Manual and Automated Cu-Mediated Radiosynthesis of the PARP Inhibitor [^{18}F]Olaparib

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Abstract

Positron emission tomography (PET) is a diagnostic nuclear imaging modality that relies on automated protocols to prepare agents labelled with a positron-emitting radionuclide (e.g. ^{18}F). In recent years, new reactions have appeared for the ^{18}F-labelling of agents that are difficult to access applying traditional radiochemistry, for example those requiring ^{18}F-incorporation onto unactivated (hetero)arenes. However, automation of

these new methods for translation to the clinic has progressed slowly; this is because extensive modification of manual protocols is typically required when implementing novel ^{18}F-labeling methodologies onto automated modules. Here, we describe the workflow that led to the automated radiosynthesis of the Poly(ADP-ribose) polymerase (PARP) inhibitor [^{18}F]olaparib. Firstly, we established a robust manual protocol to prepare [^{18}F]olaparib from the protected *N*-[2-(Trimethylsilyl)ethoxy]methyl (SEM) arylboronate ester precursor in 17% ± 5% (*n* = 15, synthesis time 135 mins) non-decay-corrected (n.d.c) activity yield, and molar activity (A_m) up to 34.6 GBq/µmol. Automation of the process, consisting of a copper-mediated ^{18}F-fluorodeboronation followed by deprotection, was also achieved on an Eckert & Ziegler Modular-Lab radiosynthesis platform, and afforded [^{18}F]olaparib in 6% ± 5% (*n* = 3, synthesis time 120 mins) n.d.c. activity yield, and A_m up to 319 GBq/µmol.

Introduction

Positron emission tomography (PET) is a powerful non-invasive nuclear imaging technique used for clinical diagnosis and treatment monitoring as well as for drug discovery and development.[1,2] In contrast to anatomical imaging techniques, such as X-ray imaging or ultrasound, PET provides information on metabolic status, physiology, and molecular events.[3] Regardless of the application, all PET imaging studies require a molecule labelled with a positron-emitting radioisotope. In the context of drug discovery, the drug itself or a structurally related radioligand can be used for biodistribution studies, target tissue delivery, or quantitative receptor occupancy measurements.[4]

Whilst various fluorine-containing functional groups are represented amongst marketed fluorine-containing drugs, (hetero)aryl fluorides are by far the most prevalent.[5] Efficient radiosynthetic routes to prepare structurally complex radiotracers containing one or more (hetero)arenes are therefore in high demand.[6,7] Several reactions are available to access ^{18}F-(hetero)arenes from cyclotron-produced [^{18}F]fluoride, with precursors including (hetero)aryl halides,[8] nitroarenes,[9] trimethylammonium salts,[10] sulfonium salts,[11] sulfoxides,[12] iodonium salts,[13] iodonium ylides,[14] stannanes,[15] phenols,[16,17] sydnones,[18,19] and pre-formed organometallic complexes of palladium[20] or nickel.[21] Since the suitability of each method is highly dependent on the steric and electronic properties of the starting material as well as accessibility, this area of research remains highly active.

First described in 2014, the copper-mediated nucleophilic ^{18}F-fluorodeboronation of (hetero)aryl boronic esters is a powerful method developed in our laboratory to introduce an ^{18}F-substituent onto electron rich, neutral and poor (hetero)arenes.[22] This reaction

enabled facile access to eight clinically relevant radiotracers.[23] Various groups have applied this method to prepare ^{18}F-labelled arenes for imaging enzymes and receptors relevant to oncology, including carbonic anhydrase IX,[24] prostanoid EP4 receptor, and indoleamine, and tryptophan 2,3-dioxygenases.[25,26] In 2015, the Sanford and Scott groups reported a variant of the ^{18}F-fluorodeboronation using aryl boronic acids;[27] Neumaier and co-workers optimised the [^{18}F]fluoride elution step.[28] One of the main advantages of boronic ester precursors is that they are bench stable (room temperature, up to one year) and accessible using one of many methods reported in the literature for their preparation.[29-36]

Our initial report established the compatibility of the Cu-mediated ^{18}F-fluorodeboronation with common functional groups, and demonstrated that improved results could be obtained by protecting nucleophilic groups such as phenols and amines.[22] Subsequently, a more detailed study revealed that caution should be exercised when applying this radiosynthetic method to ^{18}F-radiotracers containing one or more heteroarenes because some have been shown to be challenging substrates in metal-catalysed cross-coupling reactions.[37]

These findings prompted a study aimed at providing radiochemists with guidelines to plan the optimal retro-radiosynthetic route to complex ^{18}F-radiotracers when selecting Cu-mediated fluorodeboronation for ^{18}F-labelling; these guidelines were inspired by the robustness screening approach described by Collins and Glorius,[38] and enabled successful application of our Cu-mediated radiofluorination protocol to complex *N*-heterocyclic-containing ^{18}F-radiotracers.[37] Recently, Schirrmacher and co-workers demonstrated that the copper-mediated ^{18}F-fluorodeboronation is amenable to automation on Scintomics GRP and TRACERLAB FX_{FN} platforms. This protocol enabled

access to [^{18}F]TRACK which was used for in-human brain imaging.[39] Herein, we report that the manual radiosynthesis[41] of the Poly(ADP-ribose) polymerase (PARP) inhibitor [^{18}F]olaparib is amenable for automation on an Eckert & Ziegler Modular-Lab. These developments are significant because automation paves the way towards routine use of this methodology for future applications in the clinic.

Experimental design

In general terms, the first step for any radiosynthesis is to design a suitable synthetic route that can provide the agent required for PET studies. Our laboratory typically relies on the Cu-mediated ^{18}F-fluorodeboronation for ^{18}F-labelling, and routinely applies a robustness screening approach aimed at determining rapidly whether it is possible to perform ^{18}F-fluorodeboronation as the last step in the synthesis. If not possible, this screening approach also enables us to decide which step(s) (ideally no more than one or two) should be implemented post ^{18}F-fluorination. For decision making, a commercially available arylboronic ester responding well to ^{18}F-labelling (RCY = 34% ± 15%, *n* = 122), for example 2-(4-cyanophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, is subjected to Cu-mediated ^{18}F-fluorodeboronation in the presence of stoichiometric amounts of the agent requiring labelling (in this study olaparib).

