Electronic Supplementary Information (ESI)

Positron detection in silica monoliths for miniaturised quality control of PET radiotracers

Mark D. Tarn,[a,b,‡] Dzmitry Maneuski,[c,‡,*] Richard Alexander,[d] Nathaniel J. Brown,[d] Val O'Shea,[c] Sally L. Pimlott,[e] Nicole Pamme[b,*] and Stephen J. Archibald[a,b,*]

[a.] *Positron Emission Tomography Research Centre, University of Hull, Cottingham Road, Hull, HU6 7RX, UK. Email: s.j.archibald@hull.ac.uk; Tel: +44 (0) 1482 465488; Fax: +44 (0) 1482 466410.*

[b.] *Department of Chemistry, University of Hull, Cottingham Road, Hull, HU6 7RX, UK. Email: n.pamme@hull.ac.uk; Tel: +44 (0) 1482 465027; Fax: +44 (0) 1482 466410.*

[c.] *School of Physics and Astronomy, University of Glasgow, Glasgow, G12 8QQ, UK. Email: dima.maneuski@glasgow.ac.uk.*

[d.] *School of Engineering, University of Hull, Cottingham Road, Hull, HU6 7RX, UK.*

[e.] *School of Medicine, University of Glasgow, Glasgow, G12 8QQ, UK.*

[§] Current address: *Centre for Regional and Rural Futures, Faculty of Science, Engineering and Built Environment, Deakin University, Geelong, Victoria, 3216, Australia.*

‡ Authors contributed equally to this work.

** Corresponding authors.*

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1. Preparation of fluorine-18

Fluorine-18 radioisotope was prepared via the $^{18}O(p,n)^{18}F$ nuclear reaction, by proton bombardment of ^{18}O-enriched target water in a cyclotron (GE PETtrace 6 cyclotron). Irradiation of the target water was performed with a 16.5 MeV proton beam (40 μA). The water containing the fluorine-18 from the irradiation was removed for another use. A target wash was then performed using 1.3 mL of ^{16}O-water. The fluorine-18 solution was collected in a 10 mL vial and measured 162.5 MBq at start time of measurement. A 20 μL aliquot of the fluorine-18 solution was removed and placed on a coverslip with a circular region defined using a hydrophobic pen. Measurements were taken over a 90 minute period. The amount of fluorine-18 in the 20 μL aliquot ranged from approximately 2.5 - 1.4 MBq during the measurement period.

