# Initial and Subsequent Approach for the Synthesis of $^{18}$FDG

Joanna S. Fowler and Tatsuo Ido

**2-deoxy-2-[$^{18}$F] fluoro-D-glucose ($^{18}$FDG) was developed in 1976 in a collaboration between scientists at the National Institutes of Health, the University of Pennsylvania, and Brookhaven National Laboratory. It was developed for the specific purpose of mapping brain glucose metabolism in living humans, thereby serving as a tool in the basic human neurosciences. With $^{18}$FDG it was possible for the first time to measure regional glucose metabolism in the living human brain. Around the same time, the use of $^{18}$FDG for studies of myocardial metabolism and as a tracer for tumor metabolism were reported. After the first synthesis of $^{18}$FDG via an electrophilic fluorination with $^{18}$F gas (produced via the $^{20}$Ne(d,α)$^{18}$F reaction), small volume enriched water targets were developed that made it possible to produce large quantities of [$^{18}$F]fluoride ion via the high-yield $^{18}$O(p,n)$^{18}$F reaction. This was followed by a major milestone, the development of a nucleophilic fluorination method that produced $^{18}$FDG in very high yield. These advances and the remarkable properties of $^{18}$FDG have largely overcome the limitations of the 110-minute half-life of $^{18}$F so that $^{18}$FDG is now available to most regions of the United States from a number of central production sites. This avoids the need for an on-site cyclotron and chemistry laboratory and has opened up the use of $^{18}$FDG to institutions that have a positron emission tomography (PET) scanner (or other imaging device) but no cyclotron or chemistry infrastructure. Currently, $^{18}$FDG is used by many hospitals as an off the shelf radiopharmaceutical for clinical diagnosis in heart disease, seizure disorders, and oncology, the area of most rapid growth. However, it remains an important tool in human neuroscience and in drug research and development.**


THE FIRST SYNTHESIS of $^{18}$FDG for human studies took place in 1976, the result of a collaboration between scientists at the National Institutes of Health, the University of Pennsylvania, and Brookhaven National Laboratory (BNL), which had begun 3 years earlier. $^{18}$FDG was developed for the specific purpose of mapping glucose metabolism in the living human brain, thereby serving as a tool in the basic human neurosciences.[1,2] With $^{18}$FDG it was possible for the first time to translate the $^{14}$C-2-DG autoradiographic method[3] to the clinical arena. Around the same time that $^{18}$FDG was developed, preclinical studies suggested the use of $^{18}$FDG for studies of myocardial metabolism[4] and for tumor metabolism.[5]

In the first human studies and many that followed, $^{18}$FDG was synthesized at Brookhaven National Laboratory on Long Island and sent by a small plane to Philadelphia Airport and then transported to the Hospital of the University of Pennsylvania where the first images of a human volunteer were made (Fig 1). Despite the 110-minute half-life of $^{18}$F and the relatively low yields of $^{18}$FDG, this remote supply of $^{18}$FDG served to show its unique properties and its use as a scientific tool for basic research and clinical diagnosis. In the next few years, BNL supplied $^{18}$FDG to the Hospital of the University of Pennsylvania and also to the National Institutes of Health. Soon, however, most of the major institutions that had a cyclotron produced $^{18}$FDG for their own use. It is remarkable that 25 years later, the production of $^{18}$FDG at regional cyclotron-synthesis centers and its distribution to remote hospitals and other institutions for clinical use particularly in cancer is the major mode for supplying $^{18}$FDG.