If the presence of the agent to be labelled does not affect radiochemical yield (RCY, calculated based on radio-TLC and HPLC analysis of the crude product),[40] a last step ^{18}F-fluorination is likely viable. However, if the RCY is drastically decreased, or no ^{18}F-incorporation is detected (RCY < 5%), it is necessary to identify which group or sub-motif prevents ^{18}F-radiofluorination. This group must be introduced post ^{18}F-labelling, or

would require suitable protection prior to ^{18}F-labelling. Having established a viable radio-retrosynthetic plan, one can focus on the radiosynthesis. For structurally complex agents requiring multi-step synthesis to access the necessary aryl boron precursor, we recommend fine-tuning the reaction conditions for the key ^{18}F-fluorodeboronation with a boron precursor that is easier to prepare, yet matching the electronic and steric properties of the radiotracer required. Figure 1 illustrates how this workflow was successfully applied to the radiosynthesis of [^{18}F]olaparib.

In brief, the robustness screening experiments illustrated in step 1 show that [^{18}F]olaparib is not within reach applying a last step fluorination because of the presence of the unprotected phthalazin-1(2*H*)-one motif; *N*-protection of this motif restores reactivity. With this information in hand, step 2 focuses on optimising the key step consisting of replacing the BPin substituent with ^{18}F. Since the aryl BPin precursor necessary for ^{18}F-radiolabelling requires multi-step synthesis, the ^{18}F-fluorodeboronation step was optimised with a more readily accessible aryl boron precursor matching reasonably well the arene motif present in olaparib. With optimised conditions secured, the manual and automated radiosyntheses of [^{18}F]olaparib were successfully implemented applying a Cu-mediated ^{18}F-radiofluorination from cyclotron-produced [^{18}F]fluoride followed by a single *N*-deprotection step. The detailed commentary of this workflow is provided below (Scheme 1).

Stage 1: Robustness screening approach applied to [^{18}F]olaparib.

When the radiofluorination of 2-(4-cyanophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **1** was performed under standard conditions (0.06 mmol of boron precursor **1**, and 0.1 equivalent (0.0053 mmol) of [Cu(OTf)$_2$(py)$_4$] at 110°C) in the presence of stoichiometric

amount of olaparib (0.06 mmol), no ^{18}F-incorporation was observed. This result prompted further investigation to identify which structural motif within olaparib prevents ^{18}F-radiofluorination. Experiments, consisting of spiking **1** systematically with stoichiometric amounts of olaparib sub-fragments, rapidly identified the unprotected phthalazinone as responsible for the failure of ^{18}F-fluorodeboronation, a result demonstrating the incompatibility of the free NH group.

To overcome this limitation, a selection of *N*-protected phthalazinones were tested in additional spiking experiments. No ^{18}F-radiofluorination was observed when the reaction was performed in the presence of the *N*-Boc protected phthalazinone **4**, possibly due to chelation and/or instability under the reaction conditions. The *N*-methyl and *N*-allyl protected fragments **5** and **6** showed satisfactory radiochemical yields, but the harsh conditions necessary for *N*-demethylation, and the requirement of a Pd catalyst for *N*-deallylation discourage their use as protecting groups. *N*-[2-(Trimethylsilyl)ethoxy]methyl (SEM) was deemed suitable based on the finding that the presence of phthalazinone **7** did not affect significantly the radiofluorination, and the knowledge that this protecting group could be easily removed under acidic conditions. Taken together, these data suggest that a suitable route towards [^{18}F]olaparib would involve ^{18}F-fluorodeboronation of the *N*-SEM protected aryl boron precursor **10** (see Supplementary Information) shown in step 3, followed by a single *N*-deprotection step post ^{18}F-fluorination.

Stage 2: Optimisation of the Cu-mediated ^{18}F-fluorodeboronation step.

Step 2 focused on the optimisation of the copper-mediated ^{18}F-fluorodeboronation. For time and cost efficiency, this study was performed using the aryl boron precursor **8** (two

step synthesis), which is easier to access than precursor **10** (eleven step synthesis), yet matching closely the steric and electronic properties of the aryl motif of olaparib.

In previous work,[37] we observed that the efficiency of ^{18}F-fluorodeboronation was dependent on the amount of precursor used, and stoichiometry with the copper complex. Typically, 0.02 mmol of precursor and 0.03 mmol of copper complex (1.5 equivalents) in 0.3 mL of N,N-dimethylacetamide (DMA, 0.06 M) offered the best radiochemical yields (RCYs). Furthermore, this study revealed that the novel copper complex $[Cu(OTf)_2(impy)_4]$ is superior to $[Cu(OTf)_2(py)_4]$ for many aryl boron reagents. Consequently, different copper complexes and solvents were tested for the ^{18}F-labelling of **8**. This study demonstrated that the use of $[Cu(OTf)_2(impy)_4]$ (instead of $[Cu(OTf)_2(Py)_4]$ or $[Cu(OTf)_2]$) in 1,3-dimethyl-2-imidazolidinone (DMI) (instead of dimethylformamide (DMF) or dimethylacetamide (DMA)) as the reaction solvent was optimal for ^{18}F-fluorodeboronation (RCY = 82% ± 1%, n = 2). The first generation copper complex $[Cu(OTf)_2(py)_4]$ in DMA led to significantly lower RCYs, and was not retained for further olaparib optimisation studies.[41]

Stage 3: Manual radiosynthesis of [^{18}F]olaparib.

The radiosynthesis of [^{18}F]olaparib in manual mode was performed in the Siemens Oxford Molecular Imaging Laboratory (SOMIL) on a NanoTek® module with [^{18}F]fluoride supplied by Alliance Medical Radiopharmacy Ltd. With the results of steps 1 and 2 in hand, we were confident that a ^{18}F-radiosynthetic route to olaparib consisting of ^{18}F-labelling the SEM-protected aryl BPin precursor **10** using $[Cu(OTf)_2(impy)_4]$ in DMI, followed a single deprotection step would be adequate. When performing full isolation of [^{18}F]olaparib, we showed that the best radiochemical yields for the ^{18}F-fluorination step

were obtained with 13 mg of **10** (the SEM *N*-protected BPin precursor of olaparib, 0.02 mmol), and 25 mg of the copper complex (0.03 mmol) in 0.3 mL of DMI (0.06 M) at 120 °C for 20 mins.