2. Effect of distance between radioisotope and detector

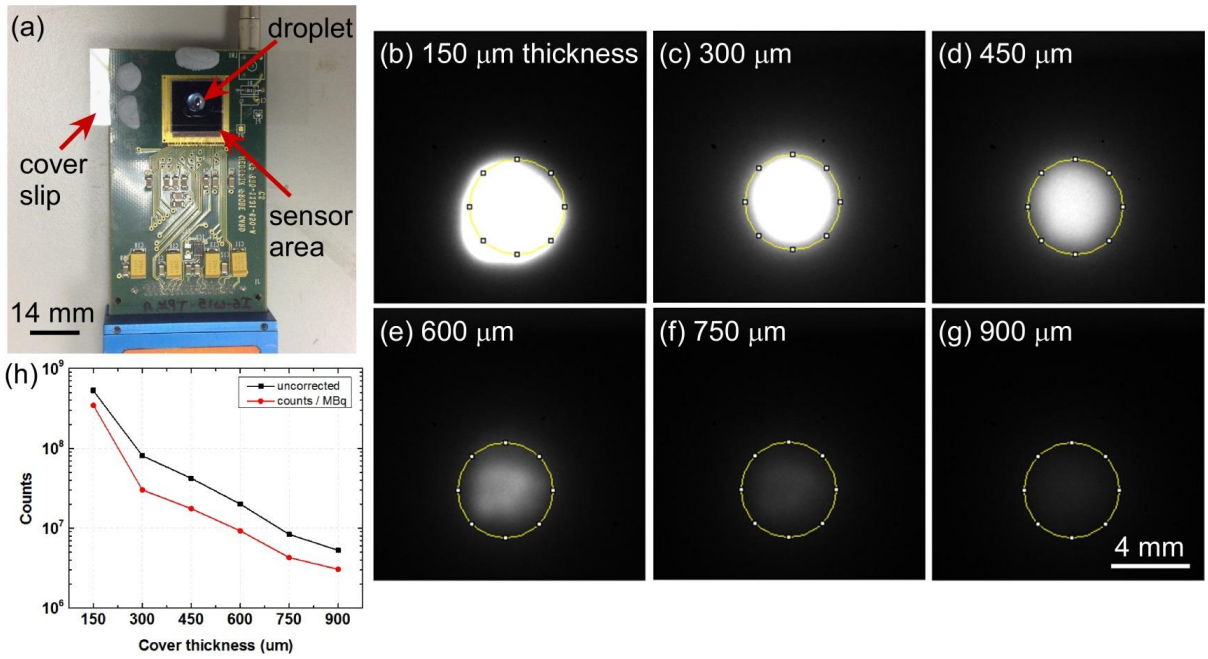

Fig. S1 *Investigation into the effect of glass thickness between the Medipix sensor area and a 20 μL droplet of fluorine-18 solution, achieved by stacking 150 μm thick cover slips on top of the sensor. The image acquisition time was 0.1 seconds, and 600 images were acquired for analysis (i.e. 15 min integration time). (a) Photograph of the Medipix detector, showing a droplet of fluorine-18 on the 14 x 14 mm^2 sensor area. (b)-(g) Acquired Medipix images of the fluorine-18 signal at varying distances (150-900 μm). (h) Plot showing the effect of total cover slip thickness on the Medipix signal, both uncorrected (black line) and corrected (red line) for decayed activity.*

3. Chemicals and reagents

Solutions were prepared in purified water (18.2 MΩ cm at 25 °C) purified through an ELGA Option 4 system and an ELGA UHG PS system (ELGA Process Water, Marlow, UK). Hydrochloric acid (37 %) and citric acid were purchased from Fisher Scientific (Loughborough, UK). Sodium phosphate monobasic monohydrate, polyethylene oxide (PEO, MW 100,000), tetraethyl orthosilicate (TEOS), ammonium hydroxide (5 M), nitric acid (1 M) was purchased from Sigma-Aldrich (Dorset, UK).

A 0.6 M HCl solution was prepared via dilution of the stock HCl in water for elution of the ^{68}Ge/^{68}Ga generator. A solution of 0.1 M citric acid was prepared for complexation of gallium-68 to ^{68}Ga-citrate, and for elution of ^{68}Ga-citrate and free $^{68}Ga^{3+}$ from the silica-based monolith. A solution of sodium phosphate (0.4 M) was prepared for the trapping of $^{68}Ga^{3+}$ on the silica-based monolith.[1] Ammonium hydroxide was diluted to 1 M for monolith preparation.

4. Preparation of gallium-68 and ^{68}Ga-citrate

A solution of $^{68}GaCl_3$ was eluted from a 740 MBq ^{68}Ga/^{68}Ge generator (iThemba LABS/IDB Holland) in ~3 mL of 0.6 M HCl. The radioisotope solution was processed for synthesis as described previously.[2] The eluate was added to a strong cation exchange column (Strata-X-C, Phenomenex, Macclesfield, UK) under vacuum, whereupon the gallium-68 was trapped on the column while the other components of the solution passed to waste. The gallium-68 was then eluted from the column into a vial via a 98:2 solution of acetone and 0.1 M hydrochloric acid. The purified gallium-68 was dried at 90 °C in a heating block while under vacuum, then 0.1 M citric acid solution added and the vial agitated for 15 min to form ^{68}Ga-citrate.

