# Present Status of the [18F]FDG Production at CYRIC

# III. 2. Present Status of the [$^{18}$F]FDG Production at CYRIC

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At CYRIC 2-deoxy-2-[$^{18}$F]fluoro-D-glucose ([$^{18}$F]FDG) was prepared for clinical PET studies for the first time in 1983 after a fully automated synthesis system based on the original method[1] had been developed[2]. Approximately 120 preparations were made for 3 years with the average yield of 16 mCi and then the synthesis system was replaced with a new automated synthesis system based on the improved method utilizing [$^{18}$F]acetyl hypofluorite[3] in 1985. This second automated system was used until quite recently at CYRIC although a novel excellent synthesis method by the nucleophilic fluorination with no-carrier-added [$^{18}$F]fluoride was developed in 1986[4]. In total, nearly 330 preparations were made with the average shipped yield of 33 mCi for 9 years.

We developed a new automated system for the preparation of no-carrier-added [$^{18}$F]FDG[5]. The third synthesis system was, however, used only to supply the labeled compound for basic animal studies, while we modified the system to simplify the procedure for future routine use. A new 3D PET (Shimadzu SET 2400W) was installed at CYRIC in 1994 and began to be available for clinical use early in 1995. The demand for [$^{18}$F]FDG was thus increased and this situation led us to decide to introduce the third system for routine production of [$^{18}$F]FDG.

The present report describes the development of the automated system for the preparation of no-carrier-added [$^{18}$F]FDG together with the improvement made on the target system for the [$^{18}$F]fluoride production with $^{18}$O-enriched water.

## [$^{18}$F]Fluoride production

A static target was substituted for the circulating target used for a long time at CYRIC[6] to reduce the volume of expensive $^{18}$O-enriched water (50 atom%) to a minimum and to increase the specific activity of [$^{18}$F]fluoride. As shown in Fig. 1, 1.5 mL of the target water was remotely loaded into the irradiation chamber (the body: Ag, the beam window: 30 mm Ti, the net volume: *ca.* 1.2 mL) via two pneumatic 6-way valves (Valco) using an HPLC pump and an overflow was recovered in a reservoir. The irradiation was carried out using a 18 MeV proton beam at a beam current of 10 mA for 90 min. The target pressure was always

monitored with a small pressure sensor and displayed on a computer CRT (see Fig. 2). After the irradiation the target water was transferred to the automated system with a $H_2$ flow at 30 mL/min. The chamber and the transfer line (i.d 0.8 mm and 20 m long polyethylene tube) was washed with another 1 mL of the enriched water. The combined water was passed through an anion exchange membrane filter (Bio-Rad) to conveniently recover the target water[7] and the [$^{18}$F]fluoride retained by the membrane was then eluted with a carbonate solution for subsequent use in the [$^{18}$F]FDG synthesis.

A new window cooling system with a circulating cold He flow was introduced to efficiently cool the beam window during the beam irradiation, in addition to a water cooling at the back side of the target. Figure 2 illustrates two typical pressure profiles during the irradiation at 10 mA. A sudden drop in the target pressure indicates that the increase in the pressure is mainly due to vaporization of the water and a remaining pressure can be ascribed to gaseous products radiolytically produced. When the Ti window was replaced with a 25 mm Havar foil to enhance the window strength, a gradual increase in the pressure was observed and it stayed at the same level when the irradiation was interrupted. This attempt was abandoned. The pressure increase changed day by day and it seemed to be affected by surface conditions of the beam window apart from cooling conditions.

The average production yield of [$^{18}$F]fluoride was 350 mCi/10 mAhr and the specific activity of the [$^{18}$F]fluoride was determined to be about 4 Ci/mmol by ion chromatography with a Dionex QIC Analyzer quipped with an Ion Pac A S4A-SC 4 mm column.

