Supplementary Information

Radiochemistry on chip: towards dose-on-demand synthesis of PET radiopharmaceuticals

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Optimisation of FDG synthetic steps via commercial microfluidic apparatus (towards modules 2 and 4)

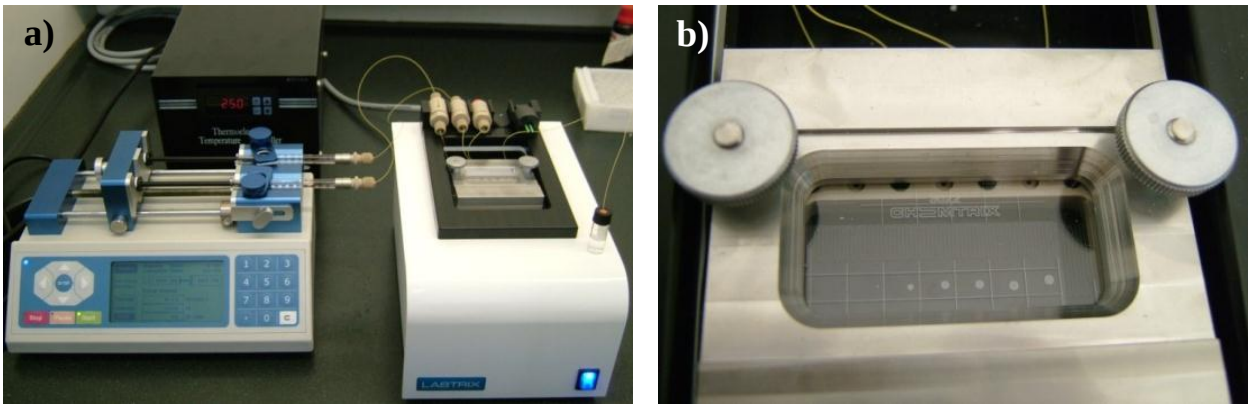

Fig. S1 (a) Labtrix Start (Chemtrix BV) system employed for the optimisation of the synthetic steps. (b) Glass microreactor supplied with the instrument, situated in a heating block with temperature controller.

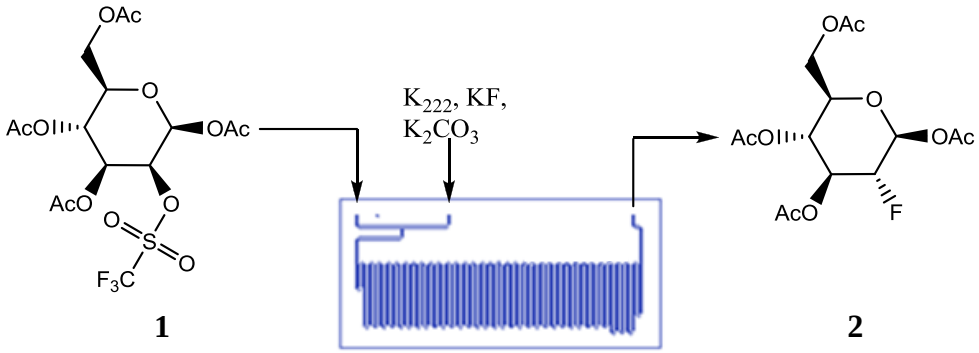

Fig. S2 Microreactor design (T-Mixer 3023, Chemtrix BV) used for optimisation of the radiolabelling (fluorination) reaction of **1** to **2**.

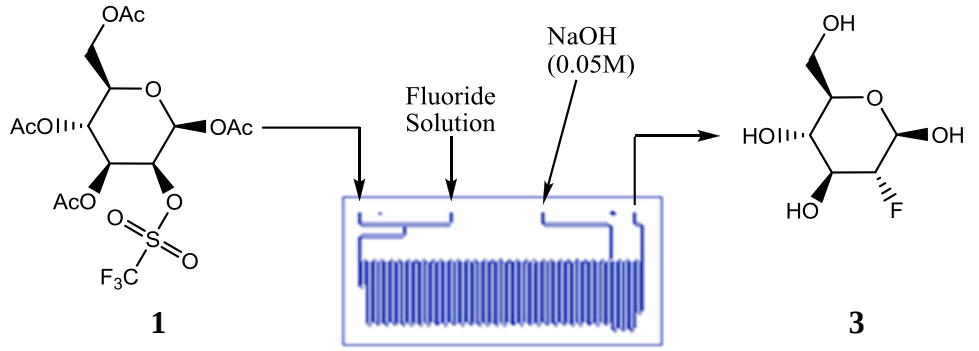

Fig. S3 Microreactor design (T-Mixer 3023, Chemtrix BV) employed for two-step optimisation of the radiolabelling of **1** to **2**, and the subsequent hydrolysis of **2** to **3**.