Since incorporation of air is beneficial for ^{18}F-labelling to proceed,[42] air was introduced after addition of the reagents to the reaction vessel, containing dry [^{18}F]fluoride, by flushing a 20 mL syringe inside the reactor. After ^{18}F-fluorodeboronation (20 mins), excess trifluoroacetic acid (TFA) (370 µL) was added to the reaction mixture at 120 °C to enable *N*-SEM deprotection (20 mins). In our previous study,[41] we show that the protodeborylated side-product of the precursor was formed upon radiofluorination. This renders purification challenging, so we developed a robust method to achieve optimal separation between olaparib and this undesired side-product (see Supplementary Figure 2).

The reaction mixtures contains DMI and TFA which must be removed for easy HPLC purification. Hydrophilic-Lipophilic Balance (HLB) cartridge allows effective trapping and easy elution of small molecules. By trapping [^{18}F]olaparib on an HLB cartridge, we were able to efficiently remove DMI and TFA prior to eluting the radiotracer off the cartridge with acetonitrile. Purification was performed by radio-HPLC leading to a solution of radiochemically pure [^{18}F]olaparib in a mixture of solvents (acetonitrile, aqueous ammonium formate buffer).

For imaging studies, reformulation was required with an additional step consisting of passing the collected solution of [^{18}F]olaparib onto a second HLB cartridge followed by elution with ethanol. After evaporation of ethanol, [^{18}F]olaparib was dissolved in a solution of 10% dimethyl sulfoxide (DMSO) in phosphate-buffered saline (PBS), a

solvent system suitable for injection and imaging experiments. This protocol gave [^{18}F]olaparib in 17% ± 5% (*n* = 15) non-decay-corrected activity yields with a total synthesis time of 130 mins. Starting from 3.48 GBq of [^{18}F]fluoride, we produced up to 735 MBq of [^{18}F]olaparib with a molar activity reaching up to 34.6 GBq/μmol 60 mins after the end of the synthesis (E.O.S.).

Part 4: Automated radiosynthesis of [^{18}F]olaparib.

The automated radiosynthesis of [^{18}F]olaparib was performed at the PET Radiopharmacy Oxford facility (PROx) on an Eckert & Ziegler platform.[^{18}F]Fluoride was supplied by the Wales Research and Diagnostic PET Imaging Centre. Identical loadings of precursor **10** (13 mg, 0.02 mmol), and [Cu(OTf)$_2$(impy)$_4$] (25 mg, 0.03 mmol) in 0.3 mL of DMI (0.06 M) were used for automation. For this reaction, the main challenge arising from translating manual to automated radiosynthesis was the necessity to carry out the Cu-mediated fluorodeboronation under air.

Reagents were added in the reaction vessel containing azeotropically dried [^{18}F]fluoride prior to adding air. Air incorporation was achieved by connecting the reactor to an outlet opened to the hotcell. By subjecting the reactor to vacuum, air can be transferred in the reactor thereby improving radiolabeling. After five minutes of reaction at 120 °C, additional air injections (three times) were performed at regular intervals until completion. Deprotection was achieved by addition of TFA (500 µL) at 125 °C for 20 mins.

The protocol for purification required significant modifications as the use of HLB cartridges required inconveniently high pressure to efficiently elute [^{18}F]olaparib. Our module uses gas flow or vacuum to transfer solutions through the automated system, and elution through the HLB cartridges require flow rate not within reach with our module. This problem was solved by eluting the crude reaction mixture through a polyethylene frit instead of an HLB cartridge, a processaffording a solution suitable for HPLC purification. All steps following HPLC purification are similar to the protocol detailed in manual mode except for the use of a C18 light cartridge instead of HLB, an advantageous modification enabling efficient elution of [^{18}F]olaparib using minimal volumes of ethanol or DMSO. This fully automated protocol afforded [^{18}F]olaparib in 6% ± 5% (*n* = 3) n.d.c. RCY with a total synthesis time of 120 mins. Starting from 11 GBq of [^{18}F]fluoride, up to 1200 MBq of [^{18}F]olaparib was isolated with a molar activity of up to 319 GBq/μmol 50 mins after E.O.S.

Materials

Reagents

!CAUTION Handling of ^{18}F-activity should be done with appropriate shielding to avoid radiation exposure. If unfamiliar with handling of radioactivity, consult with your Radiation Safety Officer to determine the appropriate protective measures and radioactivity monitoring devices.

(A) Manual radiolabelling

- [^{18}F]Fluoride was produced by Alliance Medical (UK) via the $^{18}O(p,n)^{18}F$ reaction and delivered as [^{18}F]fluoride in 5 mL [^{18}O]H_2O.
- 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclohexacosane (Kryptofix® 222; Sigma-Aldrich, cat. no. 8.14925).
- Potassium carbonate, 99.995% (K_2CO_3; Sigma-Aldrich, cat. no. 367877).
- Potassium oxalate monohydrate, ≥ 98.5% ($K_2C_2O_4.H_2O$; Sigma-Aldrich, cat. no. P0963).
- Acetonitrile, HPLC grade ≥ 99.9% (MeCN; Sigma-Aldrich, cat. no. 34851).
- Tetrakis(imidazo[1,2-b]'pyridazine) copper(II) triflate [$Cu(OTf)_2(impy)_4$]; prepared following a literature procedure (see Supplementary information).[41]
- 1,3-Dimethyl-2-imidazolidinone, anhydrous 99.8%, (DMI; Sigma-Aldrich cat. no. 193453).
- [^{19}F]Olaparib, ≥ 98% by HPLC (Cambridge Bioscience Ltd, cat. no. 10621).
- Olaparib precursor **10** for radiolabelling was prepared following a literature procedure (see Supplementary information).[41]
- Trifluoroacetic acid, ≥ 99% (CF_3COOH; Fluorochem, cat. no. 001271).
- Ammonium formate, ≥ 99.995% (AMF, NH_4HCO_2; Sigma-Aldrich, cat. no. 516961).
- Ethanol Absolute, ≥ 99.8% by GC (EtOH; Sigma-Aldrich, cat. no. 32221).
- Water (H_2O, milli-Q^R, 18 MΩ/cm).
- Phosphate buffered saline (PBS, 0.01 M phosphate buffer, 0.0027 M potassium chloride, 0.137 M Sodium chloride, pH 7.4; Sigma-Aldrich, cat. no. P4417).
- Dimethylsulfoxide, anhydrous, ≥ 99.9% (DMSO; Sigma-Aldrich, cat. no. 276855).