5. Linearity of detector

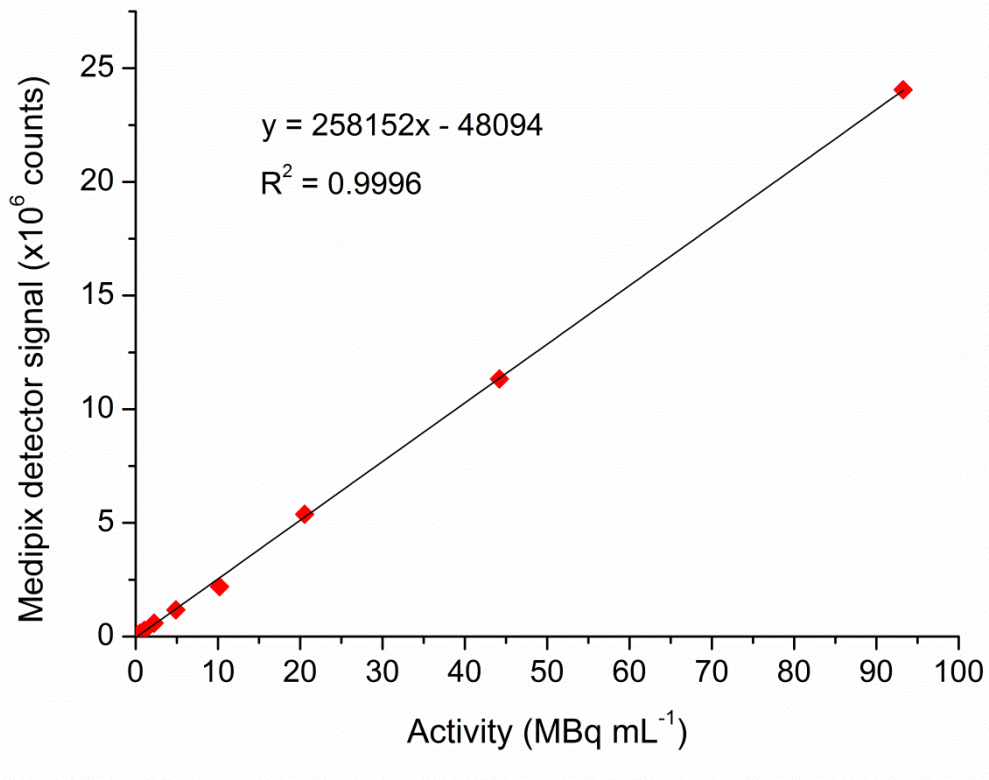

Fig. S2 *Plot showing the linearity of the positron detection signal with varying radioactivity levels of the* ^{68}*Ga-citrate radiotracer on a linear scale (n = 1).*

6. Fabrication of silica-based monoliths

Silica-based monoliths were prepared as described in the literature.[3] 0.282 g of PEO (MW 10,000) was added to a 50 mL centrifuge tube (VWR, UK) and cooled in an ice bath. 2.537 mL nitric acid (1 M) was added to the tube and stirred with a magnetic stirrer bar. 0.291 mL water was then added and the mixture allowed to stir for 1 h with cooling in ice. Following this, 2.256 mL of TEOS was added and the mixture stirred in the ice bath for a further 1 h until a transparent solution was formed. The solution was drawn into a syringe, before being filled into two-part PTFE moulds (14 mm long x 4 mm wide x 1.5 mm thick) that would be used to form the shape of the final monoliths. The moulds were sealed using a clamp with a parafilm layer over the mould inlets, and left in a 40 °C oven for 72 h to form a wet, partially solidified gel monolith. The mould halves were separated and the gel monoliths were removed from the moulds, washed with purified water, and soaked in water for 24 hours, during which time the water in the dish was replaced regularly to remove any residue. The monoliths were placed in a conical flask that had been modified to have a square bottom (in order to avoid the monoliths adopting the rounded shape of a conventional conical flask) to which 50 mL ammonium hydroxide (1 M) had been added. The solution was refluxed at 90 °C in an paraffin oil bath for 16 h, then the monoliths were removed before undergoing the washing procedure again with purified water, and then allowed to dry at 40 °C. Finally, the monoliths were placed in a furnace at 555 °C for 3 h for calcination, yielding the final solid, porous monoliths.

In order to integrate a monolith into a flow system, it was placed in a length of heat-shrinkable PTFE tubing with a 4:1 shrinkage ratio (4.80 mm ID before shrinkage, 1.27 mm ID after shrinkage, 0.30 mm wall thickness, TR48, Adtech Polymer Engineering Ltd., UK), with pieces of standard PTFE tubing (0.3 mm ID, 1.58 mm OD, Sigma-Aldrich, UK) also placed inside the TR48 heat shrink tubing either side of the monolith. The assembly was carefully placed inside a 350 °C furnace until the heat shrink had shrunk around the monolith and the standard PTFE tubing to form a flow system. The shrunk TR48 tubing had a final wall thickness of 0.30 mm, which dictated the minimum distance between the positron sensor and the gallium-68 solution that would be flowing through the monolith (with the maximum distance thus being 1.80 mm and the average distance being 0.75 mm).