Solvent exchange device (module 3)

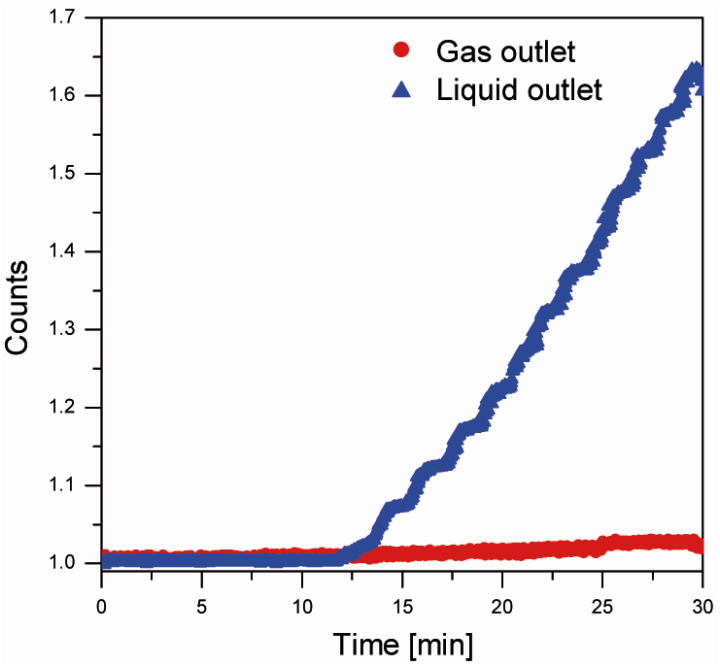

Fig. S4 Performance of the solvent exchange module. The graph shows radioactivity counts at the liquid outlet (blue) and the gas outlet (red) over the duration of an experiment. The results demonstrated that less than 1 % of the radioactivity exited via the gas outlet, with most remaining in the liquid during the solvent exchange process.

Radioactivity detector

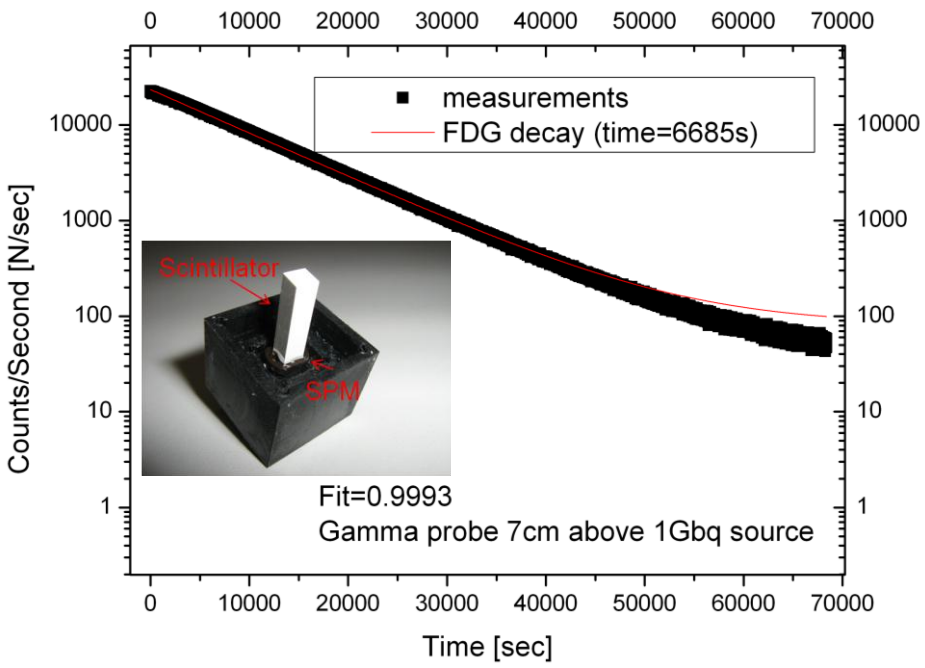

Fig. S5 Testing of the radioactivity detector developed for the ROC platform. The graph shows radioactivity counts from the radiation probe, a SensL SPM (Silicon PhotoMultiplier) coupled to an LSO (cerium-doped lutetium oxyorthosilicate) scintillator (shown in the photograph inset), which was located 7 cm above a 1 GBq ^{18}F-FDG source. The measurements show a similar result to the theoretically expected decay of ^{18}F-FDG.

