACKR3 (previously CXCR7) have been shown to be overexpressed in many different cancers[1] and usually indicate a poor prognosis. Many imaging agents and therapeutic compounds have been studied for the targeting of CXCR4; however, few exist for ACKR3. Given the collaborative nature of CXCR4 and ACKR3, targeting both receptors simultaneously could yield more favourable therapeutic outcomes.

[^{64}Cu]CuCB-Bicyclam is a high-affinity radiotracer for the PET imaging of CXCR4-overexpressing tumours[2,3]. Copper(II), zinc(II), nickel(II), and manganese(II) analogues of this compound have been developed in our research group and show high affinity for CXCR4 and ACKR3. Radiolabelling selected candidates with ^{64}Cu (PET) and ^{67}Cu (SPECT and radionuclide therapy) has shown promising preliminary results for both imaging and therapy of these chemokine receptors.

The lead candidates exhibit high affinity for the two chemokine receptors, with nM IC_{50} values for CXCR4 and ACKR3. The successful ^{67}Cu radiolabelling of novel dual CXCR4/ACKR3-targeting agents is reported here with subsequent *in vitro* and *in vivo* evaluation. SPECT/CT imaging of the lead candidate, [^{67}Cu]SJA999, showed significant tumour uptake in animals implanted with CXCR4- and ACKR3-overexpressing xenografts, with high tumour uptake maintained at least 3 days post-injection. Specificity of [^{67}Cu]SJA999 for CXCR4 was confirmed in blocking studies using the high-affinity CXCR4 antagonist, Cu_2CB-Bicyclam.

Future work will focus on extending the *in vivo* validation of our novel dual CXCR4/ACKR3 inhibitor to better understand how this derivative interacts with the two chemokine receptors of interest. Further evaluation will be carried out across a range of tumour models, including those with heterogeneous CXCR4 and ACKR3 expression, as well as in radiopharmaceutical therapy experiments.

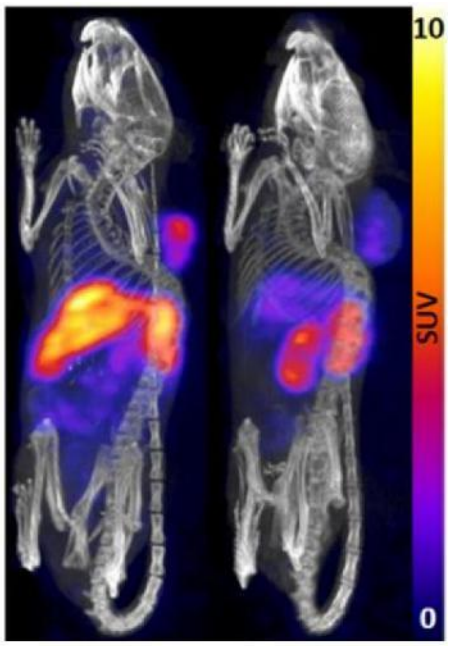

Figure. Representative 30 min SPECT/CT scan of ^{67}Cu-radiolabelled CXCR4/ACKR3 dual inhibitor in U87-CXCR4 tumour-bearing mice, unblocked (left) and blocked with 5 mg/kg (i.p.) of Cu_2CB-Bicyclam (right), imaged at 3 d post-injection.

Acknowledgements:

This work is supported by the EPSRC Doctoral Training Programme (Grant number 2904200).

