Technical Report DOE/ER/64645-1

DOE grant DE-FG02-08ER64645

Simplification of Methods for PET Radiopharmaceutical Syntheses

P.I., Michael R. Kilbourn, Ph.D.

Abstract

In an attempt to develop simplified methods for radiochemical synthesis of radiopharmaceuticals useful in Positron Emission Tomography (PET), current commercially available automated synthesis apparati were evaluated for use with solid phase synthesis, thin-film techniques, microwave-accelerated chemistry, and click chemistry approaches. Using combinations of these techniques, it was shown that these automated synthesis systems can be simply and effectively used to support the synthesis of a wide variety of carbon-11 and fluorine-18 labeled compounds, representing all of the major types of compounds synthesized and using all of the common radiochemical precursors available. These techniques are available for use to deliver clinically useful amounts of PET radiopharmaceuticals with chemical and radiochemical purities and high specific activities, suitable for human administration.

Aims and Scope:

The goal of this project was to evaluate innovative ways to simplify the preparation of radiopharmaceuticals for routine use in Positron Emission Tomography. Based upon more than three decades of experiences in the delivery of PET radiopharmaceuticals for routine animal and clinical PET imaging studies, we have identified that in fact the single greatest effort in the process involves isolation and purification of the final radiochemical product. In particular, separation of the desired radiochemical from unwanted precursors, organic solvents and toxic co-reagents (e.g., Kryptofix, heavy metal ions) represents the larger challenge to more widespread development and utilization of PET radiopharmaceuticals. The problems of product purification also contributes to the difficulties in obtaining the expected very high specific activities for ^{11}C- and ^{18}F-labeled compounds: chemical impurities (including precursors and byproducts) can contribute to chemical mass levels quantified by HPLC analyses, and are thus assigned as cold mass of the radiochemical and dilute the "apparent" specific activity.

Hypothesis to be tested: Novel synthetic methods employing solid phase supports can speed synthesis of PET radiopharmaceuticals, improving yields and specific activities. These techniques, however, would need to be adaptable to currently available automated synthesis apparatus compatible with the concepts and goals of cGMP (current Good Manufacturing Practice).

Specific Aims:

-syntheses of PET radiochemicals by methods which provide injectable solutions of products without the need for purification to remove undesired precursors or solvents
-syntheses of PET radiochemicals by methods which either eliminate organic solvents or toxic co-reagents, or utilize components compatible with simple formulation and injection
-improvements in measured "apparent" specific activities by reducing or eliminating unrelated mass peaks assigned to product cold mass

Progress report

A number of approaches were taken to try to simplify the overall radiosynthetic procedures. All studies were done using the TracerLab automated synthesis systems produced by General Electric Medical Systems, as these provide a reliable and docuimented synthesis apparatus.

Synthetic approaches attempted included:

Direct reaction of [^{11}C]methyl iodide with solid-phase supported precursors for radiotracer synthesis, in the absence of organic solvents, and selective elution of the desired radiochemical product from the solid phase with solutions of ethanol and water that would be directly useful as intravenously injectable solutions. Studies into the synthesis of [^{11}C]raclopride were performed using a variety of solid pahses, reaction conditions, and elution profiles. Success was achieved at reaction to deliver the radiopharmacetuical, but no solid phase system was identified that allowed for absolutely complete removal (retention) of the synthesis precursor from the final product.

Reactions of [^{18}F]fluoride ion with organic resin-bound synthesis precursors, without an added base or Kryptofix (a chelator for potassium ion), were evaluated. No success was achieved.

Significant success was achieved at adapting the automated synthesis apparatus to accommodate combinations of solution reaction, thin-film radiochemical reactions (so-called "loop" chemistry), and solid-phase supported radiochemical syntheses. It was shown to be possible to thus utilize one reaction apparatus for multiple types of radiochemistry and multiple classes of chemical structures without severe alterations in the design or operation of the apparatus. In particular, use of thin-film and solid-phase supported radiochemistry allows for reductions in the amounts of precursors and organic solvents necessary for production of radiopharmacetuicals. Use of carefully selected solid phases for synthesis can also remove the need for final chromatographic purifications.

Postdoctoral fellows trained

Hoareau, Raphael, Ph.D.

Undergraduate students trained

Runkle, Adam
Schnau, Paul

Publications

Shao X, Hoareau R, Runkle A, Tluczek LJM, Hockley BG, Henderson BD, Scott PJH. Highlighting the Versatility of the Tracerlab Synthesis Modules.
Part 2: Fully Automated Production of [^{11}C]Labeled Radiopharmaceuticals using a Tracerlab FXC-Pro. *J Label Compd Radiopharm*. 2011:54;819-838.

Shao X, Hoareau R, Hockley BG, Tluczek LJM, Park JY, Lee JD, Padgett HC, Walsh JC, Kolb HC, Scott PJH. Highlighting the Versatility of the Tracerlab-FXFN Synthesis Module through Fully Automated Production of [^{18}F]FLT; [^{18}F]MPPF; [^{18}F]NaF; [^{18}F]SFB; [^{18}F]Fluorocholine and [^{18}F]RGD-K5. *J Label Compd Radiopharm*. 2011:54;292-307.

Runkle A, Shao X, Tluczek LJM, Henderson BD, Hockley BG, Scott PJH. Automated production of [^{11}C]acetate and [^{11}C]palmitate using a modified GE Tracerlab $FX_{c\text{-}Pro.}$ *Appl Radiat Isot*. 2011:69;691-698.

Shao X, Hockley BG, Hoareau R, Schnau P, Scott PJH. High efficiency, fully automated preparation and quality control of [^{11}C]choline and [^{18}F]fluoromethylcholine for routine clinical application. *Appl Radiat Isot*. 2011:69;403-409.

Scott PJH, and Shao X. Fully automated, high yielding production of *N*-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB), and its use in microwave enhanced radiochemical coupling reactions. *J Label Compd Radiopharm* 2010:53;586-591.

Hoareau R, Scott PJH. A Novel One-pot Palladium-mediated Synthesis of *N*-[(2-Hydroxyphenyl)methyl]-*N*-(4-phenoxy-3-pyridinyl) Acetamide, the Precursor to [^{11}C]PBR28, a PET Biomarker for the Peripheral Benzodiazepine Receptor. *Tetrahedron Lett* 2010:51;3353-3355.