High temperature processing

Three Minco heating foils and three Minco heaterstat temperature controllers (models CT198-1001, -1002 and -1005) were integrated into the fluidic platform of the ROC system for the precise temperature control of modules 2, 3 and 4 (Fig. S6). The maximum temperature was tunable up to 225 °C for the first microreactor device (module 2; radiolabelling reaction). The solvent exchange (module 3) and hydrolysis (module 4) processes were performed at lower temperatures using different Minco heaterstat temperature controllers (CT 198). The temperature was measured and controlled using known standard reference resistivity versus temperature diagrams, which were different for each temperature controller used. Additionally one point thermal couples were fixed on top of the heating foils for precision control.

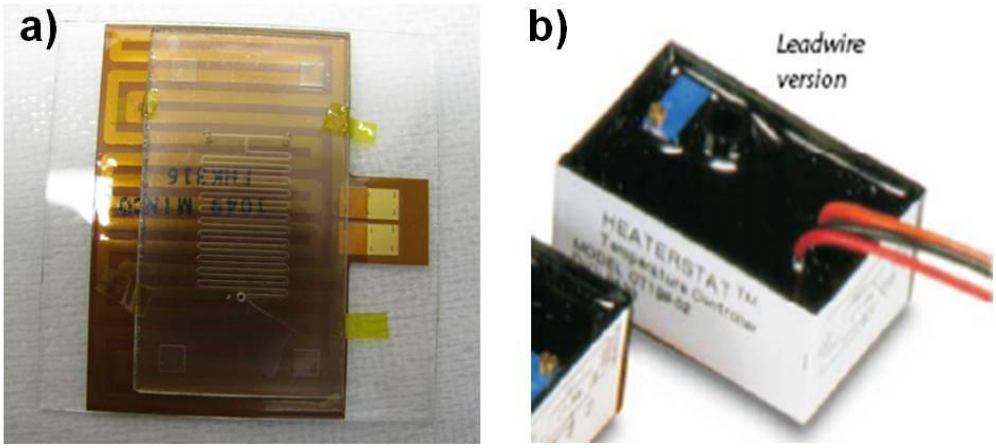

Fig. S6 (a) Photograph of a Minco heating foil, with a glass microfluidic device (module 4) placed on top of it, and (b) photograph of a Minco heaterstat temperature controller that was used for the temperature control of modules 2 - 4.

Chip alignment device

The use of an alignment device for each module (Fig. S7) simplified and expedited the precise positioning of the glass chips in relation to the contacting bridges. The device consisted of two units:

(i) The *main body*, fabricated from PEEK, which held a square glass substrate onto the fixed heater foil.

(ii) The *cover plate*, also in PEEK, held the glass chip and a hole template. The hole template was prepared from a thin plastic sheet and was used as an optical reference for alignment of the input and output ports of the glass chips.

The two units, equipped with a glass chip and hole template, were aligned using four guiding pins, which allowed the chip to be situated correctly on the heater foil. The glass chip was then inserted into the plug-in module of the fluidic platform and screwed down, after which the electrical and fluidic connections were completed using of the steel contacting bridge.