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POSTER PRESENTATIONS

Developing Non-invasive and Selective PET/Optical Imaging Probes To Image Transplanted Stem-Cell Derived Islets in Type 1 Diabetes

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Keywords: PET, [^{18}F]AlF, Fluorine-18

Abstract:

Type 1 diabetes (T1D) is an autoimmune disease in which the immune system destroys the insulin-producing ß-cells in the pancreas, leading to uncontrolled glucose levels. Lifelong insulin injection is the major management for T1D yet offers no cure. Current islet transplantation holds curative potential, but is limited by donor scarcity and transplant-triggered inflammation (IBMIR).[1,2]

Transplanting human embryonic stem cell-derived islets (SC-islets) offer a promising solution to donor scarcity, but the technology remains immature.[2] In this study, the SC-islets will be co-transplanted with micro-vessels to promote vascularisation and reduce IBMIR, enhancing the graft-survivals. To monitor and optimise transplantation, selective PET/optical imaging probes will be developed to validate the pancreatic ß-cells specificity and signal reproducibility post-transplantation, to quantify ß-cell mass and immune-mediated losses simultaneously, and to compare SC-islets graft survivals and function in subcutis, portal vein, and anterior eye chamber for identifying the optimal transplantation site.

Exendin-4, a glucagon-like-peptide-1 (GLP-1) analogue with high affinity for the GLP-1 receptor (GLP-1R) on pancreatic ß-cells, was selected as the probe targeting moiety. An additional cysteine at position 40 enables simple conjugation to the imaging moiety via a selective thiol-maleimide click reaction (**Fig. 1**).[3,4] Aluminium fluoride (AlF) complexation was employed using an aqueous method for radiolabelling that results in high purity ligands.

The optical imaging probe, rho-pip-[Cys^{40}]-Ex4 demonstrated high selectivity to the GLP-1 receptor on MIN6 cells *in vitro*. The PET probe, [^{18}F]AlF-NODAGA-[Cys^{40}]-Ex4 is expected to have similar selectivity but greater sensitivity and tissue penetration which are suitable for non-invasive *in vivo* PET experiments. [^{18}F]AlF-NODAGA-[Cys^{40}]-Ex4 has been successfully synthesised with a radiochemical yield (RCY) of $<$6 % (decay-corrected). Its *in vitro* binding affinity for GLP-1R is currently under assessment.

Ultimately, the study aims to enhance the SC-islet transplantation efficiency and provide a viable replacement for lifelong insulin therapy, enabling T1D patients to achieve long-term glycemic control

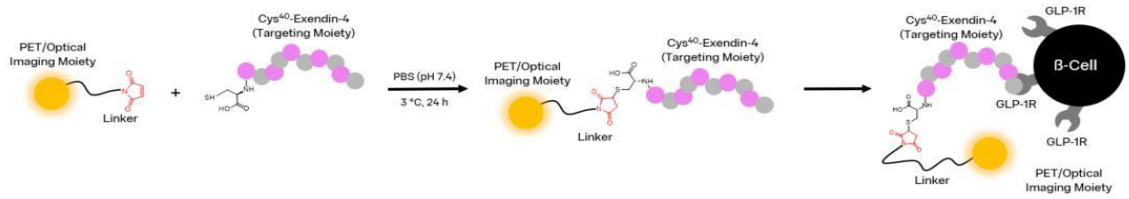

Fig. 1. Illustration of thiol-maleimide click reaction between the PET/optical imaging moiety and the targeting moiety ([Cys^{40}]-Ex4) and its binding selectivity towards the abundant GLP-1R on the pancreatic ß-cells.

Acknowledgements:

This work is supported by Breakthrough T1D. We thank the staff from the Platform of Laboratory of Radiochemistry & Cyclotron (CRCHUM).

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Production of [^{11}C]MRB on Synthra MeI plus in a GMP environment

