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Supporting Information

Azeotropic drying free [^{18}F]FDG synthesis and its application to a lab-on-chip platform

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1. GENERAL

All reagents were purchased from commercial sources and were used without further purification. Solvents of at least p.a. quality were used. Kryptofix®2.2.2 was obtained from Merck, Mannose triflate from ABX. Sep-Pak Accell Plus QMA carbonate, Sep-Pak tC18, Oasis HLB and Sep-Pak Alumina A cartridges were obtained from Waters. Analytical HPLC was done on an Agilent 1200 system using a Luna NH_2 (5 µm, 250 × 4.6 mm, Phenomenex, Germany) column. Radio-TLC was done on a mini-GITA system from Raytest. Water content measurements were performed on a Karl-Fischer pocket titrator (ECH Elektrochemie Halle GmbH, Germany).

2. EXPERIMENTAL PROCEDURES

2.1. Preparation of [K⊂2.2.2]OH, [K⊂2.2.2]O*t*Bu, [K⊂2.2.2]HCO_3 and [K⊂2.2.2]H_2PO_4

Kryptofix®2.2.2 (141 mg, 375 µmol) was dissolved in an aqueous solution of the corresponding potassium salt (1M, 250 µL). The mixture was lyophilized to dryness overnight, thightly sealed and stored in the freezer. Immediately before use the complex was dissolved in 1.5 mL anhydrous solvent (*t*BuOH, MeCN, *t*BuOH + 1% H_2O or MeCN + 1% H_2O) to give a 250 mM solution of Kryptofix®2.2.2 and a 170 mM solution of the potassium salt.

2.2. Preparation of [K⊂2.2.2]C_2O_4 and [K⊂2.2.2]HPO_4

Kryptofix®2.2.2 (282 mg, 750 µmol) was dissolved in an aqueous solution of the corresponding potassium salt (1M, 250 µL). The mixture was lyophilized to dryness overnight, thightly sealed and stored in the freezer. Immediately before use the complex was dissolved in 1.5 mL anhydrous solvent (MeCN, *t*BuOH + 1% H_2O or MeCN + 1% H_2O) to give a 500 mM solution of Kryptofix®2.2.2 and a 170 mM solution of the potassium salt.

2.3. Synthesis of [^{18}F]FTAG

No carrier added [^{18}F]fluoride was produced via ^{18}O(p, n)^{18}F reaction by proton irradiation of an ^{18}O-enriched water target of a PETtrace cyclotron. The [^{18}F]fluoride was trapped on an ion exchange cartridge (QMA carbonate, 46 mg) which was previously preconditioned with water. The QMA was dried by passing through 20 mL of air, followed by rinsing the cartridge with anhydrous MeCN (5 mL) and flushing it again with air (20 mL). The [^{18}F]fluoride was eluted into an Eppendorf vial using the corresponding cryptate solution (500 µL). Mannose triflate (20 mg) was dissolved in MeCN (25 µL) and added to the [^{18}F]fluoride solution. The vial was placed in a heating block and heated for 10 minutes at 90 °C with shaking (400 rpm).