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*This article is dedicated to the memory of Alfred P. Wolf, whose vision and contributions to the development of $^{18}$FDG, to the advancement of radiotracer chemistry, and to the training of scientists have had an enormous, worldwide impact on the field of nuclear medicine.*

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In this article we highlight the major milestones in chemistry from the conceptual design through the evolution of its chemical syntheses. We note that there have been other reviews of various aspects of $^{18}$FDG design and chemistry,[6,7] including a very recent article on $^{18}$FDG chemistry.[8]

## DESIGN OF $^{18}$FDG: THE IMPORTANCE OF C-2

$^{18}$FDG was modeled after $^{14}$C-2-DG. 2-DG is a derivative of glucose in which the hydroxyl group (−OH) on Carbon-2 (C-2) is replaced by a hydrogen atom (Fig 2). The biologic behavior of 2-DG is remarkably similar to glucose, with a few important differences. Like glucose, 2-DG undergoes facilitated transport into the brain followed by phosphorylation by hexokinase because the hydroxyl group on C-2 is not a critical element for either of these processes. In contrast to glucose, however, metabolism does not proceed beyond phosphorylation because the hydroxyl group on C-2 is crucial in the next step, phosphohexose isomerase. As a result, 2-DG-6-P is trapped in the cell, providing a record of metabolism. In essence, removal of the hydroxyl on C-2 isolates the hexokinase reaction. This property of 2-DG was noted in 1954 by Sols and Crane,[9] who remarked:

*"2-Deoxy-glucose possesses certain advantages over glucose as a substrate for experimental studies with crude preparations of brain and other tissue hexokinases. The phosphate ester formed from 2-deoxyglucose is not inhibitory and it is not a substrate for either phosphohexose isomerase or glucose-6-phosphate dehydrogenase. Thus, the use of 2-deoxyglucose isolates the hexokinase reaction."*

The translation of the $^{14}$C-2-DG method to humans required that 2-DG be labeled with an isotope that decayed by body-penetrating radiation and that the chemical properties of the isotope and its position on the deoxyglucose skeleton would not significantly perturb its biochemical and transport properties. Of course, this could be achieved by isotopic substitution of stable carbon in the 2-DG structure with $^{11}$C, and this synthesis was accomplished shortly after the development of $^{18}$FDG.[10] However, $^{18}$F was chosen for initial studies because both the C-F bond is a strong bond and because its 110-minute half-life was sufficiently long for transport from Long Island to Philadelphia where the first human studies were performed on the Mark IV scanner.[11]

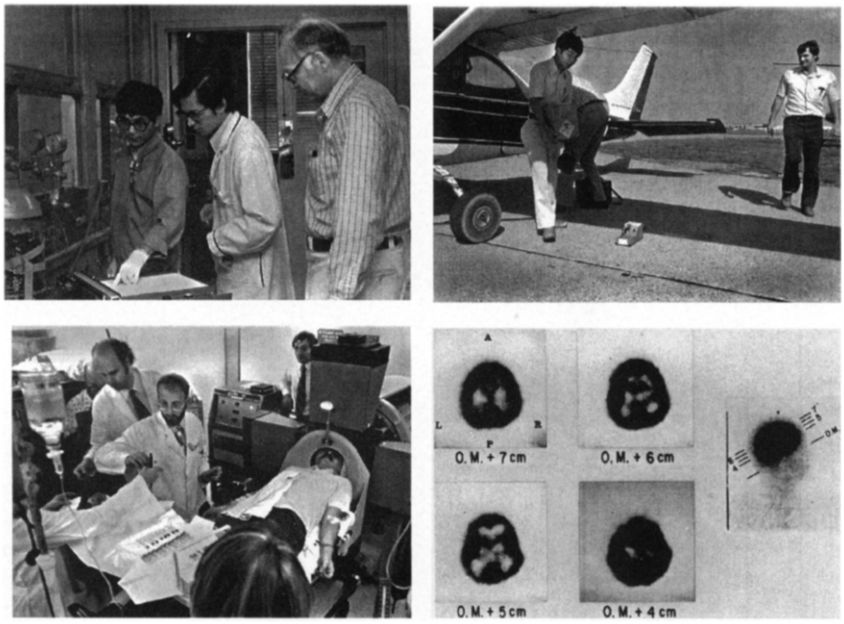


**Fig 1. (A) Synthesis of $^{18}$FDG for the first human study (left to right, Tatsuo Ido, C-N Wan, and Alfred P. Wolf). (B) Delivery of $^{18}$FDG to the Philadelphia Airport (Tatsuo Ido and Vito Casella). (C) $^{18}$FDG injection and imaging in Mark IV scanner (Martin Reivich and Joel Greenberg). (D) Brain images.**