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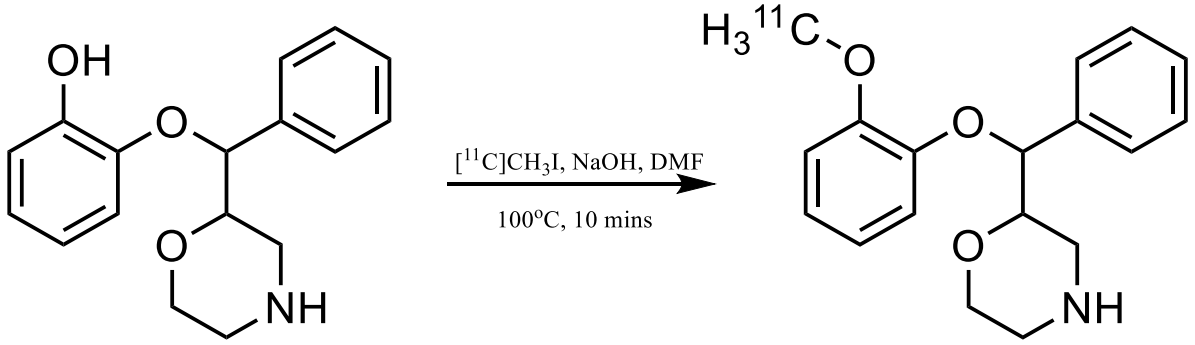
Introduction: [^{11}C]Methylreboxetine (MRB), is a PET radiopharmaceutical recently validated at the Radiopharmaceutical Unit (RPU). It is used in clinical settings for diagnosis of progressive supranuclear palsy (PSP) which is often misdiagnosed as Parkinsons due the similarity of the clinical symptoms.

Materials and Methods: The Synthra MeIplus is used for the synthesis of [^{11}C]MRB. [^{11}C]CO_2 is produced from the GE PETtrace 800 cyclotron in 50 min. Irradiation produces ~45-50 GBq of [^{11}C]CO2 radioactivity which is converted via [^{11}C]CH_4 to [^{11}C]CH_3I. The radiosynthesis of [^{11}C]MRB proceeds via methylation of the MRB precursor (0.5 mg) in a NaOH/DMF solution. After approx. 1 minute delivery to the reactor, the reaction is heated at 100°C for 10 minutes. The solution is cooled then diluted with water before being injected onto the semi-preparative column. The product peak is collected in water and immobilised on an MCX cartridge before washing with water. Pure [^{11}C]MRB is then eluted from the cartridges with ~1 mL of Ethanol and 1 mL of PBS into a solution of 14 mL 0.9 % NaCl, then delivered to the dispensing system (Clio dispenser). For quality control, a 10-minute HPLC method was employed using isocratic elution with 35% THF in water at a flow rate of 1 mL/min, with detection at 235 nm, on a C18 column to confirm radiochemical identity and purity.



Scheme 1. Radiosynthesis of [^{11}C]MRB

Results: Currently in routine production at the RPU for one patient dose at a time. Typical synthesis time is 60 minutes, and average non-decay radiochemical yield was 11 %, (n = 4, from [^{11}C]CH_3I).

Conclusions: [^{11}C]MRB has been validated for clinical production in RPU. The manufacturing/QC process is robust, semi-automated with minimal user interaction and provides enough radiotracer for 1 patient dose on-site.

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Radiosynthesis and preliminary *in vitro* evaluation of a technetium-99m labelled D-amino acid for imaging bacterial infection

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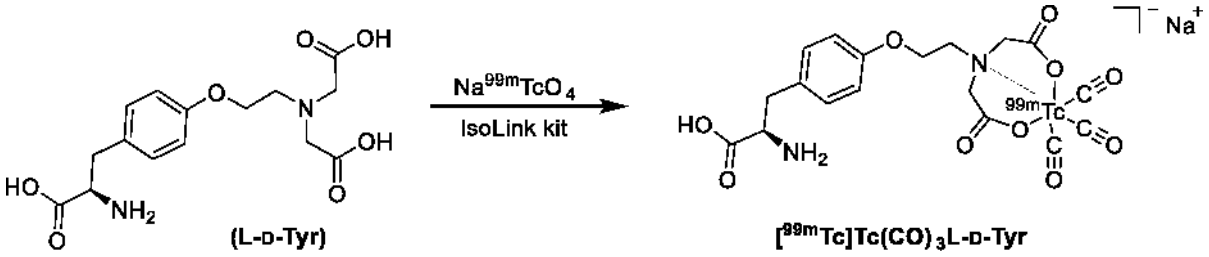
Keywords: Technetium-99m, Infection, D-Amino acids