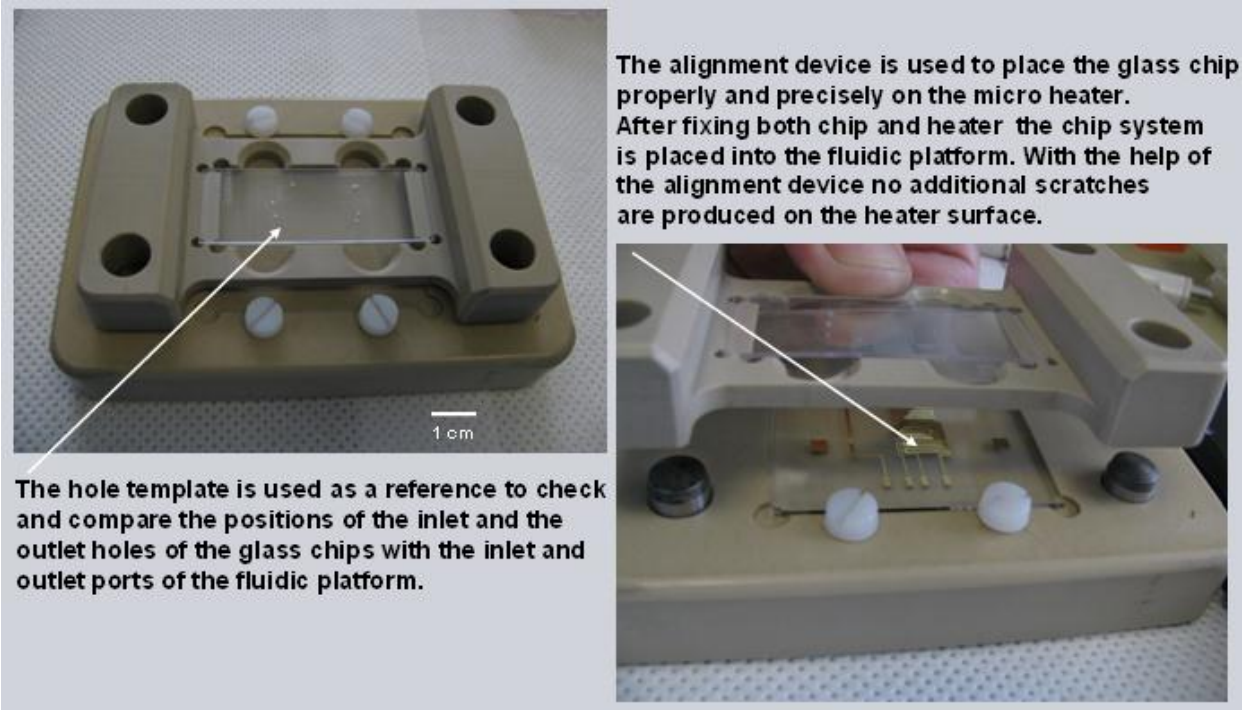

Fig. S7 Photographs of the alignment device employed to simplify and expedite the precise positioning of the glass chips in relation to the equipped contacting bridges.