7. Setup of the sample injection system

The general setup of the injection system is shown in Fig. S2, although the monolith and the positron detector are not shown here. The monolith was fixed over the detection area of the Medipix detector. The outlet of the monolith tubing was connected to the PEEK tubing of a conventional radio-HPLC detector that utilises a thallium-doped sodium iodide (NaI(Tl)) crystal (1" diameter x 1" thick) for generation of scintillation light when a gamma ray passes through it, and a photomultiplier tube (PMT) for detection of the scintillated light (PN-FXX-03 1" NaI/PMT detector, Dual Scan-RAM, LabLogic Systems Ltd., UK) via HPLC fittings (Upchurch). Radio-HPLC signals were recorded using Laura software (LabLogic Systems Ltd., UK). The outlet of the NaI/PMT radio-HPLC detector was fed to a waste bottle. The inlet of the monolith tubing was connected at one end to a piece of fused silica capillary (150 μm ID, 363 μm OD, CM Scientific, UK) that was used to connect it to the sample injection system. The capillary was connected to a four-way cross-piece (LabSmith C360-204 Interconnect Cross, Mengel Engineering, Denmark) via a one-piece fitting (LabSmith), with capillary also connected to the other three ports of the cross-piece. The internal volume of the cross part of the four-way piece was calculated to be ~17 nL, and this determined the sample volume injected. Two of the capillaries coming from the cross-piece were connected to disposable syringes (5 mL, BD Plastipak) that were fixed onto syringe pumps (Pump 11 Elite and Pump 11 Plus, Harvard Apparatus, UK). One syringe pump was used in withdrawal mode ("withdrawal pump") and the other in infuse mode ("infusion pump"). A similar setup employing the LabSmith four-way cross-piece has previously been demonstrated by Segato et al.[4] for sample injection in a microfluidic capillary electrophoresis platform. The syringes contained a few millilitres of mobile phase (either 0.1 M citric acid or 0.4 M phosphate buffer) in order to purge the system prior to starting experiments. The open end of the final capillary from the cross-piece was inserted into a sample vial containing gallium-68 solution, which was placed in a shielded pot with a shielded lid. A shut-off valve (Upchurch fittings, purchased from Kinesis, UK) was placed in the flow path between the withdrawal pump and the cross-piece, and another shut-off valve situated in the flow path between the sample vial and the cross-piece.

