ABX advanced biochemical compounds

Novel radiosynthesis strategy towards [^{18}F]F-PSMA 1007

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Objectives

[^{18}F]F-PSMA-1007 and [^{18}F]-DCFPyL are novel radiotracers for the molecular imaging of prostate cancer. The established radiosyntheses are based on either a multi-step approach using prosthetic groups to incorporate fluorine-18 or a more common approach which comprises a two-step sequence of labelling and hydrolysis. For commercial synthesizer modules applying single-use manifolds, the prosthetic group strategy is somehow difficult to establish since often two reactors are necessary for the radiosynthesis. In contrast, the drawback of the two-step approach is the use of harsh conditions during hydrolysis leading to loss of fluorinated product due to decomposition or side-reactions. Our aim was to develop a novel radiosynthesis approach for the direct labelling of [^{18}F]F-PSMA derivatives and the adaption of this strategy onto different commercial radiolabelling modules.

Methods

A novel precursor **1** for the synthesis of [^{18}F]F-PSMA-1007 was obtained using standard laboratory procedures as well as solid-phase chemisty. The radiolabelling was performed in a single-step reaction using remarkably low amounts of precursor. This concept was transferred onto several radiosynthesiser modules including GE TRACERlab MX$_{FDG}$, Ora Neptis, Ora Mosaic RS and IBA Synthera. The final radiotracers were purified using SPE.

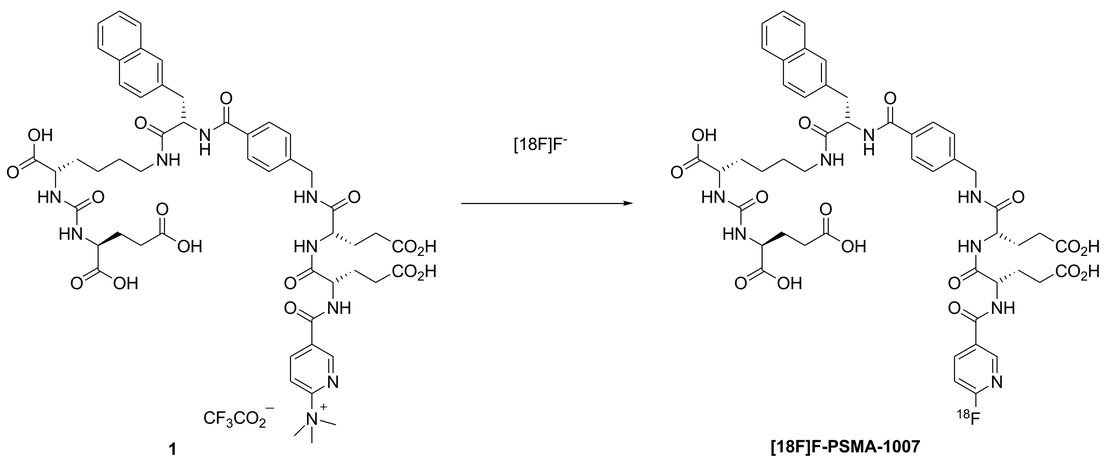


Figure 1: Reaction scheme for the preparation of [^{18}F]F-PSMA-1007.

[^{18}F]F-Fluoride was produced by irradiation of [^{18}O]H_2O (CIL) with 9.6 MeV proton beam by the ^{18}O(p,n)^{18}F nuclear reaction. Irradiations were performed with the GE Minitrace 700S cyclotron at ABX GmbH in Radeberg, Germany. Acetonitrile (for DNA synthesis) and ethanol were acquired from Merck. Anhydrous DMSO and sodium ascorbate were received from Aldrich. 0.9% Sodium chloride solution was obtained from BBraun Melsungen GmbH.