Setup of the ROC platform and standard operations for ^{18}F-FDG synthesis

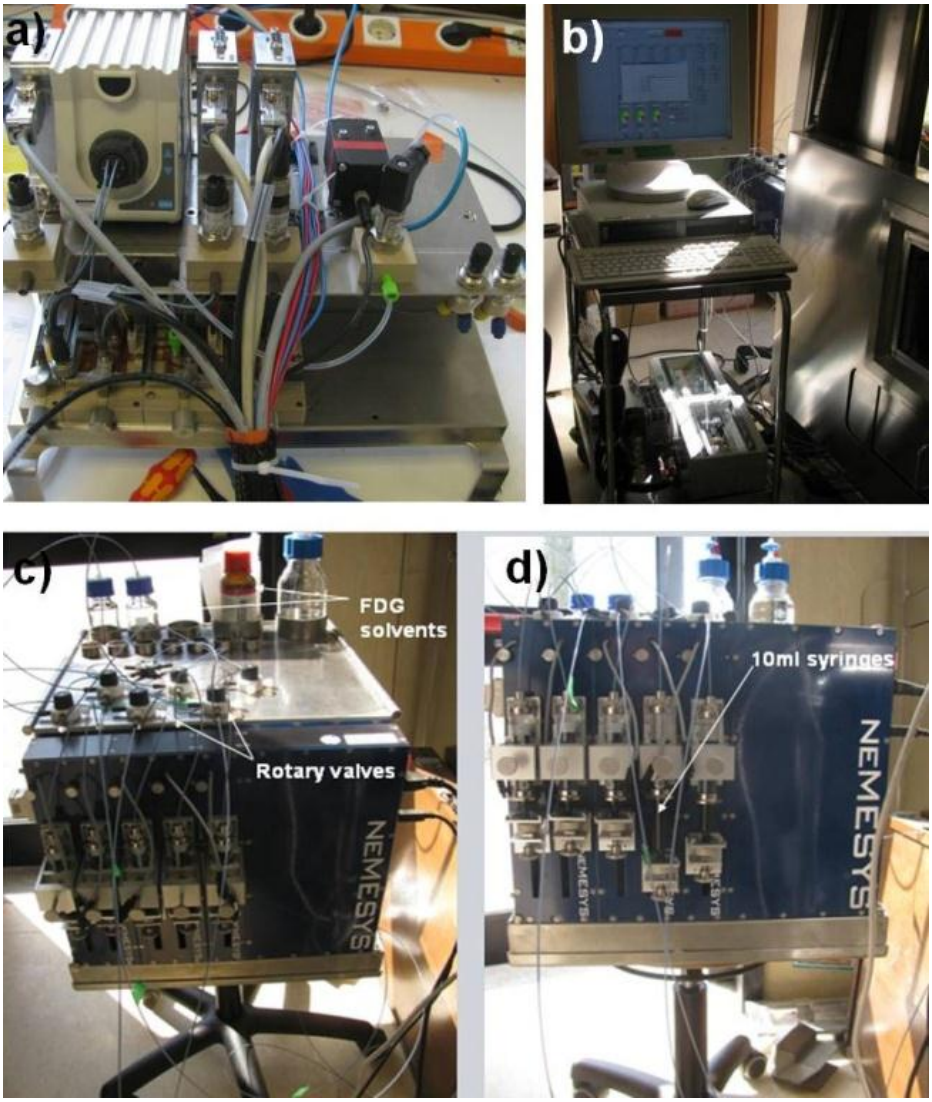

Fig. S8 Photographs of (a) the fluidic platform, showing the valves and pressure regulators on the upper level, and the microfluidic modules on the lower level, (b) the PC control system and voltage supply, and (c)-(d) the pumping platform, consisting of a Cetoni neMESYS syringe pump on the side of the platform, and solvent and reagent bottles on the top that were routed to the syringes via tubing and rotary valves.

The setup of the ROC platform consisted of three main parts: the *fluidic platform*, the *control system*, and the *pumping platform*. The fluidic platform (Fig. S8a) was the unit in which the synthesis of ^{18}F-FDG was performed, and was formed of two levels. The lower level featured the microfluidic modules and holders, while the upper level contained the Auto Valve Switch (2-position, 6-port valve) and pressure regulators. The control system (Fig. S8b) was formed of a computer with a LabView program for controlling the processes occurring on the ROC platform, as

well as a voltage supply for enabled control of the Minco foil heaters and monitoring of the pressures within each module. The pumping platform (Fig. S8c-d) was composed of a frame, onto the side of which was mounted a Cetoni neMESYS syringe pump with five syringes. The pump was positioned vertically in order to reduce the possibility of introducing bubbles into the ROC platform. The top of the frame held bottles of solvents and reagents, which were routed to the syringes via tubing and rotary valves, with the valves allowing the syringes to be filled from the bottles and the liquid then dispensed into the microfluidic modules. Since the radioactive material was only used within the fluidic platform, this was the only component that was situated in a hot cell, with the pumping platform and control system located outside the hot cell, thereby saving a great deal of space.

A schematic of the components of the ROC platform is shown in Fig. S9, which shows the interconnection of the pumps, tubing, valves, and microfluidic devices. The neMESYS system comprised five individually controlled syringe pumps, which were filled from the reagent and solvent bottles on top of the pumping platform, a process that could be performed either simultaneously or in series, and which were charged with the following:

Pump 1) Kryptofix 2.2.2/potassium carbonate in acetonitrile ($K_{222}/K_2CO_3/CH_3CN$)

Pump 2) Mannose triflate in acetonitrile

Pump 3) Aqueous sodium hydroxide solution (0.1 M)

Pump 4) Acetonitrile

Pump 5) Water

The ROC platform was employed for synthesising ^{18}F-FDG by following the step-by-step procedure below. A LabView program was used to drive each syringe station independently, while mass flow meters and pressure sensors for each syringe pump station provided feedback for allowing accurate control over the processing conditions.

1) Using the syringe pump from an Advion NanoTek system located inside the hot cell, the pre-concentration chip (module 1) was flushed with ^{18}F-fluoride/H_2O (via Valve 7, the Auto Switch Valve, set to the "no-production" position). The output port of the pre-concentration module was connected to the waste line during this step, such that the ^{18}O-water was collected at a waste outlet.
2) The Auto Valve Switch (Valve 7) was turned to the "production" position, flushing $K_{222}/K_2CO_3/CH_3CN$ solution from Pump 1 (via Valve 1) into the pre-concentration chip. This eluted the ^{18}F-fluoride from the pre-concentration module and into the first

microreactor chip (module 2; radiolabelling). Simultaneously, mannose triflate from Pump 2 (via Valve 2) was flushed into module 2, which mixed and reacted with the ^{18}F-fluoride in the serpentine channel to form acetylated-^{18}F-FDG.