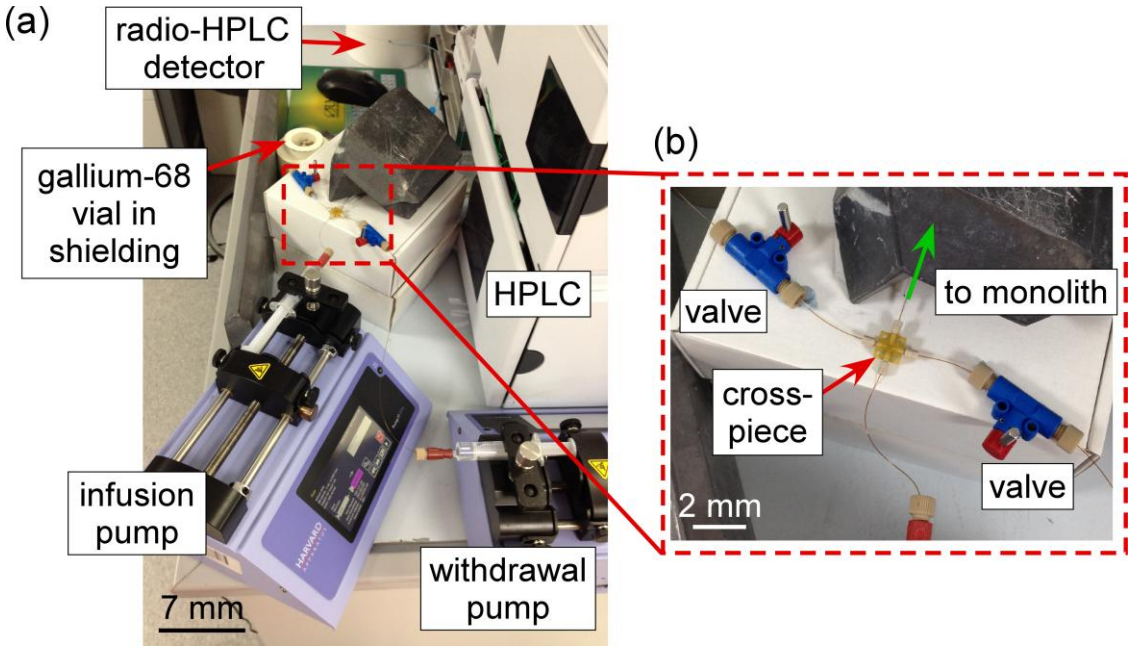

Fig. S3 *Sample injection setup. (a) Photograph showing the two syringe pumps used for introduction of sample into the monolith, the NaI/PMT radio-HPLC detector used for comparison of detection signals, and a shielded pot in which a vial of gallium-68 was placed (with a shielded lid). (b) Close-up photograph of the four-way cross-piece (volume ~17 nL) and valves used as part of the sample loading and injection process. The monolith and Medipix positron detector are not shown here, but were placed in the flow path between the cross-piece and the radio-HPLC detector.*

8. Sample injection procedure

The injection of gallium-68 solutions into the monolith was achieved following a conventional cross-injection methodology employed in microfluidics that comprises two main steps (Fig. S3): sample loading and sample injection.[4-6] In the sample loading step, the shut-off valves were opened and gallium-68 solution pulled, at 100 μL min^{-1}, from the sample vial, through the four-way cross-piece, and into the sample waste syringe via the withdrawal pump (Fig. S3a), while no flow was applied from the infusion pump. The sample was injected into the monolith by stopping the withdrawal pump, closing the shut-off valves, and starting the infusion pump (either at 50 or 200 μL min^{-1}) (Fig. S3b). This caused the contents of the cross part of the four-way cross-piece (~17 nL of gallium-68 solution) to be injected into the monolith.

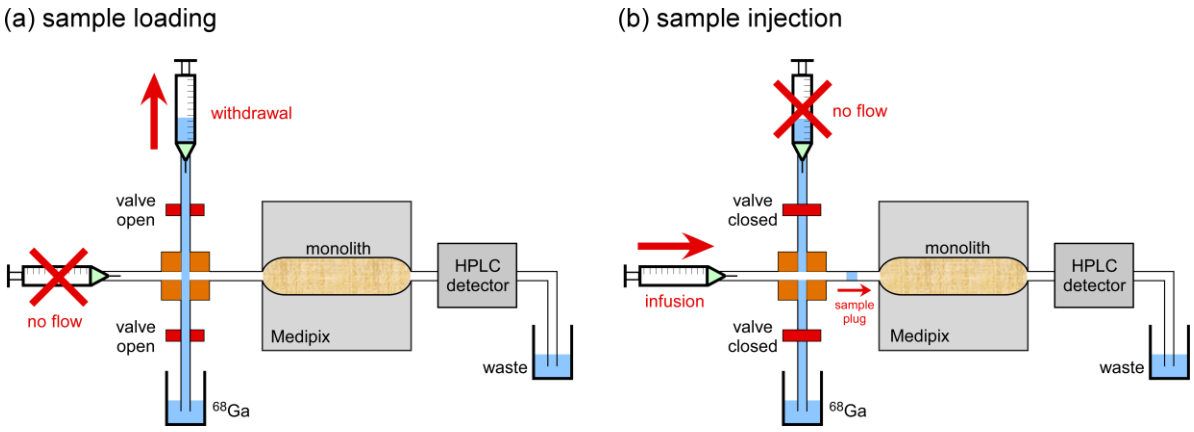

Fig. S4 *Sample injection into the monolith of gallium-68 solutions, using cross-injection methodology. (a) Sample loading: gallium-68 solution is drawn through the cross-piece using negative pressure from a syringe pump. (b) Sample injection: valves are closed in order to isolate the cross-piece from the sample source vial and sample waste syringe. Positive pressure is then applied from a second syringe pump in order to introduce the sample volume in the cross-piece (~17 nL) into the monolith.*