(B) Automated radiolabelling

- Potassium carbonate, anhydrous, 99% (K_2CO_3; Alfa Aesar, cat. no. A16625).
- Ethanol Absolute, for HPLC (EtOH; Fisher Scientific, cat. no. 10428671).
- Ammonium formate, reagent grade, 97% (AMF, NH_4HCO_2; Scientific Laboratory Supplies Limited, cat. no. 156264-500G).
- Trifluoroacetic Acid, 99+%, for HPLC (TFA; Fisher Scientific, cat. no. 10294110).
- 4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (Kryptofix® 222), (Sigma-Aldrich, cat. no. 8.10647.8250).
- Acetonitrile anhydrous, 99.8% (MeCN; Sigma-Aldrich, cat. no. 271004).
- Acetonitrile, for HPLC (MeCN; Sigma-Aldrich, cat. no. 34851).
- Potassium oxalate hydrate, 99% ($K_2C_2O_4.H_2O$; Alfa Aesar, cat. no. A12289.30).
- 1,3-Dimethyl-2-imidazolidinone, anhydrous 99.8% (DMI; Sigma-Aldrich, cat. no. 40727).
- Sodium chloride 0.9% solution (BBraun, cat. no. 9999-00).
- H_2O for injection (BBraun, cat. no. 352-8820).

Equipment

(A) Manual radiolabelling

- NanoTek® Liquid Flow (LF) Microchemistry System (Advion, cat. no. 900-0003) with NanoTek® Concentrator Evaporator (CE) Module (Advion, cat. no. 900-0002).
- 1260 isocratic pump (Agilent Technologies) equipped with a Knauer - UVD 2.1S Detector UVD with Flow Cell UV and Carroll Ramsay Radioactivity Detector, and a 2 mL injection loop.

- Analytical HPLC (ThermoFisher scientific, UltiMate 3000 HPLC system) coupled with a Flow-RAM radiodetector.
- Synergi™ 4 µm Hydro-RP 80Å LC column 150 x 4.6 mm (Phenomenex, cat. no. 00F-4375-E0).
- Synergi™ 4 µm Hydro-RP 80Å LC column 250 x 10 mm (Phenomenex, cat. no. 00G-4375-N0).
- Vials, screw top V-Vials® with open-top cap, 1 mL (Sigma-Aldrich, cat. no. Z115134).
- Vials, screw top V-Vials® with open-top cap, 5 mL (Sigma-Aldrich, cat. no. Z115150).
- Wheaton® W986217NG NextGen™ V Vial® 3mL Clear Glass High Recovery Vials with 20 mm Crimp Top, Non-Graduated (Wheaton®, cat. no. W986217NG).
- PTFE/silicone septa for 22 mL Vial (Sigma-Aldrich, cat. no. 27177).
- Sep-Pak® Light (46 mg) Accell plus QMA (Quaternary Methyl Ammonium) carbonate cartridge (Waters, cat. no. 186004540).
- Oasis® HLB plus LP extraction cartridge (Waters, cat. no. 186000132).
- Injekt® single-use syringes 10 mL (Braun, cat. no. 4606108V).
- Injekt® single-use syringes 2 mL (Braun, cat. no. 460627V).
- Injekt® single-use syringes 1 mL (BBraun, cat. no. 9166017V).
- BD PrecisionGlide needle™ 21G x 1 (0.8 mm x 25 mm) (Sigma-Aldrich, cat. no. Z192511).
- BD Microlance™ 3 21G x 1.5 Nr.2 (0.8 mm x 40 mm) (BD, cat. no. 305895).
- STERICAN cannula 20 G x 2 4/5 (0.9 x 70 mm) (Braun, cat. no. 2057984).
- 20 mm Crimp Cap (Fisher Scientific, cat. no. VGA-105-010V).

(B) Automated radiolabelling

- Eckert & Ziegler Modular-Lab 4.3.2.0 and the following modules: a Peltier reactor equipped with a camera, valve modules for liquid and gas transport (such as solenoid valves and single stopcock modules), syringe module and an HPLC module equipped with shielded ADII and a stainless steel 5 mL loop.
- Knauer Azura Compact pump with pressure sensor and 10 mL/min stainless steel pump head. Knauer Azura UVD 2.1 S detector, Thermo Scientific Dionex Ultimate 3000 equipped with manual injector, DGP-3600SD dual pump, SRD-3600 solvent rack with degasser, TCC-3000SD column thermostat, MWD-3000 detector, ATLAS-64060 A2D converter, LabLogic Flow-RAM with 1" NaI PMT radiodetector, Capintec CRC-55tPET dose calibrator and Thermo Scientific Chromeleon 7.
- Kinetex™ 5 µm F5 100 Å, LC column 250 x 4.6 mm (Phenomenex, cat. no. 00G-4724-E0).
- Kinetex™ 5 µm F5 100 Å 250 x 10 mm (Phenomenex, cat. no. 00G-4724-N0).
- 10 ml Internally Sterile Nitrogen Filled, Stoppered and Crimped Glass Vials (Adelphi, cat. no. VNS10RB).
- Autosampler vial, screw top with 8 mm screw cap (Fisher Scientific, cat. no. 10246133).
- 100 mL Wheaton® glass bottles (Sigma Aldrich, cat. no. Z114006-12EA).
- Sep-Pak® C18 light (Waters, cat. no. WAT023501).
- Sep-Pak® Light (46 mg) Accell plus QMA carbonate cartridge (Waters, cat. no. 186004540).
- STERICAN disposable needles, 120 mm x 0.89 mm x 21G (BBraun, cat. no. 612-0161).