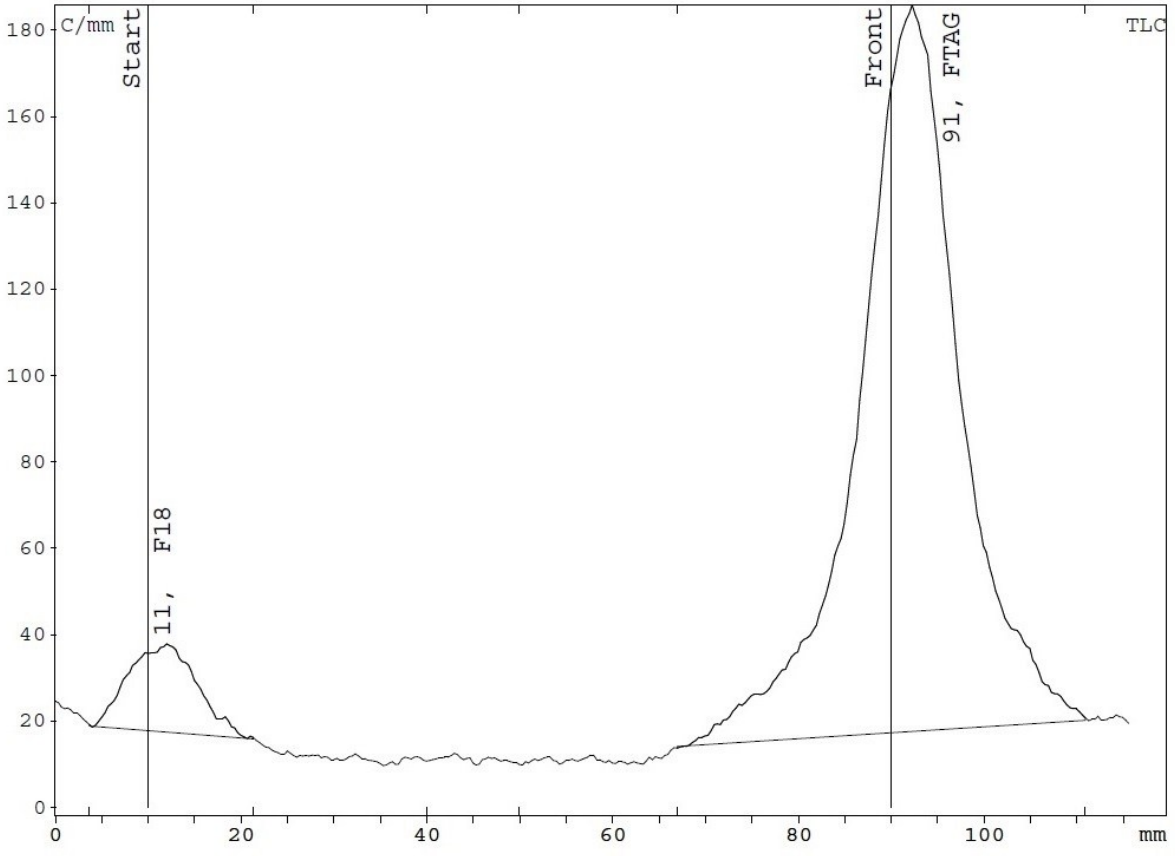
2.4. Synthesis of [^{18}F]FDG

No carrier added [^{18}F]fluoride was produced via ^{18}O(p, n)^{18}F reaction by proton irradiation of an ^{18}O-enriched water target of a PETtrace cyclotron. The [^{18}F]fluoride was trapped on an ion exchange cartridge (QMA carbonate, 10 mg) which was previously preconditioned with water. The QMA was dried by passing through 5 mL of air, followed by rinsing the cartridge with anhydrous MeCN (1 mL) and flushing it again with air (5 mL). The [^{18}F]fluoride was eluted into an Eppendorf vial using [K⊂2.2.2]H_2PO_4 in *t*BuOH + 1% H_2O (300 µL). Mannose triflate (20 mg) was dissolved in MeCN (25 µL) and added to the [^{18}F]fluoride solution. The vial was placed in a heating block and heated for 10 minutes at 90 °C with shaking (400 rpm). The mixture was diluted with H_2O (5 mL) and passed through a Sep-Pak tC18 cartridge (900 mg). The cartridge was washed with H_2O (5 mL) and dried with air. Subsequently, the cartridge was wetted with NaOH (2M, 400 µL) to allow the hydrolysis to proceed on solid support. After 3 minutes at ambient temperature, the product was eluted with H_2O (800 µL) followed by neutralization with H_3PO_4 (2.29M, 200 µL). The mixture was passed through an Oasis HLB (150 mg) and a Sep-Pak Alumina A cartridge which were finally washed with H_2O (1 mL) to yield the final [^{18}F]FDG solution.