3) Originally, the acetylated-^{18}F-FDG emerging from module 2 would have been mixed with water (from Pump 5, via Valve 5) at a T-connecter, before being directed into the solvent exchange chip (module 3). Nitrogen gas from a pressure regulated gas cylinder would have been directed into a second outlet on the chip, allowing the acetonitrile to be removed while the acetylated-^{18}F-FDG remained within the water. While the gas was removed via a waste outlet, the water would have been transferred to the second microreactor device (module 4; hydrolysis). However, optimisation of the synthetic steps prior to the operation of the ROC platform had shown that the solvent exchange step was not required for the hydrolysis reaction. Hence, in this instance the solvent exchange step was removed from the process, and so the acetylated-^{18}F-FDG from module 2 was coupled directly into module 4.
4) Simultaneous to the transfer of acetylated-^{18}F-FDG from module 2 to module 4, aqueous sodium hydroxide solution was flushed from Pump 3 (via Valve 3) into module 4, allowing the acetylated-^{18}F-FDG to be base hydrolysed within the serpentine channel to form ^{18}F-FDG.
5) The ^{18}F-FDG generated in module 4 was directed into series of off-platform modules, the same configuration as the pre-concentration module, which were filled with four different types of solid-phase extraction resin for the removal of the various unwanted components of the solution.

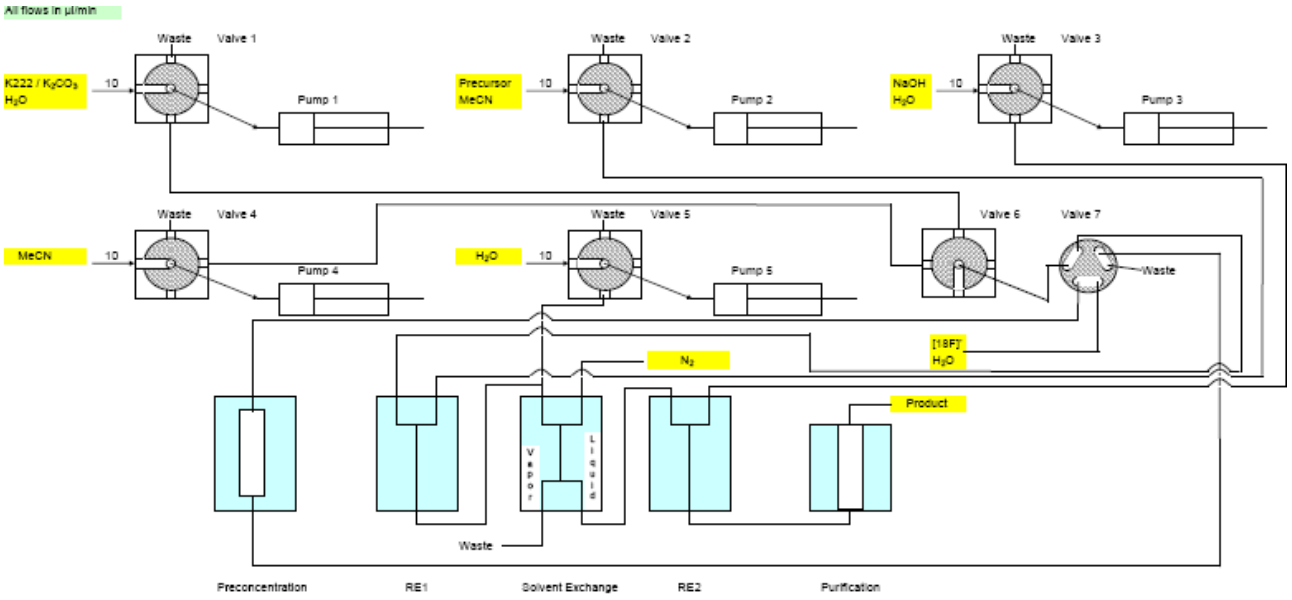

Fig. S9 Schematic showing the interconnection of the microfluidic modules, pumps, tubing, and valves required for the synthesis of ^{18}F-FDG via the ROC platform.