The design of an $^{18}$F-labeled version of 2-DG hinged on substituting the $^{18}$F on a carbon atom which would preserve the properties of the parent molecule. The choice of C-2 for the fluorine substitution was an obvious one. C-2, unlike other carbon atoms in the molecule, can be modified without interfering with either facilitated transport required to bring the molecule across the blood brain barrier (BBB) or the hexokinase reaction. It was also reasonable to assume that 2-deoxy-2-fluoro-D-glucose would not be a substrate for phosphohexoseisomerase. Thus, it was predicted that $^{18}$FDG would be a good substrate for hexokinase and that, with the absence of a hydroxyl group on C-2, the phosphorylated product would be intracellularly trapped at the site of metabolism, providing a record of metabolic activity that could be imaged externally (Fig 3). The development of $^{18}$FDG was further supported by the fact that FDG had been synthesized in unlabeled form and shown to be a good substrate for hexokinase.[12] The importance of substituting the fluorine atom on C-2 is shown by the dramatic reduction in affinity for hexokinase with 3-deoxy-3-fluoro-D-glucose and 4-deoxy-4-fluoro-D-glucose (Table 1).[23,47]

To test the hypothesis that FDG would be a good model for $^{2}$DG, FDG was labeled with $^{14}$C.[1] Autoradiographic studies with $^{14}$C-FDG in the rat gave similar results as those obtained for $^{14}$C-2-DG and phosphorylation by hexokinase also proceeded as predicted.[2]

These studies formed the groundwork for developing a synthesis for $^{18}$FDG for studies of brain glucose metabolism in humans. However, $^{18}$FDG's unique high uptake in rapidly growing tumors[5] as a result of enhanced tumor glycolysis,[13] coupled with its low body background, resulted in a very high signal-to-noise ratio to detect tumors in the body. The low body background from $^{18}$FDG is caused in part by the fact that $^{18}$FDG, which is not phosphorylated by hexokinase, is excreted.[14] This contrasts to the behavior of glucose, which is not excreted because of resorption from urine to plasma via active transport across the renal tubule. The presence of a hydroxyl group on C-2 that occurs in glucose but not $^{18}$FDG is required for active transport.[15] This property of low body background resulting from $^{18}$FDG excretion, which was not anticipated in the initial design of $^{18}$FDG for brain studies, has elevated it to the forefront as a tracer for managing the cancer patient.[16]

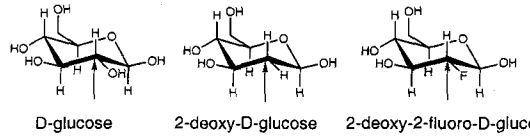


**Fig 2. Structure of glucose, 2-DG, and FDG showing modifications at C-2.**

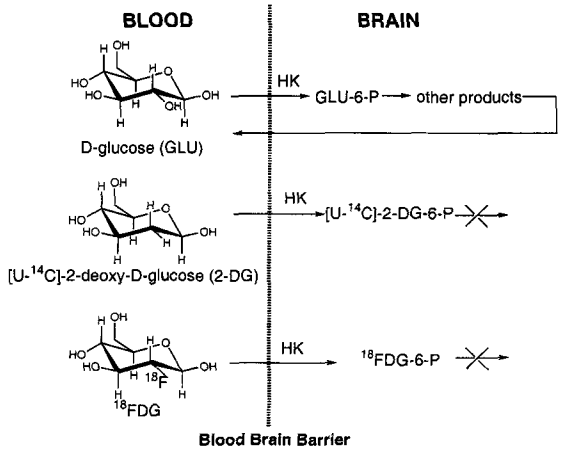


**Fig 3. $^{18}$FDG model compared with glucose and 2-DG. Note that replacement of the hydroxyl (−OH) group at C-2 does not alter facilitated transport or phosphorylation by hexokinase but does prevent metabolism beyond the phosphorylation step.**