- STERICAN disposable needles, 25 mm x 0.89 mm x 21G (BBraun, cat. no. 720-2531).
- Empty polypropylene SPE Tube with PE frits, 20 µm porosity (Sigma Aldrich, cat. no. 54221-U).
- Adaptor Cap for 1, 3 and 6 mL SPE Tubes (Phenomenex, cat. no. AH0-7191).
- White septa, PTFE/silicone (Sigma Aldrich, cat. no. 27361).
- Aluminium crimp seals (Sigma Aldrich, cat. no. 27016).
- Gray butyl rubber stoppers (Sigma Aldrich, cat. no. 27232).

Reagent Setup

Solutions for [^{18}F]fluoride elution (for Procedures 1 and 2)

Prepare fresh solutions of Kryptofix® 222 (6.3 mg) in MeCN (800 µL) in a 1 mL V-Vial®, $K_2CO_{3(aq)}$ (1 mg/mL), and $K_2C_2O_{4(aq)}$ (10 mg/mL) in two separate 10 mL vials. Add 100 µL of the K_2CO_3 and $K_2C_2O_4$ aqueous solutions to the previous 1 mL V-Vial®.

Buffer (72% aqueous NH_4HCO_2 28.5 mM in MeCN) for semi-preparative radio-HPLC (Procedure 1)

Dissolve NH_4HCO_2 (1.29 g) in H_2O (720 mL), and add MeCN (280 mL).

Buffer (76% aqueous NH_4HCO_2 25 mM in MeCN) for semi-preparative radio-HPLC (Procedure 2)

Dissolve NH_4HCO_2 (1.19 g) in H_2O (760 mL), and add MeCN (240 mL).

Equipment setup

QMA Sep-Pak® cartridge preconditioning: slowly pass H_2O (2 mL) using a 2 mL syringe through the cartridge to ensure a dropwise elution.

HLB Plus cartridge preconditioning: slowly pass MeOH (2 mL) through the cartridge followed by H_2O (10 mL) using 2 mL and 10 mL syringes to ensure a dropwise elution.

Preparation of vials.

- Drying and reaction vial: place a small stirring bar inside a 5 mL V-Vial®, seal it with a cap holding a PTFE/silicone septum (silicone layer side facing inside the vial), and install a vent needle.
- Crude mixture elution vial: place a small stirring bar inside a 5 mL V-Vial®, seal with a cap holding a PTFE/silicone septum (silicone layer side facing inside the vial), and install a vent needle.
- Waste vial for crude filtration: seal with a cap holding a PTFE/silicone septum (silicone layer side facing inside the vial), and install a vent needle. Collection vial for semi-preparative radio-HPLC: add H_2O (15 mL) to a 35 mL glass vial, seal with a cap holding a PTFE/silicone septum (silicone layer side facing inside the vial), and install a vent needle.
- Waste vial for transfer: seal a 35 mL glass vial with a septum-holding cap, and install a vent needle. Olaparib delivery vial: seal a Wheaton® 3 mL V-Vial® with a crimp cap, and install a vent needle.

Preparation of the analytical radio-HPLC for quality control: condition the Synergi™ (4 µm Hydro-RP 80Å LC column 150 x 4.6 mm) column with 25% MeCN and 75% H_2O using a flow rate of 1 mL/min for 30 mins. Then, connect a 3 mL V-Vial® to the collection valve for peak collection and molar activity determination. Radio-HPLC method for quality control: isocratic flow of 25% MeCN/75% H_2O with a flow of 1 mL/min.

Preparation of the semi-preparative radio-HPLC for isolation: install the Synergi™ (4 µm Hydro-RP 80Å LC column 250 x 10 mm) column, and condition with the buffer (28% MeCN/72% 28.5 mM NH_4HCO_2 in H_2O) using a flow rate of 1

mL/min for 90 mins. Then, purge the collection line with the buffer, and connect to the [^{18}F]olaparib collection vial containing 15 mL of H_2O. Radio-HPLC method for isolation: isocratic flow 28% MeCN/72% 28.5 mM NH_4HCO_2 in H_2O with a flow of 4 mL/min.

Procedure 1: Manual radiosynthesis of [^{18}F]olaparib • Total synthesis time 130 mins

1| Place the drying and reaction vials inside the NanoTek® concentrator module and connect the N_2 line, and the two lines required for azeotropic drying (^{18}F-elution and MeCN).

2| **Trap and dry [^{18}F]fluoride using a NanoTek® automated microfluidic device syringe pump (steps 2-6).** Trap the [^{18}F]fluoride delivered in an [^{18}O]H_2O solution on an Sep-Pak® QMA cartridge by taking up the solution of [^{18}F]fluoride in [^{18}O]H_2O and pass it through the cartridge (7 x 1 mL, 2 mL/min).

3| Rinse the [^{18}O]H_2O vial with MeCN (2 x 400 µL), and pass it through the cartridge (2 mL/min).

4| Elute [^{18}F]fluoride off the cartridge with an elution solution of $K_{222}/K_2C_2O_4/K_2CO_3$ (900 µL, 6 x 150 µL portions) into a 5 mL V-Vial®.

5| Rinse the cartridge with MeCN (200 µL). Dry the [^{18}F]fluoride azeotropically at 105°C with MeCN (1 mL, 5 x 200 µL portions) under a flow of N_2.

6| Charge a 1 mL glass vial with the BPin precursor **10** (13.4 mg, 0.02 mmol) and $[Cu(OTf)_2(impy)_4]$ (25 mg, 0.03 mmol), and add DMI (300 µL).

▲**CRITICAL STEP** The solution must be homogenous and dark-green coloured to ensure optimal yields, and should be freshly prepared prior to transfer to the reaction vessel.

7| Transfer with a 1 mL syringe the solution from **(iii)** to the the 5 mL V-Vial® containing dry [^{18}F]F/K_{222} inside the hot cell.

8| Add 20 mL of air to the reaction vial using a 20 mL syringe. Air is not bubbled inside the reaction mixture.

▲**CRITICAL STEP** The addition of air is beneficial in order to achieve a high radiochemical yield.[23,36,37]

9| Remove the vent needle, place the vial inside the NanoTek® concentrator module and stir for 20 mins at 120 °C. **?TROUBLESHOOTING**

10| Place the reaction vial in a vial holder inside the hotcell, install a vent needle, add TFA (370 µl) *via* a 1 mL syringe, remove the vent needle, place it inside the NanoTek® concentrator module, and stir for 20 mins at 125 °C.