9. Multiple injections of ^{68}Ga-citrate through the monolith

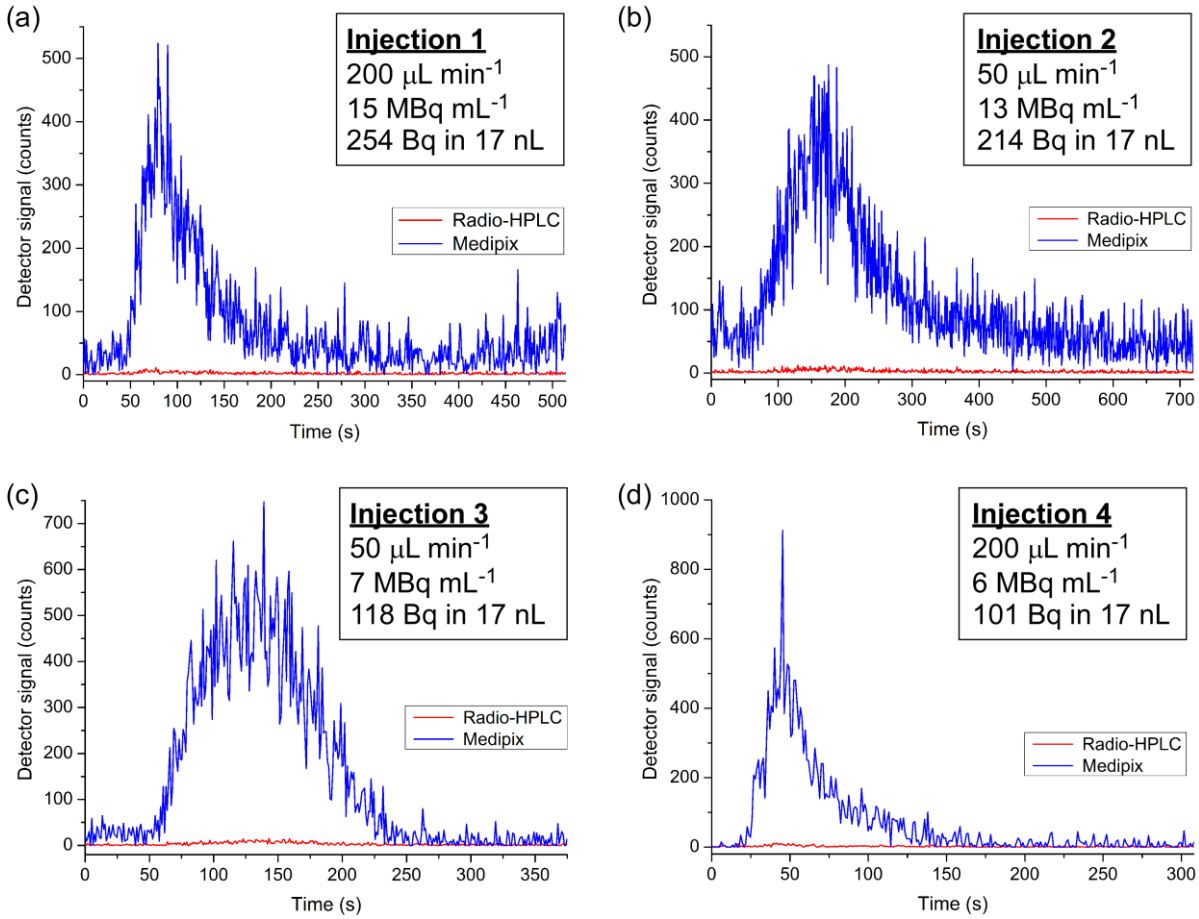

Fig. S5 *Signals for ^{68}Ga-citrate sample plugs passed through the silica monolith, with detector signals plotted on the same scale to show the differences in absolute signal intensity. The blue data shows the positron detection signal, while the red data is from the radio-HPLC detector. The detector integration times were each 1 second. (a)-(d) correspond to injections 1-4. GIFs of each injection recorded from the positron detector are available in the ESI (GIFs 1 to 4; flow direction is right-to-left).*

