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SUPPORTING INFORMATION

Ion beam induced ^{18}F-radiofluorination: Straightforward Synthesis of Gaseous Radiotracers for the Assessment of Regional Lung Ventilation Using Positron Emission Tomography

V. Gómez-Vallejo,[a] A. Lekuona,[a] Z. Baz,[a] B. Szczupak,[a] U. Cossío[a] and J. Llop[a,†]

[a]Molecular Imaging Unit, CIC biomaGUNE, Paseo Miramón 182, 20009 San Sebastián, Guipúzcoa, Spain.

[†]E-mail: jllop@cicbiomagune.es

Experimental section

Production and analysis of $[^{18}F]CF_4$ and $[^{18}F]SF_6$

Two different strategies were used for the production of $[^{18}F]CF_4$. The first strategy (method A) was based on a single irradiation of a mixture CF_4/Ne with 18 MeV protons, using a commercial target for the production of $[^{18}F]F_2$, consisting of an aluminium target body with an internal volume around 50 mL and coupled to an IBA Cyclone 18/9 HC cyclotron. The target was first filled with CF_4 to a final pressure (P_1) of 2-4 bar. The target was then topped with Neon to a final pressure of 20 bar and submitted to proton irradiation using a proton intensity of 15 μAh and an integrated current (C_1) in the range 4-8 μAh. After finalising the irradiation, the target gas was transferred by depressurization to the radiochemistry laboratory and collected in a cryogenic trap cooled with liquid nitrogen. This strategy was also applied to the preparation of SF_6. In this case, P_1 was fixed to 4 bar and C_1 was fixed to 4 μAh.

The second strategy (method B) was based in a double shoot method using the same target. The process consisted of four steps: (i) The target was filled with $[^{18}O]O_2$ (P = 20 bar) and was irradiated with 18 MeV protons using a proton intensity of 15 μAh and an integrated current (C_2) in the range 1-4 μAh; (ii) after irradiation, the target gas was removed by cryogenic retrieval using liquid nitrogen; (iii) the target was filled with CF_4 to a final pressure of 4 bar, topped with Neon gas to a final pressure = 20 bar and irradiated with 18 MeV protons using a proton intensity of 15 μAh and an integrated current (C_3) in the range 1-4 μAh; (iv) after the second irradiation, the target gas was transferred by depressurization to the radiochemistry laboratory and collected in a cryogenic trap cooled with liquid nitrogen. Parallel experiments were performed by adding a soda-lime trap before the cryogenic trap. For the production of $[^{18}F]SF_6$, C_1 and C_2 were fixed to 4 μAh. In all cases, the amount of radioactivity collected in the cryogenic trap was measured in a dose calibrator (Capintec CRC®-25 PET, New Jersey, USA). Samples of the radioactive gas were withdrawn and were analyzed by gas chromatography (GC) coupled to mass spectrometry (MS). Analyses were performed using an Agilent 7820A network GC connected to an Agilent 5975c inert XL MSD with Triple axis detector and a radioactivity detector. A J&W PoraPlot column (length: 27.5 m, internal diameter: 0.32 mm) was used as stationary phase. The inlet conditions

were 150°C, 6.8 psi and a flow rate of 2.5 ml/min. Helium (99.9999%) was used as the carrier gas. The oven temperature was set to 36°C. The analyses were made in scan mode. Eventually, a radioactivity detector (Gabi, Raytest) was connected via a post-column split to identify the radioactive gases.

Imaging studies

Male rats (n = 2) weighing 350±14 g were used. Animal studies were approved by the ethical committee of CIC biomaGUNE and local authorities, and were conducted in accordance with EU Directives on animal ethics and welfare. Anaesthesia was first induced with 5% isoflurane in 100% O_2. The animals were then moved to the PET/CT scanner (eXplore Vista CT, GE Helthcare) and anaesthesia was maintained with isoflurane in 100% O_2 (1 L/min) administered through a face mask. Breathing frequency was adjusted to 50 ± 10 breaths/minute. The PET acquisition (list mode, 400-700 keV energetic window) was started, and 1 minute later the radioactive gas (74±8 MBq) was introduced in the O_2 main stream over 70 s using a syringe pump (Figure S2). After the PET scan, a whole-body CT acquisition (140 mA/40kV) was performed. The PET list-mode data were formatted into 19 frames (3x20s, 10x10s, 4x20s and 2x30s) and PET images were reconstructed using the 2D-OSEM algorithm (2 iterations, 16 subsets) into 175x175x61 arrays with a voxel size of 0.3875x0.3875x0.775 mm and were corrected for decay, scatter and random events. The CT images were reconstructed using a cone-beam Feldkamp algorithm into 262x262x688 arrays with a voxel size of 0.246 mm^3. Images were analysed using PMOD image analysis software. Volumes of interest (VOIs) were manually drawn in the lungs on the CT images, transferred to the PET images and the concentration of the radioactivity was obtained for each time frame. All frames were finally summed in order to obtain more accurate images of the radioactivity distribution within the lungs.