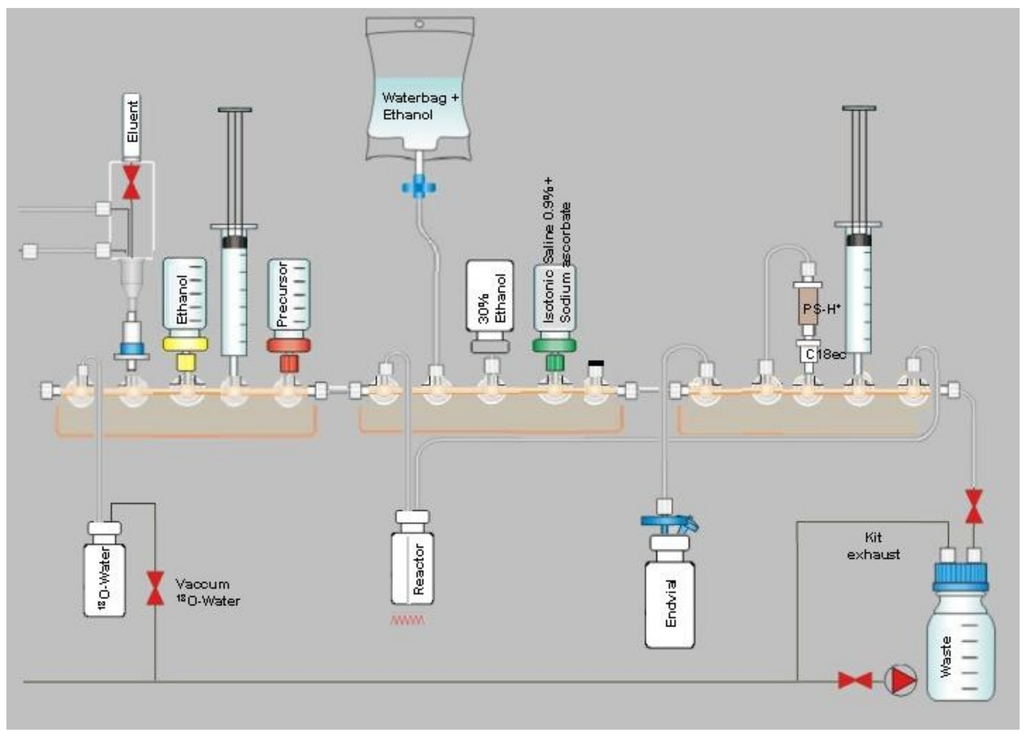


Figure 2: Hardware and reagent kit for [^{18}F]F-PSMA-1007 using the GE TRACERlab® MX$_{FDG}$

Quality control

Radiochemical/chemical purity: HPLC analysis was performed on an Ultimate 3000 system with variable wavelength detector RS 3000 (both Dionex) and a gamma-detector HERM LB500 (Berthold) for radioactivity detection, equipped with a X-Terra C18 250X4.6 mm column (Waters). The system was controlled by Chromeleon software version 7.1.2 (Dionex). For the analysis, a multi-step gradient was applied using acetonitrile (solvent A) and 0.1 % TFA (solvent B): 0 to 0,3 minutes, 20 % A; 0,3 to 2 minutes to 30 % A; then isocratic 30% A fo 15 minutes, then to 95 % A in 6 minutes; isocratic 95% A for 2 minutes; back to 20% A in 1 minute; 9 minutes isocratic at 20% A (A + B = 100 %, flowrate = 1 ml/min, total run time = 35 minutes).

Experimental details

^{18}F-Fluoride fixation, desorption and drying Separation of n.c.a. [^{18}F]-fluoride from [^{18}O]-enriched water is accomplished via fixation of ^{18}F-fluoride on an anion exchange cartridge (Sep-Pak QMA Light cartridge). Subsequently, the activity is eluted using TBA·HCO_3/EtOH/H_2O solution and dried in *vacuo*.

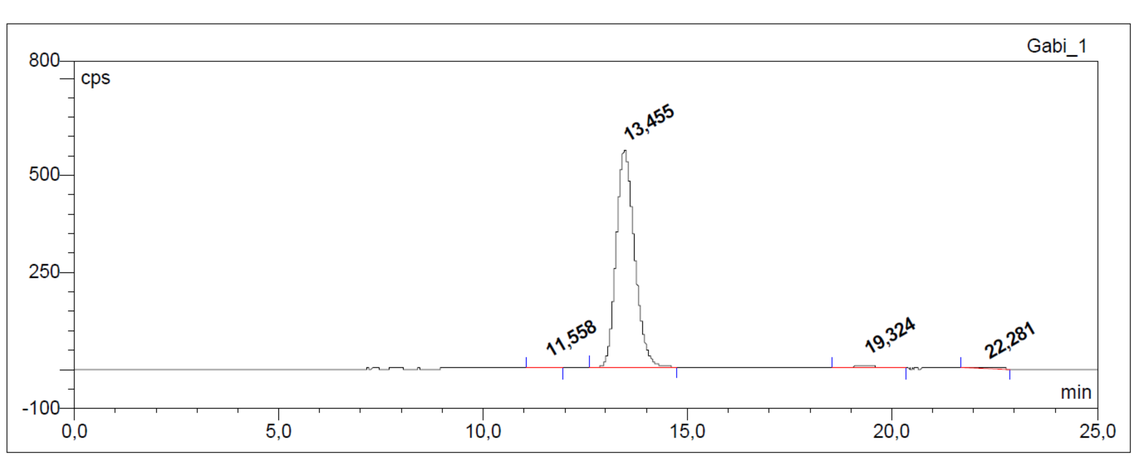
Nucleophilic fluorination with ^{18}F ^{18}F-fluoridation of the **1** (1.6 mg) was realised in 2 ml DMSO. The mixture was heated at 85 to 95 °C for 10 min. Incorporation of [^{18}F]-fluoride was up to 95%. After labelling, the mixture was purified by SPE.