Background: Existing clinical radiotracers for imaging infection are not selective for bacteria. Radiotracers such as FDG and gallium-67 citrate accumulate in the immune cell response to an infection, rather than in bacteria. This can cause difficulties distinguishing infection from other conditions such as cancer and sterile inflammation. Radiolabelled D-amino acids (D-AAs) are promising bacteria-specific radiotracers because D-AAs are components of bacterial peptidoglycan cell walls, a feature absent from human cells. We have previously reported the fluorine-18 labelled D-methionine derivative D-[^{18}F]FPHCys, which showed specific uptake in live *Staphylococcus aureus* infection over sterile inflammation in a mouse model.[1] Here, we present preliminary results of a new technetium-99m complex linked to a D-AA, in a complementary strategy for SPECT imaging.

Methods: We synthesised a tridentate pro-ligand for the technetium-99m tricarbonyl core, linked to D-tyrosine.[2] Technetium-99m tricarbonyl was generated using sodium pertechnetate and an IsoLink kit, followed by addition of the pro-ligand. The purified tracer was applied to cultures of *S. aureus* and *Pseudomonas aeruginosa* (live, and heat-killed), with uptake measured by gamma counting up to 4 h.

Results: The desired pro-ligand was prepared in 5 steps. Radiolabelling proceeded smoothly, yielding the desired complex [^{99m}Tc]Tc(CO)$_3$L-D-Tyr in radiochemical purity of >96%. [^{99m}Tc]Tc(CO)$_3$L-D-Tyr showed modest uptake in live *S. aureus*, which increased over 4 h. Although lower than in live cells, uptake also increased in dead *S. aureus* over the time course. In *P. aeruginosa*, there was low uptake in both live and dead cells.

Conclusions: The unexpected uptake of [^{99m}Tc]Tc(CO)$_3$L-D-Tyr in dead *S. aureus* needs further investigation to determine the mechanism. A range of ligand scaffolds coupled to D-AAs are now being investigated to improve bacterial uptake, and to understand selectivity.



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Preparation of $^{89}ZrCl_4$ from Commercial ^{89}Zr-Oxalate for Radiometal Chelation and Comparison of Radiolabelling Performance with DFO, DFO* and DOTA containing compounds

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Keywords: (up to 3 max) e.g. PET, Zirconium-89 chloride, DOTA

Abstract

^{89}Zr is an established positron-emitting radionuclide for PET imaging, with a half-life that matches the biological residence time of monoclonal antibodies. However, it can also be used to radiolabel molecules with shorter biological half-lives such as peptides, small proteins, and small molecules. DOTA, a widely used chelator suitable for multiple radionuclides, does not form stable complexes with ^{89}Zr in its oxalate form. This limits its use for the radiolabelling of new and commercially available DOTA-conjugates and restricts the application of ^{89}Zr in theranostic pairs.

In its chloride form, $^{89}ZrCl_4$ forms stable complexes with DOTA and was successfully used to radiolabel clinically important DOTA-conjugates.[2] $^{89}ZrCl_4$ is not commercially available; despite being usable when freshly prepared, it is unstable during shipping/storage. Nevertheless, it can be prepared from ^{89}Zr-oxalate using a commercially available anion exchange (SAX) column. Using this approach, we converted ^{89}Zr-oxalate into $^{89}ZrCl_4$ and evaluated the radiolabelling of various DOTA-based compounds with $^{89}ZrCl_4$.[1,2]

In this work, we compared the ^{89}Zr radiolabelling and stability of an antibody conjugated with DFO, DFO* (radiolabelled using ^{89}Zr-oxalate), and DOTA (radiolabelled using $^{89}ZrCl_4$). The stability of the resulting radiolabelled complexes was evaluated through EDTA challenge, and acid stability studies. As expected, the DFO complex exhibited the lowest stability in the presence of EDTA. However, the DOTA complex exhibited stability comparable to that of the DFO* complex.