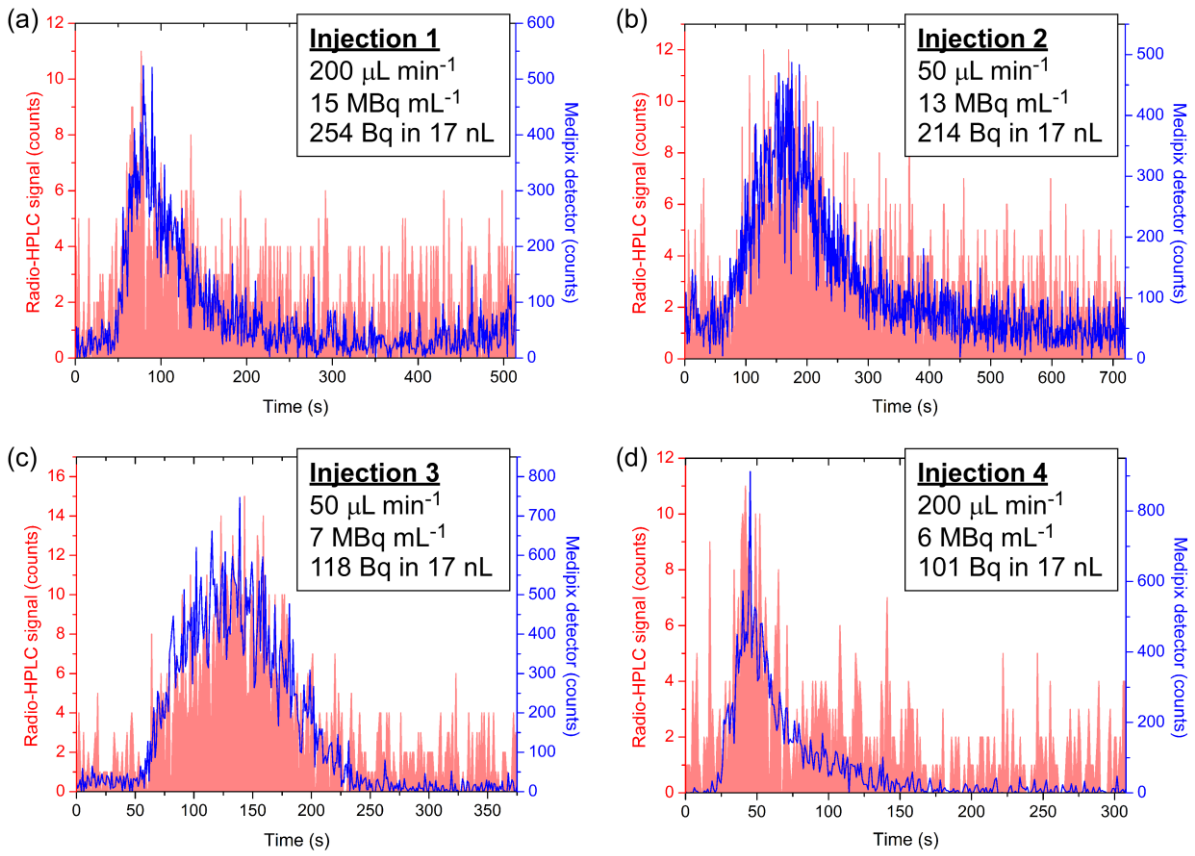

Fig. S6 *Signals for ^{68}Ga-citrate sample plugs passed through the silica monolith, showing the same data from Fig. S2 plotted on different scales for the radio-HPLC detector (shown in red) and Medipix positron detector (shown in blue) signals. The data is plotted to show the difference in signal-to-noise ratio for both detectors. (a)-(d) correspond to injections 1-4.*

Table S1 *Parameters of each ^{68}Ga-citrate injection through the monolith. The signal-to-noise ratios (S/N) of the positron detector and the conventional NaI/PMT radio-HLPC detector are shown for each injection.*

	Injection number			
	1	**2**	**3**	**4**
Flow rate (μL min^{-1})	200	50	50	200
Activity (MBq mL^{-1})	14.9	12.6	7.0	6.0
Activity in 17 nL (Bq)	254	214	118	101
Positron detector (S/N)	**14**	**10**	**35**	**48**
Radio-HPLC detector (S/N)	**3**	**3**	**6**	**7**

10. References

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