**Table 1. Substrate Specificities for Hexokinase**

| Substrate | Hexokinase Source | Km (mmol) | Reference |
|---|---|---|---|
| D-glucose | Yeast | 0.17 | 23 |
| $^{2}$DG | Yeast | 0.59 ± 0.11 | 23 |
| 2-deoxy-$^{2}$FDG | Yeast | 0.19 ± 0.03 | 23 |
| 2-deoxy-$^{2}$FDG | Bovine brain | 0.2 | 47 |
| 2-deoxy-$^{2}$FDG | Yeast | 0.41 ± 0.05 | 23 |
| 3-deoxy-$^{3}$FDG | Yeast | 70 ± 30 | 23 |
| 4-deoxy-$^{4}$FDG | Yeast | 84 | 23 |

NOTE. Substitutions at C-2 retain specificity for hexokinase whereas substitutions on C-3 and C-4 result in increases of more than 100 in Km.

## FIRST SYNTHESIS OF $^{18}$FDG FOR ANIMAL AND HUMAN STUDIES

With $^{18}$FDG as a goal, the options for rapid incorporation of $^{18}$F in the C-2 position were assessed. Fortunately, there were 2 syntheses for unlabeled FDG in the chemical literature at the time that $^{18}$FDG was being developed. One of these involved the electrophilic fluorination of 3,4,6-triacetylglucal with the electrophilic fluorination reagent trifluoromethylhypofluorite ($CF_3OF$),[17] which was used in the synthesis of $^{14}$C-FDG.[1] The other synthetic approach to unlabeled FDG involved the use of potassium bifluoride ($KHF_2$) in a nucleophilic displacement reaction.[18] Though neither $CF_3OF$ nor $KHF_2$ nor the synthetic schemes were directly applicable to the synthesis of $^{18}$FDG, it was likely that elemental fluorine ($F_2$) could be substituted for $CF_3OF$ based on initial reports that its reactivity could be controlled in diluted form.[19] This approach was successful and the fluorination of 3,4,6-tri-O-acetylglucal with elemental fluorine represented a new synthetic route to unlabeled FDG.[20] Fortunately, the methodology for producing $[^{18}F]F_2$ by the irradiation of a neon target containing $F_2$ via the $^{20}Ne(d,\alpha)^{18}F$ reaction by using a specially prepared nickel irradiation vessel had already been developed[21] and applied to the first synthesis of 5-[$^{18}$F]fluorouracil.[22] Thus, electrophilic fluorination of 3,4,6-tri-O-acetyl-D-glucal with $[^{18}F]F_2$ produced a 3:1 mixture of the $^{18}$F-labeled 1,2-difluoroglucose isomer and the 1,2-difluoro-mannose isomers that were separated by preparative gas chromatography. The 1,2-difluoroglucose isomer was hydrolyzed in HCl to produce $^{18}$FDG (Fig 4). The yield was about 8%, the purity was greater than 98%, and the synthesis time was about 2 hours.