Additionally, the feasibility of radiolabelling DOTA-containing small molecules with $^{89}ZrCl_4$ was evaluated using PSMA-617, FAPI-46, and DOTATATE. Each compound was radiolabelled at three target molar activities (4, 8, and 12 MBq/nmol), and the resulting complexes were characterised by RP-HPLC. Although successful radiolabelling with $^{89}ZrCl_4$ was achieved for all three compounds, the attainable molar activities were inconsistent, likely reflecting variations in the amount of residual oxalate remaining following SAX purification.[3]

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Towards the development of automated radiosynthesis of [^{11C}]Malonate for PET imaging

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Keywords: Carbon-11 HCN, carbon-11 malonate, radiolabelling, cyanation, PET,

Abstract

As a part of an ongoing study in applying acidified malonate which is a competitive inhibitor of succinate dehydrogenase (SDH) to attenuate burst of reactive oxygen species we required a Positron Emission Tomography (PET) radiotracer capable of reporting on SDH metabolic flux *in vivo*. We identified a [^{11}C]Malonate as a suitable radiotracer[1,2]. The radiosynthesis of [^{11}C]Malonate was reported in 1988 by the De Spiegeleer group.[3] Herein we describe non-automated radiolabelling of [^{11}C]Malonate and our efforts in translating radiolabelling condition to automate radiosynthesis on GE Tracerlab FXFN module.

The non-automated [^{11}C]Malonate radiosynthesis was explored including various temperatures, reaction times and amounts of precursor. Following successful identification of desired radiolabelled [^{11}C]Malonatereaction conditions were translated onto the GE Tracerlab FXFN module (Figure 1). The radiolabelling was done using cyanation reaction of bromoacetic acid with [^{11}C]HCN (Scheme 1). [^{11}C]HCN was produced on the Synthra HCN module from cyclotron-generated [^{11}C]CO_2 which was reduced to [^{11C}]CH_4 and reacted with gaseous ammonia to yield [^{11C}]HCN. Trapped [^{11C}]HCN was further reacted with bromoacetic acid, and the resulting nitrile hydrolysed under basic conditions. Semi-preparative HPLC purification was investigated to identify suitable column and eluent and different SPE cartridges were explored to establish optimal formulation of [^{11}C]Malonate.

[^{11}C]Malonate was afforded in modest radiochemical yields which increased with increasing amount of radiolabelling precursor used. The incomplete nitrile hydrolysis using aqueous sodium hydroxide was observed when smaller amounts of precursor were employed. Optimizationof purification and isolation steps led to [^{11}C]Malonate suitable for injection for *in vivo* PET imaging.

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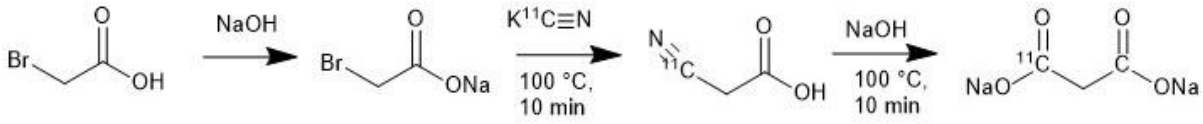

Scheme 1. *[^{11}C]Malonate* radiolabelling using bromoacetic acid as a precursor.

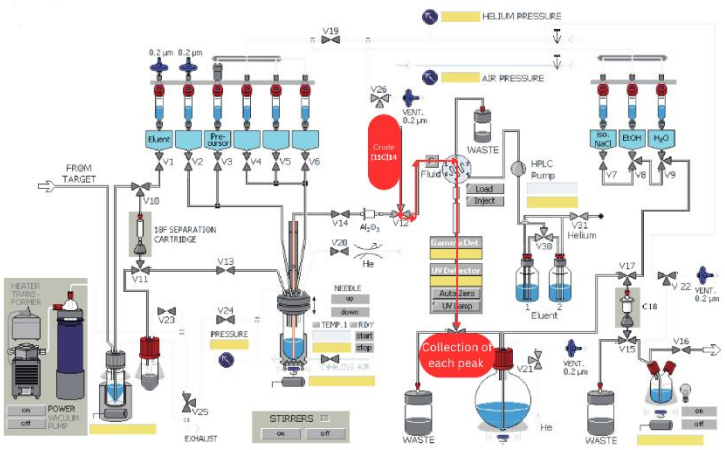

Figure 1. GE TRACERLab FXFn diagram for the automated synthesis of *[^{11}C]Malonate*