Purification and formulation After hydrolysis, the crude [^{18}F]F-PSMA-1007 was purified using a reversed-phase cartridge system consisting of a cation exchange cartridge and a C18 cartridge in series. The final product was eluted with ethanolic solution and diluted with 0,9% NaCl containing sodium ascorbate as stabiliser.

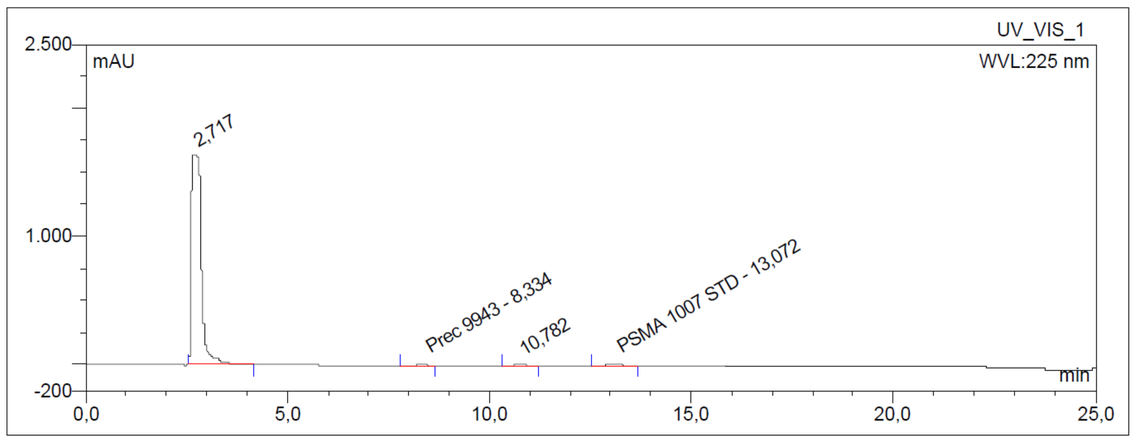
Results

It was surprisingly found that the non-protected precursor **1** could easily be radiolabelled using conventional fluorine-18 chemistry. This stands in stark contrast to the established concept where typically radiotracers are obtained *via* a two-step route consisting of a first radiolabelling reaction and a second hydrolysis step (e. g. [^{18}F]FDG, [^{18}F]FET, [^{18}F]FLT, [^{18}F]FMISO). More complicated tracers often require even more radiosynthetic steps (e. g. [^{18}F]F-DOPA).

Using this novel concept, we established a fully automated synthesis of [^{18}F]F-PSMA-1007 on the GE TRACERlab MX$_{FDG}$, Ora Neptis / Mosaic RS, IBA Synthera and Trasis AllinOne modules. The radiotracer was obtained within 45 min in >95% radiochemical purity (as evaluated by HPLC; after 6h, see radio-chromatogram) as a ready-to-inject, sterile solution. The radiochemical n.d.c yield of the whole process is typically 20-40% (depending on the synthesizer) using activities up to 2.5 Ci / 90 GBq. Individual chemical impurities are NMT 0,1 mg / V and NMT 0,5 mg / V in total. Limits for residual solvents conform to Ph. Eur. chapter 5.4. The pH of the final solution is between 5.0 and 6.0.



Radio-chromatogram of [^{18}F]F-PSMA-1007 [^{18}F]F-PSMA-1007 with 97.7%, minor radioactive side product at 11.6 min (0,27 %), 19,3 min (1,66 %) and 22,3 min (0,37%).



UV-chromatogram (225nm) of [^{18}F]F-PSMA-1007 Peak for sodium ascorbate at 2,7 min, minor impurities for the precursor at 8,3 min (2,2 mAU*min), unknown impurity at 10,8 min (2,0 mAU*min) and "cold" F-PSMA-1007 at 13,1 min (2,4 mAU*min).

Conclusion

[^{18}F]F-PSMA-1007 has been successfully synthesized by a one-step fluorination of our newly designed precursor **1** in a fully automated process on the GR TRACERlab® MX$_{FDG}$, Ora Neptis® and Mosaic RS as well as IBA Synthera and Trasis AllinOne synthesizers without the need of purification by HPLC. The [^{18}F]F-PSMA-1007 production with simple cartridge cleaning is a reliable and convenient method for routine clinical production and the product shows high radiochemical stability. Using a small cyclotron delivering about 90 GBq of fluorine-18, the tracer is available with activities of up to 40 GBq in 45 min.

Kits and cassettes for the above-mentioned modules are available from ABX. For further information please contact: **sales@abx.de**