Because $^{18}$FDG had never been administered to humans either in labeled or in unlabeled form, there was no adequate safety data to support administration to humans. The literature at the time had one report of an $LD_{50}$ for FDG of 600 mg/kg in rats.[23] This was not sufficient to support human studies. Therefore, toxicity studies were performed in mice and dogs with unlabeled FDG.[5] Doses of FDG were 14.3 mg/kg and 0.72 mg/kg administered intravenously at weekly intervals for 3 weeks for mice and dogs, respectively. There was a control group that was injected with vehicle for each species. Mice were weighed weekly and at the end of 3 weeks they were killed and their organs were examined grossly and microscopically. For dogs, baseline, 2-hour, 1-week, and 2-week blood and urine samples and a few cerebrospinal fluid (CSF) samples were obtained for analysis. At the end of 3 weeks the dogs were killed and their internal organs were examined grossly and microscopically. Neither mice nor dogs who received FDG showed any gross or microscopic differences from their respective control groups. These results indicated that the anticipated dose of 1 mg of $^{18}$FDG (.014 mg/kg) could be safely administered to human volunteers. This was a factor of 150 times less that that administered to dogs and 3,000 times less that that administered to mice without any evidence of acute or chronic toxicity.

Radiation dosimetry was estimated based on the tissue distribution of $^{18}$FDG in dogs killed at 60 minutes and at 135 minutes postinjection of $^{18}$FDG.[4] The target organ in these initial estimates was the bladder, which received 289 mrem/mCi.[2] These estimates were later refined when human distribution and excretion data became available.[24]

These developments: the design of $^{18}$FDG based on a knowledge of structure-activity relationships, the synthesis of $^{14}$C-FDG,[1] autoradiographic comparison of $^{14}$C-FDG and $^{14}$C-2-DG,[2] the synthesis of $^{18}$FDG[1] toxicologic studies of FDG,[5] biodistribution of $^{18}$FDG in mice and dogs,[4] and dosimetry calculations,[2] all combined to support the first studies in humans.

## IMPROVEMENTS AND A MAJOR MILESTONE (1976–1986)

During the next 10 years after the development of the electrophilic route to $^{18}$FDG, its use as a radiotracer in the neurosciences and in the diagnosis of heart disease and cancer grew. This stimulated the investigations of different synthetic methods to improve yields, thereby to increase availability. Other electrophilic

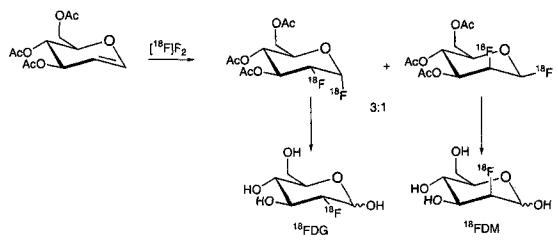


**Fig 4. Synthesis of $^{18}$FDG via fluorination with [$^{18}$F]labeled elemental fluorine.[1]**

routes were developed and nucleophilic routes were sought (Table 2). The most useful of the electrophilic routes was labeled acetylhypofluorite $CH_3CO_2[^{18}F]$, which offered advantages over $[^{18}F]F_2$ in terms of yield and experimental simplicity. Labeled acetylhypofluorite was readily synthesized via in situ formation in acetic acid or via gas-solid phase synthesis by using $[^{18}F]F_2$. However, it was subsequently found that the stereospecificity of acetylhypofluorite was dependent on reaction conditions and solvent with one of the most commonly used methods giving about 15% of 2-deoxy-2-[$^{18}$F]fluoro-D-mannose, an isomer with the fluorine atom occupying the axial position. A reinvestigation and analysis of the product distribution from other fluorination reagents derived from elemental fluorine and showed that they all produce the mannose isomer in varying amounts.[25] The synthesis producing the most acceptable product purity involved the gaseous $CH_3CO_2[^{18}F]$ fluorination of 3,4,6-tri-O-acetyl-D-glucal in freon-11. In this synthesis, the ratio of $^{18}$FDG:$^{18}$FDM was 95:5. Though the effect of using a mixture of $^{18}$FDG and $^{18}$FDM on glucose metabolic rate in the human brain has been reported to be negligible, the use of a mixture was less than ideal because the rate constants and the lumped constants for these 2 molecules could differ in a nonpredictable fashion, introducing a variable in human studies. A kinetic comparison of $^{18}$FDG and $^{18}$FDM in the rhesus monkey indicates that there is a 20% reduction in apparent cerebral metabolic rates for glucose when $^{18}$FDM is used. If this is similar in humans, it was estimated that a 15% impurity of $^{18}$FDM would lead to an underestimation of 3% in glucose metabolic rate.[26]

