Sustainable PET tracer production at Wisconsin

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Introduction

The University of Wisconsin PET tracer production facility has evolved over four decades, progressing from an EN tandem (1971), the first CTI RDS 112 (1985), an NEC pelletron (1998) and now, a GE PETtrace, bunkered in a new facility. Balancing a mixed assignment of graduate training, basic and clinical research, our emphasis has centered on achieving a *sustainable* campus-wide resource, free from unrealistic expectations or crippling service contracts. The foundation of this self-support is inherent in the state-audited charge-back account within the autonomy of the Medical Physics Department, where users cover the fair share for the development and production of the tracers that they request.

Targetry

We have continued the Wisconsin tradition of making our own cyclotron targets on the new GE PETtrace. Helium cooling has been cast aside in favour of single, gridded entrance windows. The [^{18}F]-fluoride target's niobium body houses a 1.1 mL target volume behind a havar window with a water-cooled grid support described previously.[1] The [^{13}N]NH_3 target is a 304 stainless steel volume of 2.5 mL also behind a havar foil and grid. A 3 mL/min flow of 5 mM EtOH provides a steady state production of [^{13}N]NH_3 trapped on an Alltech IC-Na Plus cartridge. [^{11}C]CO_2 and [^{11}C]CH_4 targets are electropolished 304 stainless steel tubes (25 cm x 1.6 cm dia.), TIG welded inside the water-jacket. These targets are also sealed to the vacuum by the same havar foil /grid system. All grids are approximately 2.5 cm deep with hexagonal holes (2.5 mm across the flats, 0.3 mm septa) electric discharge-machined into aluminum.

Automated chemistry

[^{18}F]-fluoride, [^{13}N]-NH_3, [^{11}C]-CO_2, and [^{11}C]-CH_4 are transported to shielded radiochemistry equipment in the lab adjacent to the vault through narrow bore lines. Aqueous fluoride and C-11 carbon dioxide or methane are remotely unloaded via FEP and stainless steel lines, respectively, and sent to two Capintec (New Jersey) hot cells, each containing a Labview-controlled Scansys (Copenhagen) automated radiochemistry module. [^{11}C] activity can also be piped to the Waisman Institute for Brain Imaging and Research via a "tuned"[2] 300 meter underground PTFE pipeline. Each Scansys module contains a syringe pump-fed 2-dimensional robot with access to reagent vials, two thermally heated, air-cooled reactors, and a microwave module. Customized inserts permit reaction vessels to range in size from 500 uL to 7 mL. Robotic access is provided to additional reagents through 4 banks of 3-way valves, a needle cleaning station, and HPLC injection loop. Three Rheodyne TitanEX 7-port selector valves direct flow through cartridges for in-line separations and filtration, all monitored by miniature Centronix ZP1300 GM tubes. The HPLC

system supports up to 5 separate columns via additional switching valves and includes a column heater as well as a linear scanner gamma viewing any column with one of 8 included ZP1300 (Centronic) GM tubes. Following HPLC purification, the Scansys module also includes a custom evaporator which is capable of removing 10 mL water in ~ 1 min. for reconstitution in appropriate solvents. Drydown, as well as fluid movement throughout the module, can be accomplished with 4 MFC-regulated gas channels, currently plumbed and calibrated for argon, nitrogen, and helium flow. Each module also contains two vacuum pumps capable of pulling approximately 50 mL/min through 1 m of 1/16" ID tube.

To date, we have successfully automated syntheses of [^{18}F]FLT, [^{18}F]FES, [^{11}C]MHED and [^{11}C]DTBZ for animal studies on these systems. Yields are comparable to those obtained with our prior manual chemistries. For [^{18}F]FLT, yields average 10.1 ± 5.1% (decay corrected to QMA trapping, using 10 mg 3-N-Boc ABX precursor) with specific activities of 3.7 ± 1.8 Ci/umol (n=30). [^{18}F]FES yields average 16.9 ± 4.2% (decay corrected to QMA trapping, using 2 mg ABX precursor) with 3.8 ± 1.5 Ci/umol (n=4). Syntheses of [^{18}F]FMISO are planned to follow.

Conversion efficiency from [^{11}C]CH_4, produced in-target, to [^{11}C]MeI by recirculating loop in the new module is 70.0 ± 0.4% (n=28). Automated syntheses of [^{11}C]MHED and [^{11}C]DTBZ on the Scansys module average yields of 16.0 ± 5.8% (n=11) and 36.3 ± 11.6% (n=3) respectively (decay corrected to methylation). Specific activities for both syntheses, decay corrected to EoB, are 8.4 ± 0.3 Ci/umol. [^{11}C]WAY, produced manually from the [^{11}C]CO_2 target, averages 1.4 ± 0.6 Ci/umol at end of synthesis (n=8); decay correction puts EoB specific activity from this target at 9.8 ± 3.3 Ci/umol.

Conclusion

The natural evolution of production capacity at Wisconsin has been driven by the increased demand for PET tracers for molecular imaging, both in basic research and in the clinic. The new PETtrace, bunkered in new facilities, easily handles the call for conventional radionuclides, freeing up the legacy prototype CTI RDS 112 for a new life concentrating on the production of ^{64}Cu for distribution,$^{18}F_2$ for electrophilic fluorination (F-DOPA, FMT), and target development for the production of orphan isotopes.

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