**Automated [$^{18}$F]FDG synthesis**

The prototype automated system of NKK Corp., based on our third automated system, was installed[8] and modified. As illustrated in Fig. 3, the system has a specially designed flask, attached to a small rotary evaporator and working as both reaction vessel and evaporation flask. Tetrabutylammonium bicarbonate ($TBAHCO_3$) instead of commonly used Kryptofix 222 was adopted as phase transfer catalyst for a simple one-pot synthesis[9]. The whole synthetic procedure is as follows:

1. One mL of water containing 50 mmol $TBAHCO_3$ was passed through the membrane to elute the [$^{18}$F]fluoride into the flask.
2. One mL of acetonitrile (MeCN) was added to the flask and the mixture was dried by azeotropic evaporation under reduced pressure. This step was repeated for complete dryness.
3. Twenty five mg of 1,3,4,6-Tetra-*O*-acetyl-2-*O*-triluoromethanesulfonyl-b-D-mannopyranose (Aldrich) dissolved in 1 mL anhydrous MeCN was added to the residue and the mixture was heated at 80∞C for 5 min.
4. The solvent was evaporated and 1 mL of 1.2 M HCl was added. The hydrolysis was carried out at 100∞C for 10 min.

5. The hydrolysis mixture was passed through a short cation exchange resin column (Alltech), an AG11A8 ion retarding resin column (Bio-Rad), a Sep-Pak C18 cartridge (Waters) and a Sep-Pak alumina N cartridge (Waters) and then collected in a large evaporating flask. The reaction flask and columns were washed with 5 mL of water and the washing was combined to the first eluate.
6. The aqueous solution containing purified [$^{18}$F]FDG was evaporated to dryness and 8 mL of saline was added to dissolve the residue and then passed through a 0.22 mm membrane filter into a sterile vial.

The above procedure, including the target irradiation and recovery, was totally automated with a personal computer (NEC 9801). The use of $TBAHCO_3$ allowed us to simplify the automated synthesis procedure to a great extent, compared with the previous method using Kryptofix 222.

The preparation of [$^{18}$F]FDG was thus completed within 90 min after the irradiation. The average yield of [$^{18}$F]FDG starting from the [$^{18}$F]fluoride (*ca.* 500 mCi at EOB) was 200 mCi at EOS. The radiochemical purity of [$^{18}$F]FDG determined by radio-HPLC on Carbohydrate (Waters) was always over 99% and $TBAHCO_3$ was not detected in the final solution by the extraction-spectrophotometric method[10] (detection limit: 0.02 mmol). The low reproducibility of the [$^{18}$F]FDG yield in the previous preparations, probably due to the low specific activity of the [$^{18}$F]fluoride produced with the circulating target, was overcome in the present method as the specific activity was greatly improved up to over 4 Ci/mmol at EOB[11].

Recently much attention has been paid to basic hydrolysis owing to its short, high-yield procedure at room temperature in contrast to acid hydrolysis[12]. Another advantage of this basic hydrolysis is that the formation of 2-deoxy-2-chloro-D-glucose is avoided[13]. From this viewpoint, hydrolysis with cation exchange resin is also an attractive alternative[14]. This hydrolysis method has the possibility of exploiting a new method for a total on-column preparation of [$^{18}$F]FDG[15]. All these things will be achieved in our next system in near future.

**References**


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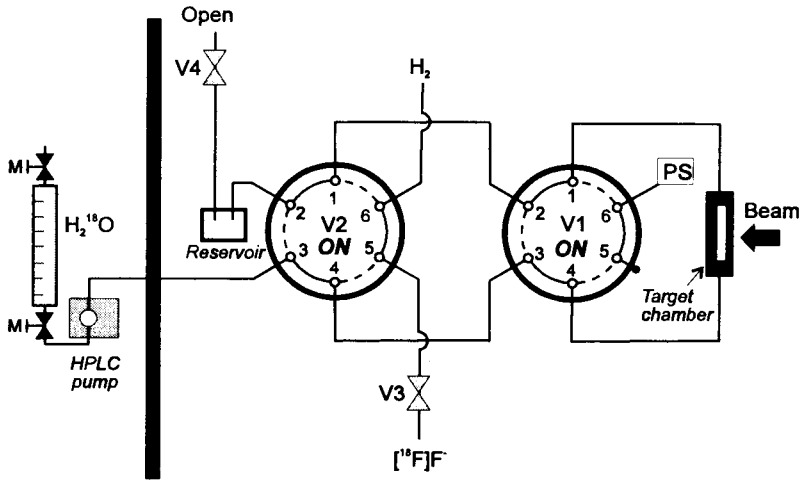


Fig. 1. The static target system for the [$^{18}$F]fluoride production.