11| Remove the reaction vial from the NanoTek® concentrator module and cool for 1 min, install a vent needle, and connect a 10 mL syringe with a STERICAN cannula containing H_2O (8 mL).

▲**CRITICAL STEP** Do not connect the cannula too tightly to the syringe, as its removal will be difficult if it is too tight.

12| Dilute the crude mixture with H_2O (2 mL), shake the orange-brown solution, and take up the entire crude mixture into the 10 mL syringe.

13| Remove the cannula from the 10 mL syringe, connect to an HLB plus cartridge, and elute the crude mixture manually.

▲**CRITICAL STEP** The elution should be performed at a rate of 2 mL/min with 10 seconds intervals after every 2 mL to increase trapping efficiency.

14| Connect a 2 mL syringe with a STERICAN cannula containing 2 mL of 10% MeCN in H_2O to the reaction vial, and add the solution. Rinse the reaction vial, shake the vial, take up the solution, remove the cannula, connect to the HLB cartridge then slowly elute.

▲**CRITICAL STEP** If MeCN is used at concentrations higher than 10%, [^{18}F]olaparib will not be trapped on the cartridge.

15| Connect the N_2 line to the HLB cartridge and blow it dry for 5 seconds.

16| Connect the HLB cartridge to a new 5 mL V-Vial®, elute the crude product with MeCN (2 mL), and dry the cartridge using N_2 for 5 seconds.

17| Place the V-Vial® inside the NanoTek® concentrator module, connect the N_2 line and three vent needles, and concentrate the solution at 110 °C to a volume of no more than 50 µL.

▲**CRITICAL STEP** A residual volume of more than 50 µL MeCN in 1.4 mL of HPLC buffer results in poor separation of [^{18}F]olaparib from the side products (two side

products were identified unambiguously as the products resulting from proto and hydroxydeboronation) during radio-HPLC purification. This may also affect retention time.

18| Using the NanoTek® syringe pump, dilute the crude solution of [^{18}F]olaparib with 1 mL buffer (28% MeCN, 72% NH_4HCO_2 (28.5 mM) in H_2O), and inject 1 mL of the solution onto the HPLC 2 mL loading loop with a flow rate of 1 mL/min.

19| Rinse the V-Vial® with 0.4 mL buffer (28% MeCN, 72% NH_4HCO_2 (28.5 mM) in H_2O), take up 1 mL, and transfer the solution to the HPLC loop with a flow rate of 1 mL/min.

20| Perfrom semi-preparative radio-HPLC purification using an isocratic flow (4 mL/min) with buffer (28% MeCN, 72% NH_4HCO_2 (28.5 mM) in H_2O) as described in the Equipment Setup.

21| Collect the product peak (t_R ~ 17 mins) into a vial containing 15 mL of H_2O. **?TROUBLESHOOTING**

22| Shake the vial containing [^{18}F]olaparib, transfer the solution to an HLB cartridge using the NanoTek syringe® pump (3 mL/min), and blow it dry with N_2 for 5 seconds. This can be achieved by connecting a N_2 line or by flushing air with a syringe.

23| Connect the HLB cartridge to the delivery vial, elute off the product with EtOH (2 mL), and blow dry the cartridge with N_2 for 5 seconds.

24| Evaporate the EtOH with a N_2 flow at 105 °C to ensure complete dryness.

25| Reformulate with buffer (PBS, 10% DMSO) to a volume suitable for *in vitro*/*in vivo* studies.

Quality control of [^{18}F]olaparib

26| Take a sample of the reformulated [^{18}F]olaparib from the final vial (approx. 5-20 MBq) and mix with DMSO (10 µL) prior to injection on the analytical radio-HPLC.

27| Collect the [^{18}F]olaparib peak, and measure the radioactivity to calculate molar activity.

28| Using the integrated UV peak area and collected fraction from 27, calculate the molar activity from a calibration curve obtained by increasing [^{19}F]olaparib concentrations (see Supplementary Method 3).[41]

Timing for Procedure 1

Steps 1-5, trapping, elution and azeotropic drying of [^{18}F]fluoride: 20 minutes

Steps 6-9, radiolabelling: 25 minutes

Step 10, deprotection: 25 minutes

Steps 11-16, end of the reaction, quenching, and pre-purification with HLB cartridge: 15 minutes

Steps 17-22, radio-HPLC purification and trapping of [^{18}F]olaparib: 30 minutes

Step 23-25, reformulation: 15 minutes

Procedure 2: Automated radiolabelling of [^{18}F]olaparib • Total synthesis time 120 mins

An automated radiosynthesis was developed on an Eckert & Ziegler Modular-Lab synthetic platform. This protocol enables scaling up the ^{18}F-labelling reaction in order to produce sufficient amount of radiotracer for clinical application, and to reduce radiation exposure to the operator. Figure 3 shows the key elements of the automated platform required for producing [^{18}F]olaparib; Supplementary Method 1 includes a more detailed description of this setup to an Eckert & Ziegler Modular-Lab synthetic platform.

Equipment setup

Prepare the platform used for automated synthesis. In our lab, we use the Eckert & Ziegler Modular-Lab synthetic platform and perform the following steps:

1. Clean all the lines prior to the radiosynthesis by flushing approximately 1 mL of acetone through the lines with a syringe and drying thoroughly with N_2 gas; the [^{18}F]olaparib delivery line is cleaned with EtOH (not acetone).
2. QMA Sep-Pak® cartridge preconditioning: slowly pass H_2O (2 mL) using a 2 mL syringe through the cartridge to ensure a dropwise elution. Next, connect the reactor vial to the outlet of the second valve.
3. Connect the QMA for [^{18}F] elution solution to the inlet of the first valve.
4. Connect the reactor to the N_2 supply, the vacuum pump, a valve open to air, 1.5 mL of MeCN, 500 µL of TFA (in a 2 mL autosampler vial), 900 µL of H_2O for injection, 1 mL of a 9:1 solution of H_2O for injection, and MeCN (in a 1 mL V-shaped vial). N_2 and

vacuum lines are made of polyurethane tubing; lines carrying liquids are made of fluorinated ethylene propylene tubing.