Evaluation of Novel Precursors for Cu-Mediated Radiosynthesis of [^{18}F]*m*FBG

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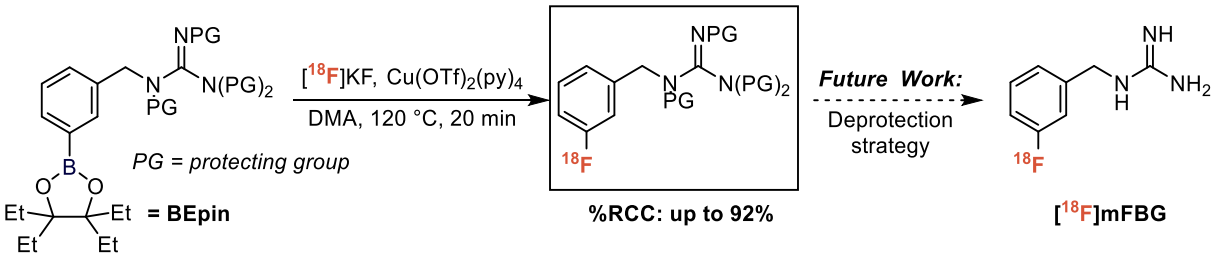
Keywords: Fluorine-18 radiochemistry

Positron emission tomography (PET) is a vital *in vivo* imaging technique in modern medicine and pharmaceutical development.[1] PET scans require drugs (PET tracers) labelled with positron-emitting isotopes, such as fluorine-18, which is routinely used because of its favourable decay properties (half-life = 109.7 min; energy = 634 keV).[2] [^{18}F]*Meta*-fluorobenzylguanidine ([^{18}F]*m*FBG) is under clinical evaluation for diagnosis of neuroblastoma – a highly aggressive paediatric brain tumour.[3,4]

In this work, synthetic approaches to four novel [^{18}F]mFBG radiolabelling precursors bearing aryl-BEpin motifs (3,4-diethylhexane-3,4-diol boronic ester) for Cu-mediated radiofluorination have been established.[5] Such motifs have demonstrated improved stability on silica and HPLC columns than aryl-Bpin motifs – easing adoption for GMP-compliant quality assurance while maintaining radiolabelling efficiency. The developed synthetic routes achieve gram-scale in yields ranging from 53-72% across 2-3 steps. Additionally, alternative protecting group strategies for the guanidine motif have been explored.

Preliminary radiolabelling achieved promising radiochemical conversions (%RCC) of up to 92%. Future work will focus on optimisation of deprotection strategies and establishing automated radiosynthesis protocols (on a TRASIS AllinOne) to obtain [^{18}F]*m*FBG in improved radiochemical yield and of sufficient quality for routine (pre)clinical production.



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^{18}F-Radiopharmaceutical Diversification Enabled by Deaminative Cross-Electrophile Couplings

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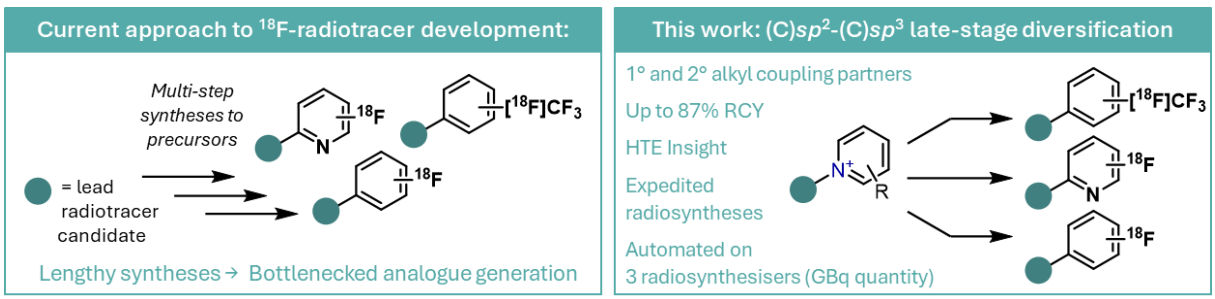
Key words: *fluorine-18 radiochemistry, cross-couplings, high-throughput experimentation*