3. TLC AND HPLC ANALYSIS

3.1. TLC analysis of [^{18}F]FTAG

The representative radio-TLC of the crude [^{18}F]FTAG (No 9, Table 1) developed in MeCN / H_2O 95:5 shows a radiochemical conversion of 92%.



TLC

Substance	R/F	Area Counts	%Area %
F18	0,02	178,357	7,8
FTAG	1,01	2120,714	92,2
Sum in ROI		2299,071	
Area RF		923,000	
BKG1		11,5096	
Remainder RF		-1376,07	-149,0

Fig. S1: Representative radio-TLC of the crude [^{18}F]FTAG.

3.2. HPLC analysis of [^{18}F]FDG

A Phenomenex Luna NH_2 column was used (250 × 4.6 mm, 5 µm) with isocratic elution with MeCN / H_2O 70:30 at a flow rate of 1 mL/min. [^{18}F]FDG is eluted at a retention time of 4.1 min. with a purity > 99%.

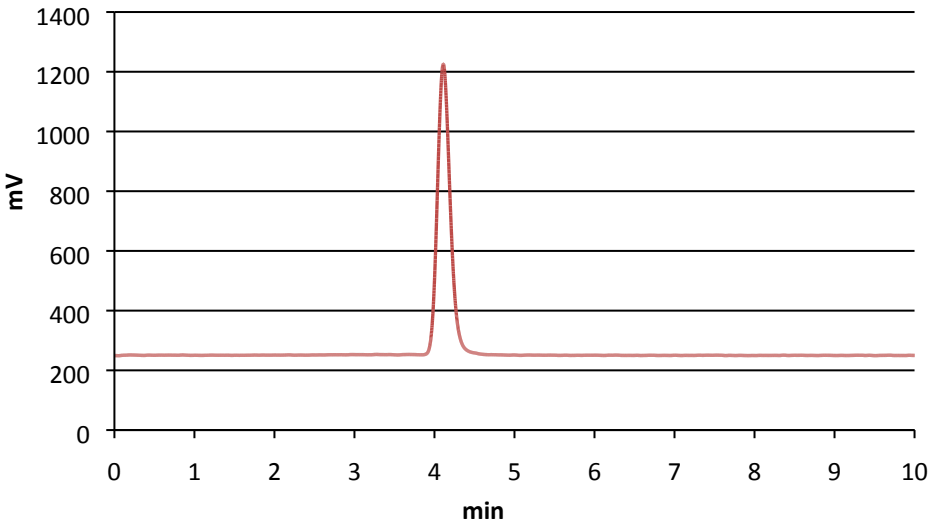


Fig. S2: Representative HPLC trace of the purified [^{18}F]FDG.

4. ON-CHIP EXPERIMENTAL

In the first step, a chip layout for the desired process was established utilizing CAD software (SolidWorks, Dassault Systèmes, SolidWorks Corp.). Subsequently, COC 6017-S04 (TOPAS® Advanced Polymers GmbH, Germany) was utilized for injection moulding of rectangular blanks (Rodinger Kunststoff-Technik GmbH, Germany) with outer dimensions of 100mm × 100mm × 2mm. One microfluidic chip (Fig. S3) consists of three separate layers (outer dimensions each 95mm × 60mm × 2mm) and one COC 6015 foil (TOPAS® 100 Advanced Polymers GmbH, Germany, thickness 100µm). All microfluidic structures on each of the layers are created utilizing a four axis computerized numerical controlled (CNC) milling machine (MDX-540 SA, Roland DGA Corp., USA). After milling, all layers including the foil were cleaned and assembled together and joined in a single thermal bonding step. No additional manufacturing processes are required.