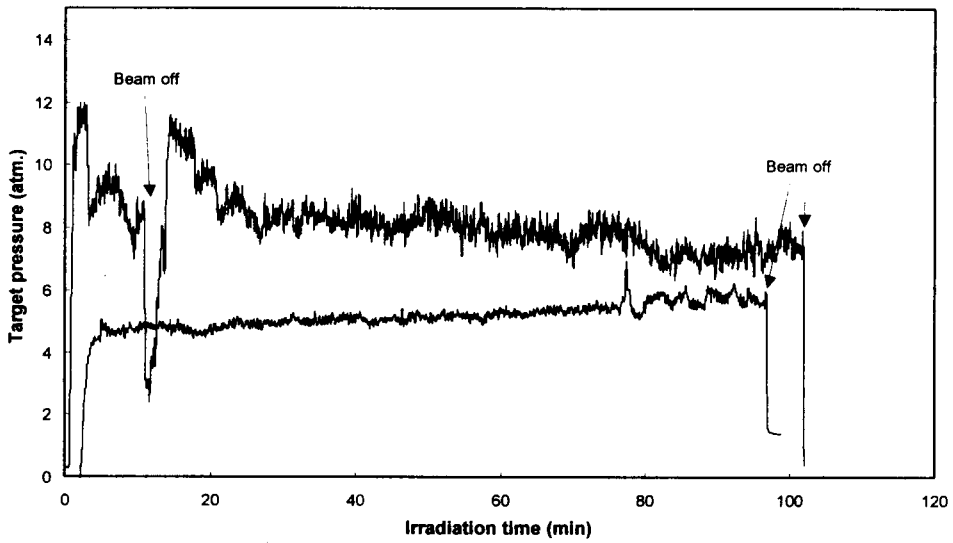


Fig. 2. Target pressure profile.

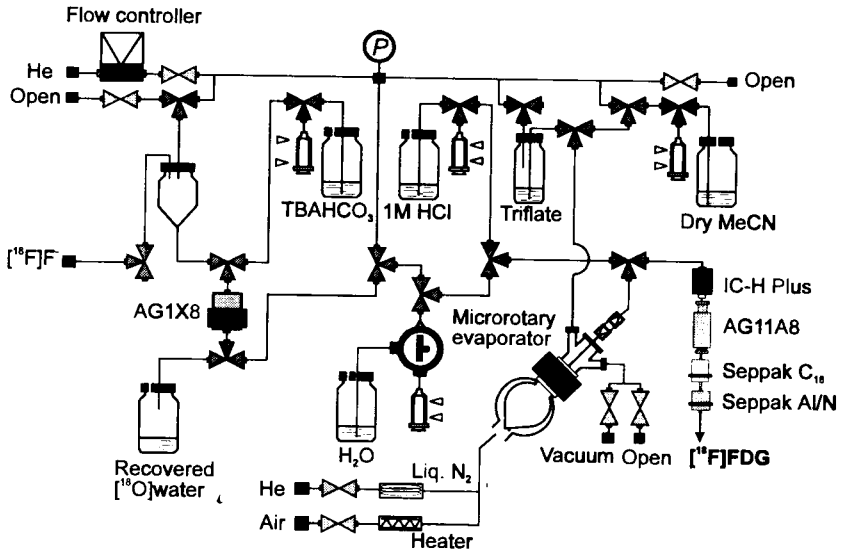


Fig. 3. The automated [$^{18}$F]FDG synthesis system.