5. Dissolve 13.4 mg (0.02 mmol) of precursor in 300 µL of DMI in a 2 mL autosampler vial, and connect to the reactor.
6. Dissolve 25 mg (0.03 mmol) of $[Cu(OTf)_2(impy)_4]$ in 300 µL of DMI in a 2 mL autosampler vial, and connect to the reactor.

▲**CRITICAL STEP** 30 to 60 seconds of vortex mixing is necessary to thoroughly dissolve $[Cu(OTf)_2(impy)_4]$ in DMI. Stability of the complex and the precursor in solution is unknown, so preparation and connection of these vials immediately prior to the delivery of [^{18}F]fluoride is recommended.

7. Pierce the reactor vial septum with a long needle reaching the bottom. Fill a 5 mL V-shaped vial with 1 mL of AMF 25 mM buffer. Prepare a fitted reservoir. Connect the inlet of the reservoir to the long needle, and the outlet to the V-shaped vial.
8. Pierce this vial with a long needle reaching the bottom; connect this needle to a 5 mL injection loop on the radio-HPLC system.
9. Connect the semi-preparative HPLC column outlet to a valve so that it can be connected to both a waste bottle and a collection bottle (a crimped 100 mL Wheaton® glass bottle). Fill the collection bottle with 80 mL of H_2O.
10. Pierce the collection bottle septum with a long needle in order to reach the bottom and with a short needle connected to the N_2 supply.
11. C18 light cartridge preconditioning: slowly pass EtOH (10 mL) through the cartridge followed by H_2O (10 mL) using 10 mL syringes to ensure a dropwise elution.

Connect the cartridge with two valves, with the first one leading to the collection bottle-cartridge-C18 light waste (first pathway), and the second one leading to the EtOH-cartridge-tracer vial (second pathway).

12. Connect the long needle piercing the collection bottle to the inlet of the first pathway. Connect a vial containing 1 mL of EtOH and a vial containing 1 mL of H_2O to the inlet, and a vial containing 9 mL of saline to the outlet of the second pathway.
13. Radio-HPLC solvent gradient method for quality control analysis

    0 min- 5 mins: isocratic 18% MeCN in AMF 25 mM pH 9

    5 mins-15 mins: gradient from 18% to 50% MeCN in AMF 25 mM pH 9

    15 mins to 20 mins: isocratic 50% MeCN in AMF 25 mM pH 9

    20 mins to 25 mins: gradient from 50% to 18% MeCN in AMF 25 mM pH 9

Trapping, elution and azeotropic drying of [^{18}F]fluoride

! CAUTION All procedures involving the use of larger amounts of ^{18}F should be performed using the appropriate level of shielding, and in accordance with local radiation protection procedures. Typically, this involves the use of a ventilated lead-shielded cabinet or hot-cell.

1. Trap [^{18}F]fluoride on the QMA carbonate cartridge and elute with the $K_{222}/K_2C_2O_4/K_2CO_3$ solution by applying vacuum to the reactor vial.
2. Close all pathways to the reactor, turn off the vacuum pump, and heat the reactor to 120˚C.

3. Start the azeotropic drying by turning on the N_2 flow and the vacuum pump to facilitate the evaporation of the MeCN-H_2O mixture. Monitor the evaporation through the Peltier reactor camera.
4. When the volume in the reactor has approximately halved, turn off the N_2 flow, and close the N_2 line connected to the reactor.
5. Add 500 µL of dry MeCN.
6. Close the dry MeCN line, turn on the N_2 flow to the reactor. Continue the azeotropic drying until the reactor is dry. Repeat with two additional aliquots of 500 µL of dry MeCN. **?TROUBLESHOOTING**
7. Turn off the N_2 flow, and close the N_2 line connected to the reactor.

Radiolabelling and deprotection

8. Add air to the reactor for 30 seconds by subjecting the reactor to vacuum followed by letting air into the reactor.

▲**CRITICAL STEP** Radiolabelling requires air. If no air is introduced in the reaction vial, the radiochemical yield the yield will be low.[23,36,37]

9. Add both the precursor and copper complex solutions to the reaction vessel.
10. Close the vacuum line and turn off the pump to start the radiolabelling step (20 mins). Every 5 min, add more air in the reaction for 10 seconds.
11. Add TFA *via* vacuum pump, then close all connections to the reactor.
12. Increase the temperature to 125 ˚C then start the deprotection step (20 mins).

13. In the meantime, start equilibrating the column with 24% MeCN in AMF 25 mM (1 mL/min). The column will stay under these conditions until the flow is increased to 4 mL/min for radio-HPLC purification.
14. At the end of the deprotection, add H_2O to quench the reaction, and cool the reactor to 25 ˚C.

Purification

15. Increase the flow of the HPLC pump to 4 mL/min.
16. Transfer the reaction mixture to 5 mL V-shaped vial, through the fritted reservoir, to remove any precipitate, by pressurising the reactor vial with N_2.

▲**CRITICAL STEP** A bright orange-red colour is expected. **?TROUBLESHOOTING**

17. Turn off the N_2 flow, and close off the reactor.
18. Rinse the reactor with H_2O:MeCN (9:1, 2 mL) to recover residual material. Turn off the pump and close off the reactor.
19. Transfer the solution to the 5 mL V-shaped vial by pressurising the reactor vial with N_2.
20. Close off the reactor and turn off the N_2 flow.
21. Inject the reaction mixture into the radio-HPLC. Follow closely both UV and radio-traces when collecting [^{18}F]olaparib.
22. [^{18}F]Olaparib elutes at 22 mins (a typical radiochromatogram is shown in Figure 3). Collect the product in the collection bottle. Close the cut peak valve after the product has eluted from the column. **?TROUBLESHOOTING**

Reformulation

23. Transfer the diluted product to the C18 light cartridge by pressurising the bottle with N_2. Turn off the N_2 flow. This step traps [^{18}F]olaparib on the cartridge. **?TROUBLESHOOTING**
24. Wash the cartridge with H_2O, by pressurising the H_2O vial with N_2. Turn off the N_2 flow.
25. Elute [^{18}F]olaparib off the cartridge with EtOH, into a 10 mL vial containing 9 mL of saline. Turn off the N_2 flow. **?TROUBLESHOOTING**

Quality control of [^{18}F]olaparib

26. Measure the activity of the 10 mL vial using a dose calibrator. Calculate the yield as a percentage relative to the starting [^{18}F]fluoride activity delivered to the hot cell.
27. Integrate the UV peak corresponding to the product. Calculate the corresponding concentration using the calibration curve obtained by injecting 20 µL of solutions of increasing concentrations of [^{19}F]olaparib. Use the calculated concentration to determine A_m (see details in Supplementary Method 3). **?TROUBLESHOOTING**

Figure 4 shows a typical analytical chromatogram of [^{18}F]olaparib.