In addition to the production of the $^{18}$F-labeled mannose isomer, there were other limitations to the electrophilic route to $^{18}$FDG. The nuclear reaction commonly used to produce $[^{18}F]F_2$ was the $^{20}Ne(d,\alpha)^{18}F$ in a high pressure neon gas target to which a small amount of $F_2$ gas was added.[27] The targetry to produce $[^{18}F]F_2$ and its maintenance at the time was cumbersome and handling elemental fluorine, the most reactive of all elements, required special precautions. However, the major limitation was that under the best circumstances, only 50% of the label is incorporated into the product. This is also the case in the use of $CH_3CO_2[^{18}F]$ because half of the label is lost in the conversion of $[^{18}F]F_2$ to $CH_3CO_2[^{18}F]$.

In terms of $^{18}$F yield, another nuclear reaction the $^{18}O(p,n)^{18}F$ reaction, was far superior as can be seen when the cross-sections are compared (Fig 5).[28] The adaptation of the $^{18}O(p,n)^{18}F$ reaction

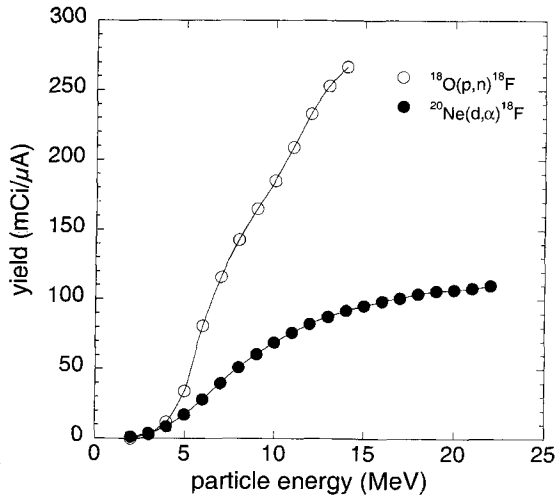


**Fig 5. Comparison of $^{18}$F yields from the $^{20}Ne(d,\alpha)^{18}F$ reaction and the $^{18}O(p,n)^{18}F$ reaction.[27,28] ○ $^{18}O(p,n)^{18}F$; • $^{20}Ne(d,\alpha)^{18}F$.**

to a practical production method that would conserve the inventory of costly and occasionally rare $^{18}$O-enriched water stimulated the development of small volume enriched water targets, which produced $^{18}$F as [$^{18}$F]fluoride in high yield.[29,30] Methods for recovering $^{18}$O-enriched water for reuse have been reported including the use of an anion exchange resin (Dowex 1 × 10) that permits a 95% recovery of [$^{18}$F]fluoride ion and a loss of $^{18}$O-enriched water of less than 5 μL from a volume of 3 mL.[31] With the availability of high yields of [$^{18}$F]fluoride, the development of a high-yield nucleophilic route to $^{18}$FDG became even more compelling. A number of approaches were reported before 1986 (Table 2 for reactions and references [1,32,48-61]). All of these were plagued with difficult steps including low incorporation of $^{18}$F and difficulty in removing protective groups. Thus, the electrophilic route, with its limitations, remained the method of choice through 1985.

