

Project title: Microfluidic Based Reactions with [¹⁸F]Fluoroform: A Toolbox for Next Generation ¹⁸F-Radiolabelled Medicinal Chemistry Compounds

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Proposal outline

The trifluoromethyl group (-CF₃) is a key medicinal chemistry bioisostere used to alter the bioavailability, metabolic stability, affinity and lipophilicity of novel pharmaceuticals.[1] It is found in a number of notable drug molecules, including fluoxetine, celecoxib and efavirenz. More recently, the CF₃ group has also become a desirable group to radiolabel with fluorine-18 for the development of Positron Emission Tomography (PET) tracers. Whilst there have been several promising reports of PET tracers containing [¹⁸F]CF₃ groups, their radio-synthesis is challenging and suffers limitations of low radiochemical yields (RCY) and low molar activities (MA). The generation of [¹⁸F]CF₃ groups via a -CF₂ carbene intermediate,[2] is one such route, however, low MA's as result of ¹⁸F/¹⁹F exchange limited its suitability for further biological evaluation. Another method based on a manganese catalysed radical fluorination method was limited by its restricted substrate scope.[3] Recently, the reaction of [¹⁸F]fluoroform ([¹⁸F]CHF₃) has been realised as route for the 'direct' or 'indirect' incorporation of [¹⁸F]CF₃ groups into potential PET tracers with improved molar activities and a much broader substrate scope that is necessary for further biological studies.[4] [¹⁸F]Fluoroform, however, is difficult to generate, process and react owing to its volatility (boiling point -82°C), chemical inertness and radioactive nature. Such volatile and inert organic radioactive compounds are therefore challenging to trap and react in a safe, efficient and reproducible way. ***This proposal aims to develop the technology and labelling chemistry to facilitate the trapping and direct reaction of [¹⁸F]fluoroform, and therefore to enable use of this important reagent for [¹⁸F]CF₃ PET radiotracer development.***

We will apply microfluidic technology for trapping, processing and reaction of [¹⁸F]fluoroform. Microfluidic reactors have certain advantages over traditional 'batch' labelling methods for handling small volumes of gases and liquids, shielding from radioactivity, and for enhancing mass and heat transfer. These advantages are due to the inherently small sizes of microchannels and the resultingly larger surface area-to-volume ratios compared to conventional chemical batch reactors.[5] We will use a microfluidic device to efficiently trap volatile [¹⁸F]fluoroform, and thus minimise losses that are currently limiting its reaction and applications for PET imaging. There is now convincing evidence that such microfluidic based reactions can improve the MAs of radiolabelling reactions.[6] We also anticipate that the improved heat and mass transfer rates within the microchannel should also enhance the reaction [¹⁸F]fluoroform and lead to higher RYCs. To demonstrate a proof-of-principle process, we will initially apply the technology to model substrate compounds (e.g. aryl iodides and boronic acids). Key parameters such as: [¹⁸F]fluoroform trapping efficiencies, substrate scope, RCYs and MAs will be benchmarked for these model reactions before attempting the radiolabelling of biologically active compounds.

Translation

There are immediate applications in the translation of this radiolabelling method to study the up-take, biodistribution, metabolism and pharmacodynamics/kinetics of a number of target molecules. A library of selected target molecules is shown in Figure 1; these compounds are chosen to exemplify the radiolabelling methodology using established oncology drugs as a template and these will be applied to imaging in cancer biology models. A focus of interest is brain cancer, specifically metastatic lesions - an area that has an urgent unmet clinical/imaging need. A key target molecule that we anticipate radiolabelling is the pan-PI3K inhibitor Buparsilib which has potential to be used for imaging breast cancer brain metastases. When the radiochemistry methodology is fully established a strategy will be available to demonstrate the BBB penetration of new CF₃-containing drug molecules. Importantly, we aim to open up new patient cohorts for clinical trials that are currently excluded because the imaging agents to show target expression do not currently exist. Ultimately, we anticipate this strategy could be used to stratify relevant cancer patients for a particular therapeutic treatment.

Figure 1. Proposed library of drug compounds for radiolabelling.

Multidisciplinary approach

This is a multidisciplinary project that will comprise elements of **engineering**: microfluidic reactor design and fabrication, development of automated systems, integration of remotely controlled labelling technology, coding etc.; **chemistry**: synthesis of novel reaction precursors, intermediates and catalysts, study of mechanistic aspects, use of state-of-the-art analytical and spectroscopic methods etc.; **radiolabelling**: development of new labelling methodology, fundamentals of fluorine-18 labelling, PET radiotracer development, radioanalytical methods etc.; **biology**: cell culture and assays, radiotracer uptake experiments, translational aspects to in vivo etc.

Supervisory team

Dr Miller will oversee the design aspects of the radiolabelling system, *i.e.* the development of appropriate microfluidic technology, investigation of trapping methods of fluorine-18, optimisation of catalytic aspects of this reaction, provide a greater understanding of the mechanistic aspects of these reactions. Dr Smith will supervise the radiochemistry experiments in laboratories at ICR where fluorine-18 radioisotope is in regular use and [¹⁸F]fluoroform can be produced safely on automated radiochemistry systems. [¹⁸F]Fluoroform has been produced in the Smith laboratories at ICR and successfully used in model reactions. Dr Kramer-Marek is an expert in pre-clinical molecular imaging and will supervise the biological evaluation of radiolabelled drugs.

Literature references

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