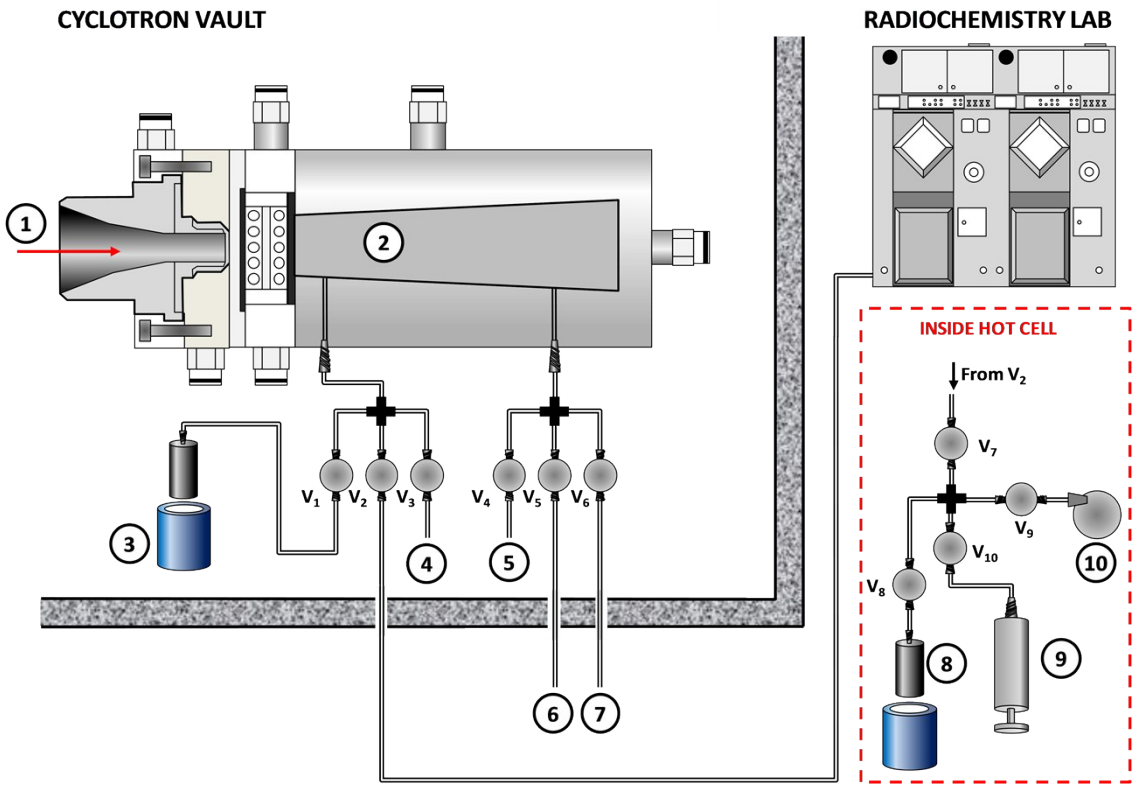

Figure S1. Configuration of the target and the recovery system used for the production of [^{18}F]CF_4 and [^{18}F]SF_6 using methods A and B; (1) proton beam; (2) target chamber; (3) stainless steel-high pressure container and liquid nitrogen cooling bath; (4) Exhaust; (5) [^{18}O]O_2 gas bottle; (6) Neon gas bottle; (7) CF_4/SF_6 gas bottle; (8) stainless steel-high pressure container and liquid nitrogen cooling bath; (9) gas-tight syringe; (10) vacuum pump. V_1-V_{10} are 2-way, normally-closed electro-valves.

