Radiochemical Breakthrough Improves PET Imaging

Clinicians rely heavily on positron emission tomography (PET) imaging to diagnose cancer and neurological diseases. Because PET procedures can pinpoint specific biochemical activity in the body, they are valuable for identifying disease in its earliest stages. The full potential of PET technology, however, has not been realized because of the radioactive tags currently available for this type of imaging.

In a typical PET scan, the patient is injected with a radioactive tracer that travels through the body and acts as a beacon — identifying tumors or the uptake of chemicals in specific tissues (*e.g.*, dopamine in the brain). The most widely used radiotag is ^{18}F-2-fluoro-2-deoxyglucose (18F-FDG), a radioactive glucose analog in which a positron-emitting fluorine isotope replaces one of the hydroxyl groups. Fluorine-18 has a short half-life (109.7 min), which allows a patient to be quickly discharged from the hospital with no concern for residual radioactivity. However, the short half-life poses challenges in the preparation of the imaging agent, as the material must be made rapidly and efficiently each day near the medical facility.

Although 18F–FDG is the most widely used radiotag, it is relatively nonspecific, so new fluorine-18 tags are needed. One potential alternative is 18F-fluoroDOPA, but its synthesis is a major challenge. The process is lengthy and involves many steps, and it uses corrosive materials such as fluorine gas — limitations that have precluded the distribution of this valuable imaging agent. In general, the difficult chemistry involved in synthesizing many such fluorine-18 compounds has limited their commercial availability, hampering full realization of the power of PET technology. That is, until now.

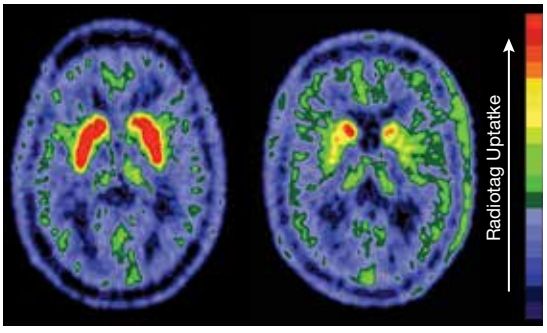
Ground Fluor Pharmaceuticals, a spinout from the Univ. of Nebraska–Lincoln, has developed new fluorination chemistry that permits a wide range of radiotracers with sufficient activity and purity to meet diverse clinical needs to be made with automated commercial radio-synthesis equipment. Ground Fluor Pharmaceuticals' innovation, a proprietary method called Swift Iodonium Fluorine Tagging (SWIFT), is based on the work of Stephen DiMagno at the Univ. of Nebraska–Lincoln.

Using the SWIFT technology, clinicians can make stable, crystalline compounds (*e.g.*, diaryliodonium salts) for fluorination of most chemical ring structures. Ground Fluor has already developed precursors (*i.e.*, formulas destined to be tagged with radioactive isotopes) of PET imaging agents for cancer, cardiac, and brain imaging.

Through research funded by the National Science Foundation that built on prior radiofluorination chemistry work by Victor Pike, currently with the National Institute of Mental Health, DiMagno has successfully demonstrated that low-polarity solvents suppress previously unknown side reactions that severely limited the yields of fluorinated compounds obtained from diaryliodonium fluorides. The discovery of these side reactions in polar solvents was a major breakthrough. Specifically, the discovery that iodine behaves like a transition metal ion suggested that a novel yet simple change in reaction conditions — namely, dissolving the ionic diaryliodonium salts in hydrocarbons and then heating them — would dramatically improve the yield of 18F-labeled compounds. Tests of this hypothesis led to the first reliable, high-yield, scalable synthesis of high-specific-activity 18F-fluoroDOPA. The synthesis time is short (45 min) and well within the half-life of 18F.

Ground Fluor collaborates with the pediatric treatment and research facility St. Jude Children's Research Hospital. "It is incredibly gratifying to see a project focused on such a fundamental process as C-F bond formation evolve into a diagnostic platform that may improve outcomes for kids with cancer," DiMagno says.

Since PET agents are typically injected, strictly controlled manufacturing processes are required to guarantee that the final pharmaceuticals are sterile and pure. Ground Fluor currently offers cGMP manufacture of such PET imaging agent precursors suitable for human use.



▶ 18F-fluoroDOPA is a PET imaging agent used to diagnose brain tumors and Parkinson's disease. In a PET scan of a normal brain (left), the uptake of 18F-fluoroDOPA (colored region) is higher than it is in the brain of a patient with Parkinson's disease (right). The lower tracer uptake (colored region) in the Parkinson's patient correlates with a decrease in neurons able to take up DOPA and make dopamine, a neurotransmitter essential for normal motor coordination. Image courtesy of Ground Fluor Pharmaceuticals.

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