The development of fluorine-18 radiotracers is central to clinical positron emission tomography (PET) imaging and supporting drug discovery campaigns. However, the preparation of complex radiolabelling precursors often limits the rapid generation and evaluation of structural analogues, restricting exploration of radiochemical space. This is highly prevalent in the syntheses of specialized precursors amenable to site-selective, late-stage radio fluorination with weakly nucleophilic [^{18}F]fluoride (^{18}F; $t_{1/2}$ =109.7 mins; 97% β+ decay; 635 keV).[1]

In this work, we present a nickel-mediated aryl (C)sp²–(C)sp³ cross-coupling strategy compatible with radiosynthesis, employing readily-accessible amine-derived 2,4,6-triphenylpyridinium salts as alkyl coupling partners.[2] In analogy to pharmaceutical discovery, this approach enables late-stage diversification from common precursors, reducing synthetic burden and facilitating access to structurally diverse ^{18}F-radiotracers.

The method is applicable to both primary and secondary *N*-alkyl pyridinium salts, achieving high radiochemical conversions (up to 86%). A tailored non-radiochemical high-throughput experimentation (HTE) assay was developed to rapidly identify optimal Ni-ligands for structurally diverse fluorinated (hetero)aryl iodides, expediting reaction optimisation. Crucially, the assay results translated well to analogous radiochemical systems.

A diversification case study targeting GSK-3 kinase inhibitors demonstrates the utility of this strategy, enabling the synthesis of six ^{18}F-labelled analogues from a single precursor, including production at gigabecquerel (GBq) scale across three commercial synthesis platforms. This work highlights a novel approach for accelerating radiotracer development through modular and scalable late-stage functionalisation.



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Synthesis, Radiolabelling and Stability of New Compounds with Terbium-161.

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Keywords: Terbium-161, SPECT, Isothiocyanate

Abstract

Terbium radioisotopes are gaining popularity due to their four matched radioisotopes that can be used for different nuclear medicine applications.[1] As terbium-161 ($t_{1/2}$ = 6.9 d, ^{161}Tb) decays, it emits β particles, γ radiation, low-energy conversion and Auger electrons, giving the potential to outperform the benchmark theranostic SPECT radioisotope, ^{177}Lu ($t_{1/2}$ = 6.7 d).[2,3] In our group we are interested in developing new imaging agents for ^{161}Tb labelling. Two compounds were prepared based on DO3A (gen I) and DOTAGA (gen II) macrocycles, with gen II featuring a common thiourea functional group. Both were labelled with "cold" terbium-159 (^{nat}Tb) and ^{161}Tb. [4] The stability of these complexes in solution was studied, as well as in the presence of competitors (EDTA, DTPA, human serum albumin and Zn). [5] When labelled with ^{161}Tb, it was found that gen I was more stable than gen II in solution and against all competitors, except with EDTA where both gen I and gen II showed marked ^{161}Tb release. To determine if the stability differences observed were chelator or linker based, a third chelator (gen III) was synthesised to structurally bridge the gap between the design of gen I and gen II. The synthesis of the third chelator involved the installation of an isothiocyanate, which was investigated in detail to determine a more accessible route to this functional group for subsequent thiourea formation. This work has informed us on linker/chelator stability and the preparation of new ^{161}Tb complexes, which can be extended to future radiolabelling work.

Acknowledgements:

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