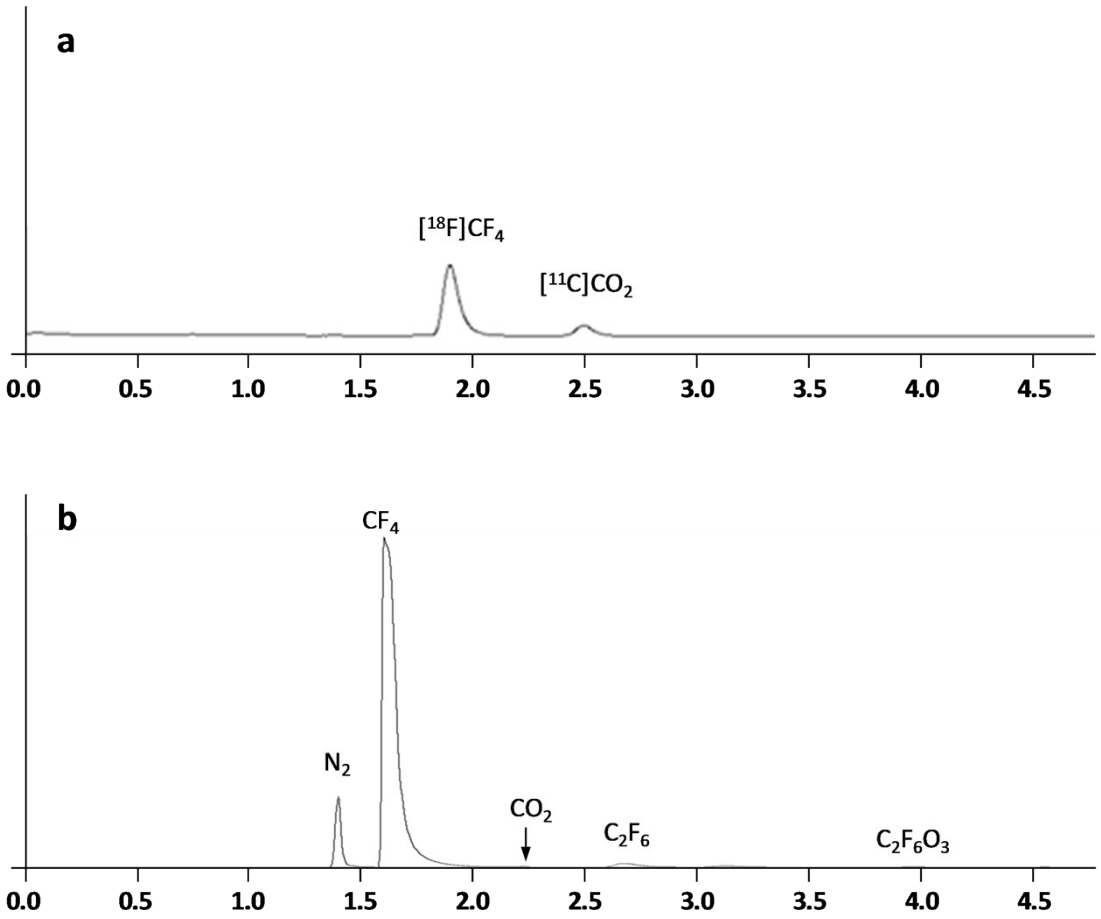

Figure S2. (a) Chromatogram (radioactivity detector) corresponding to the analysis of $[^{18}F]CF_4$ before passing through a soda lime trap using production method B; (b) chromatogram (MS detector) corresponding to the analysis of $[^{18}F]CF_4$.

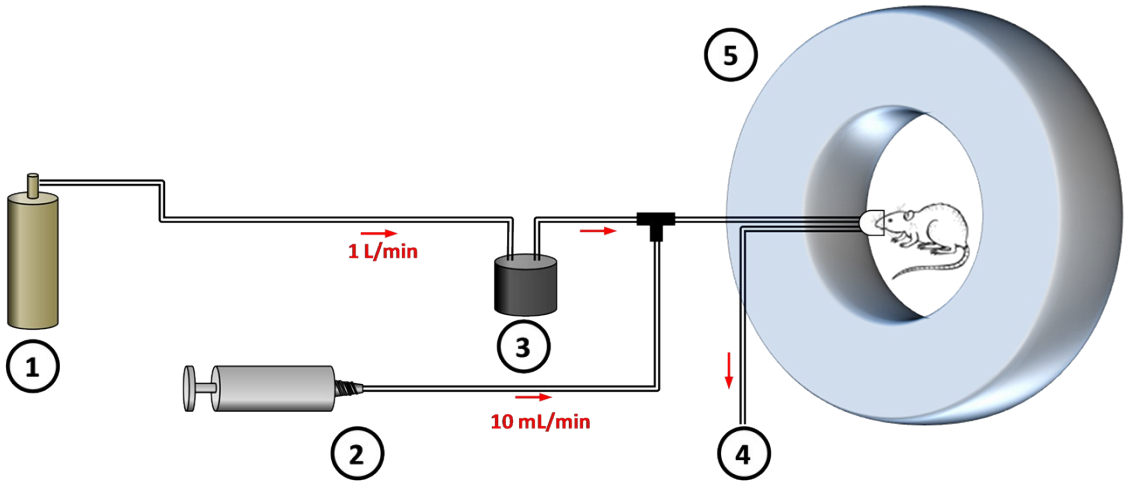

Figure S3. Configuration of the administration system; (1) O_2 gas; (2) gas-tight syringe mounted on a syringe driver; (3) isoflurane vaporizer; (4) exhaust; (5) PET-CT camera.