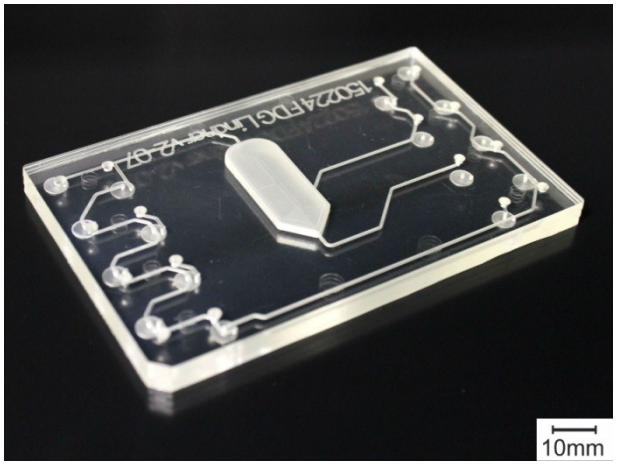


Fig. S3: Microfluidic chip utilized for fluid handling and radiolabeling of [^{18}F]FTAG

The chip is loaded into a control system identical to the one described in prior work (C. Rensch, S. Lindner, R. Salvamoser, S. Leidner, C. Bold, V. Samper, D. Taylor, M. Baller, S. Riese, P. Bartenstein, C. Wängler and B. Wängler, Lab Chip, **2014**, *14*, 2556). The miniaturized QMA cartridge (10mg) setup is schematically illustrated in figure S4 and was located external to the microfluidic chip device. However, as illustrated in prior art, the resin could be transferred on-chip (patent application WO/2014066748/A1).

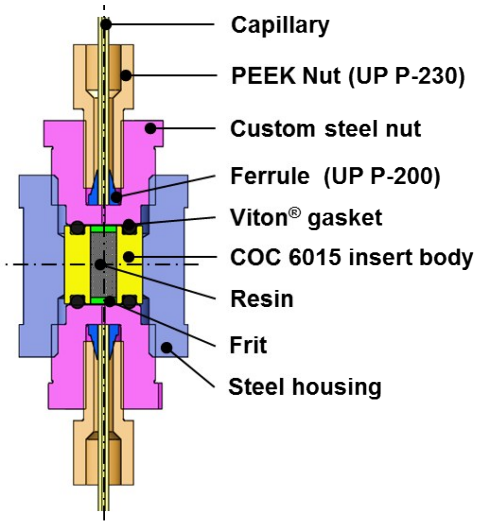


Fig. S4: Schematic of miniaturized QMA (10 mg) setup located external to the chip.

No carrier added [^{18}F]fluoride was produced via ^{18}O(p, n)^{18}F reaction by proton irradiation of an ^{18}O-enriched water target of a PETtrace cyclotron. The [^{18}F]fluoride (approx. 300 MBq) was transferred to a 2 mL starting vial which was connected to the microfluidic platform. The QMA cartridge (10 mg) was preconditioned with 5 mL Tracepur water utilizing a syringe pump of the platform. Subsequently, the [^{18}F]fluoride was transferred from the starting vial to the ion exchange cartridge by means of gas pressure. The QMA was dried by N_2 gas stream at 2 bars for 10 s, followed by rinsing the cartridge with anhydrous MeCN (5 mL, via syringe pump) and flushing it again with nitrogen at 2 bars for 10 s. The [^{18}F]fluoride was eluted into the on-chip reaction chamber using [K⊂2.2.2]H_2PO_4 in *t*BuOH + 1% H_2O (300 µL) which was transferred from a 2 mL low dead volume vial by means of gas pressure. Mannose triflate (20 mg) was dissolved in MeCN (25 µL) and added to the [^{18}F]fluoride solution by transferring it from a low dead volume vial to the on-chip reactor via gas pressure. The on-chip reactor was heated to 90 °C for 10 min to perform the labeling reaction. The on-chip reactor venting valve was open during reagent transfer to the reaction chamber and closed during the reaction to avoid evaporation and loss of activity. After labeling, the product was ejected to the [^{18}F]FTAG vial by means of gas pressure. One chip rinsing step was applied by flushing the reaction chamber with 1 mL of water (from a connected syringe pump) and ejecting the water into the [^{18}F]FTAG vial by means of gas pressure.