A major advance in the synthesis of $^{18}$FDG from [$^{18}$F]fluoride was reported in 1986 when it was discovered that kryptofix [2.2.2] could be used to increase the reactivity of [$^{18}$F]fluoride.[32] In essence, kryptofix masks the potassium ions, which are the

**Table 2. Synthetic Routes to $^{18}$FDG (1976–1986)**

| [[$^{18}$F]Labeled Precursor | Substrate | Reference |
|---|---|---|
| Electrophilic methods | | |
| $[^{18}F]F_2$ | 3,4,6-tri-O-acetyl-D-glucal | 1 |
| $[^{18}F]F_2 \rightarrow CH_3CO_2[^{18}F]$ | " | 48-50 |
| $[^{18}F]F_2 \rightarrow CH_3CO_2[^{18}F]$ | D-glucal | 51,52 |
| $[[^{18}F]F_2 \rightarrow [^{18}F]XeF_2$ | 3,4,6-tri-O-acetyl-D-glucal | 53,54 |
| Nucleophilic methods | | |
| $H[^{18}F] \rightarrow Cs[^{18}F]$ | Methyl-4,6-O-benzylidene-3-O-methyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranoside | 55,56 |
| $H[^{18}F] \rightarrow Et_4N[^{18}F]$ | Methyl or vinyl 4,6-O-benzylidene-α-D-mannopyranoside-2,3-cyclic sulfate | 57-59 |
| $H[1^{8}F] \rightarrow KH[^{18}F]F_2$ | 1,2-anhydro-3,4:5,6-di-isopropylidene-1-C-nitro-D-mannitol | 60,61 |
| $H[^{18}F] \rightarrow$ K[$^{18}$F]Kryptofix 2.2.2 | 1,2,4,6-tetra-O-acetyl-2-trifluoromethanesulfonyl-β-D-mannopyranose | 32 |

counter-ions of the [$^{18}$F]fluoride. The reaction of [$^{18}$F]fluoride with 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranose to give 1,3,4,6-tetra-O-acetyl-2-[$^{18}$F]fluoro-β-D-glucopyranose gives a 95% incorporation of $^{18}$F and the overall synthesis including purification proceeds in about 60% yield. The synthesis involves 2 steps, displacement with [$^{18}$F]fluoride and deprotection with HCl (Fig 6). This was an almost perfect solution to the need to produce $^{18}$FDG in high yield and in high purity. It also produced $^{18}$FDG in no-carrier-added form and later ion chromatographic analysis of various preparations from this route showed the presence of FDG in a mass of 1 to 40 μg.[33] Thus, this new method served an increasing need in the nuclear medicine and the neuroscience communities, which were discovering new uses for $^{18}$FDG. It is also simple and amenable to automation and in the 15 years since it was reported, a number of automated synthesis modules have become commercially available.[34]

## $^{18}$FDG SYNTHESIS (1986 TO PRESENT)

No major new developments have been made following this simple, high-yield, nucleophilic route. However, a number of variants have been investigated to improve the displacement and the deprotection steps, and considerable effort has been put into fine-tuning the reaction and to identifying impurities and contaminants that are carried through to the final product. This has become more critical with the increasing use of $^{18}$FDG in clinical practice where a pharmaceutical-quality product is required.

One of the goals has been to optimize the removal of kryptofix 2.2.2, which is used to facilitate the displacement reaction. Methods have been reported for both the removal[35,36] and the detection[37,38] of kryptofix. The simplest method to remove kryptofix is the incorporation of a short cation exchange resin in the synthesis system so that the hydrolysate (HCl) passes through the cartridge before final purification.[36]

Alternatives to the use of kryptofix 2.2.2 have been investigated to avoid its appearance as a contaminant in the final product. These include the use of tetrabutylammonium as the counter-ion[39,40] as well as the development of a resin-supported form of [$^{18}$F]fluoride for on-column fluorination.[41] The latter method is synergistic with the use of an anion exchange resin to recover $^{18}$O-enriched water for reuse. Several kinds of polymer-supported quaternary ammonium and phosphonium salts such as dimethylaminopyridinium or tributylphosphonium have been systematically examined for the on-column synthesis of $^{18}$FDG.[42]