Procedure 2: Radiosynthesis timing

Steps 1-7, trapping, elution and azeotropic drying of [^{18}F]fluoride: 20 minutes

Steps 8-10, radiolabelling: 25 minutes

Steps 11-13, deprotection: 25 minutes

Steps 14-20, end of the reaction and quenching: 10 minutes

Steps 21-24, radio-HPLC purification and trapping of [^{18}F]olaparib: 25 minutes

Step 25, reformulation: 10 minutes

Steps 26-27, delivery: 5 minutes

Troubleshooting table

Troubleshooting advice can be found in Table 1.

Table 1 Troubleshooting

Step	Problem	Possible Reason	Solution
1A (vi)	Insufficient or no stirring	Stirring bar stuck to the glass wall	Shake the vial until stirring is possible, or use a long needle to move the stirring bar?
1A (xviii)	Different retention time for radio-HPLC from the one described	More than 50 µL MeCN inside the V-Vial® Residual MeCN in the lines to the HPLC loop Column not conditioned properly	Dry the lines by flushing air through the lines leading to the radio-HPLC loop
	Mixture of [^{18}F]olaparib and protodeborylated side-product are present in the purified	Wrong HPLC method and/or column used	Use the appropriate method and column type as

	sample. Low HLB elution efficiency radio-HPLC	 Not enough H_2O for reformulation in the collection vial	described; 20 mins required for efficient conditioning of the column Ensure that enough H_2O is present in the collected peak vial to avoid a mixture which is over 10% MeCN in buffer
6	Loss of radioactivity during azeotropic drying	Excessive N_2 bubbling Short needles too close to the surface of the reaction mixture Holes in the reactor vial	Keep the N_2 flow at the recommended settings Keep short needles as high as possible Do not pierce the

		septum	reactor vial septum more than necessary to avoid tearing; do not reuse septa
16	Precipitation before radio-HPLC injection	Filtration not efficient	Ensure appropriate filtration is obtained through frit; reaction mixture should be clear with no precipitate
		Not enough water to dilute the crude reaction mixture	1 mL of H_2O is needed for dilution in the 5 mL V-shaped vial before radio-HPLC injection
22	Different retention time of product on the semi-preparative radio-HPLC	Incorrect flow	Keep the flow at 4 mL/min

		Incorrect buffer	Use AMF 25 mM
		Incorrect MeCN:buffer ratio	Use 24% MeCN in buffer
		Insufficient conditioning of the column	Follow steps 13 and 15
		Incorrect column	Use column listed in “Materials”
	Mixture of [^{18}F]olaparib and protodeborylated side-product	Wrong HPLC method and/or column used	Use column listed in “Materials” and appropriate method as described
23	C18 light cartridge disconnected from lines	Excessive pressure	Keep N_2 flow low to ensure dropwise elution
	Radiotracer not trapped on C18 light cartridge	Percentage of MeCN in the collection bottle above 10%	Make sure that the collection

			bottle is filled with a large excess of H_2O (80 mL)
25	Loss of radioactivity from vent needle	Incorrect position of vent needle	Keep vent needles as high as possible
	Product not eluted from C18 light	Incorrect solvent or volume used EtOH passed too fast through C18 light cartridge	Use 1 mL of EtOH Use a low N_2 flow setting
27	Low yield	Air was not introduced in the reaction vial before and/or during the labelling step Incomplete injection onto semi-preparative radio-HPLC	Follow steps 8 and 10 Follow step 22

Anticipated results

Preparation of Olaparib precursor 10

The olaparib-BPin precursor **10** is obtained applying an eleven steps synthesis with an overall yield of 5% (see Supplementary information).[41] This compound is purified *via* preparative HPLC and is obtained with a chemical purity >99 %.[41]

Manual preparation of [^{18}F]olaparib

The radiochemical yield measured before radio-HPLC purification should be in the range of 29-47%. The activity yield of [^{18}F]olaparib isolated by semi-preparative radio-HPLC after reformulation should be 12-22%. In a typical experiment, 735 MBq [^{18}F]olaparib is expected from 3.48 GBq [^{18}F]fluoride. Molar activity should be in the range of 0.8-34.6 GBq/µmol 60 mins after E.O.S.

Automated preparation of [^{18}F]olaparib

The activity yields of [^{18}F]olaparib isolated by semi-preparative radio-HPLC after reformulation should be 1-11%. In a typical experiment, 1200 MBq [^{18}F]olaparib is expected from 11 GBq [^{18}F]fluoride. Molar activity should be in the range of 78-319 GBq/µmol 50 mins after E.O.S.

Quality control results for [^{18}F]olaparib

The final solution of [^{18}F]olaparib should be clear, colorless, and free of particles. The retention time of [^{18}F]olaparib should be ~13.5 mins on an analytical radio-HPLC system (radioactivity detector with Synergi^{TM} 4 µm Hydro-RP 80Å LC column 250 x 10 mm

column, and elution conditions as 25% MeCN/75% H_2O using a flow rate of 1 mL/min). The radiochemical purity should be > 95%.

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Competing interests

The authors declare no competing interests.

Authors' contributions

B. C. and V. G. conceived and designed this research. F. G., P. I., T. C. W., A. P., D. M., J. B. I. S., N. J. T., S. V, S. P. and R. H. performed the experimental work. All authors analysed the data and wrote the manuscript.

Additional information

Supplementary information: radio-HPLC chromatograms of [^{18}F]olaparib and co-injection with non-radioactive reference [^{19}F]olaparib, and detailed automated radiosynthesis.

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