Alternatives to deprotection with HCl also have been investigated. The use of a cation exchange resin was investigated and reported to efficiently hydrolyze the acetylated-labeled precursor in 10 to 15 minutes at 100°, thereby eliminating the need for a neutralization step in the synthesis[43] and also serving to remove kryptofix 2.2.2. The use of base hydrolysis in the deprotection step also has been investigated as an approach to reduce the need for high temperatures and to decrease the synthesis time. Though epimerization at C-2 is a known reaction of aldoses under basic conditions and in this case would produce $^{18}$FDM as a radiochemical impurity,[44] a systematic study of the reaction conditions for basic hydrolysis determined that epimerization could be limited to 0.5% by using .33 mol/L sodium hydroxide below 40° for about 5 minutes to avoid the neutralization step in the synthesis.[45]

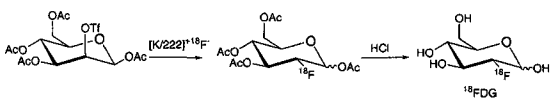


**Fig 6. Synthesis of $^{18}$FDG via fluorination with [$^{18}$F]fluoride ion.[32]**

2-Deoxy-2-chloro-D-glucose (ClDG) was identified as an impurity during ion chromatographic determination of the specific activity of $^{18}$FDG preparations from the nucleophilic route.[33] ClDG is produced as a competing displacement reaction with a chloride ion, which comes from different sources including HCl, used in the hydrolysis step. In typical $^{18}$FDG preparations, ClDG is present in a total amount of less than 100 μg as is determined by ion chromatography and pulsed amperometric detection. Larger amounts are produced when larger amounts of the triflate precursor are used. The amount of ClDG can be reduced by using sulfuic acid instead of HCl for hydrolysis. The reduction of the amount of ClDG has also been an impetus for avoiding HCl in the hydrolysis step. Though ClDG does not present a toxicity problem, its presence is not desirable from the standpoint of pharmaceutical quality.

## OUTLOOK

Advances in chemistry and the remarkable properties of $^{18}$FDG have largely overcome the limitations of the 110-minute half-life of $^{18}$F so that $^{18}$FDG is now available to most regions of the United States from a number of central production sites. This avoids the need for an on-site cyclotron and chemistry laboratory and has opened up the use of $^{18}$FDG to institutions that have a PET scanner (or other imaging device), but no cyclotron or chemistry infrastructure. Currently, $^{18}$FDG is used by many hospitals as an off the shelf radiopharmaceutical for clinical diagnosis in heart disease, seizure disorders, and oncology, the area of most rapid growth. However, its ready availability has opened the possibility to also use it in more widespread applications in the human neurosciences including drug research and development.[46] This is an important application because with $^{18}$FDG it is possible to determine which brain regions are most sensitive to the effects of a given drug. Because glucose metabolism reflects, in part, the energy involved in restoration of membrane potentials, regional patterns may be used to generate hypotheses as to which molecular targets are mediating the effects of the drug. Also, a baseline study can be run, allowing intrasubject comparison before and after the drug. Because subjects are awake and alert at the time of the study, the behavioral and therapeutic effects of the drug and their association with metabolic effects can be measured. Though the use of a functional tracer such as $^{18}$FDG is not as precise as the use of a radiotracer that is more specific for a given neurotransmitter system, it nonetheless provides a measure of the final consequences of the effects of the drug on the human brain. This is important because even though a drug may interact with a particular neurotransmitter, it may be the downstream consequences of that interaction that are of relevance to its pharmacologic effects. When radiotracer availability permits, the ideal situation is to pair an $^{18}$FDG measurement with a neurotransmitter-specific measurement and in that way to correlate neurotransmitter-specific effects with regional metabolic effects. $^{18}$FDG has many advantages as a scientific tool for preclinical

studies in small animals when it is coupled with small-animal imaging devices. Because the $^{18}$FDG method requires an approximately 30-minute uptake period before the imaging is actually performed, the animals can be awake during this period and anesthetized immediately before imaging, thus, avoiding the effect of anesthesia on the behavior of the tracer.

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