^{18}F-Fluorination Reactions and Optimizations using a Parallel Synthesis Reactor

A. Craig[1], K. Kopka[1,2], S. Stadlbauer[1], J. Pietzsch[1,2], M. Laube[1]

[1] Institute of Radiopharmaceutical Cancer Research, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany;

[2] Faculty of Chemistry and Food Chemistry, School of Science, Technische Universität Dresden, Dresden, Germany

Objectives

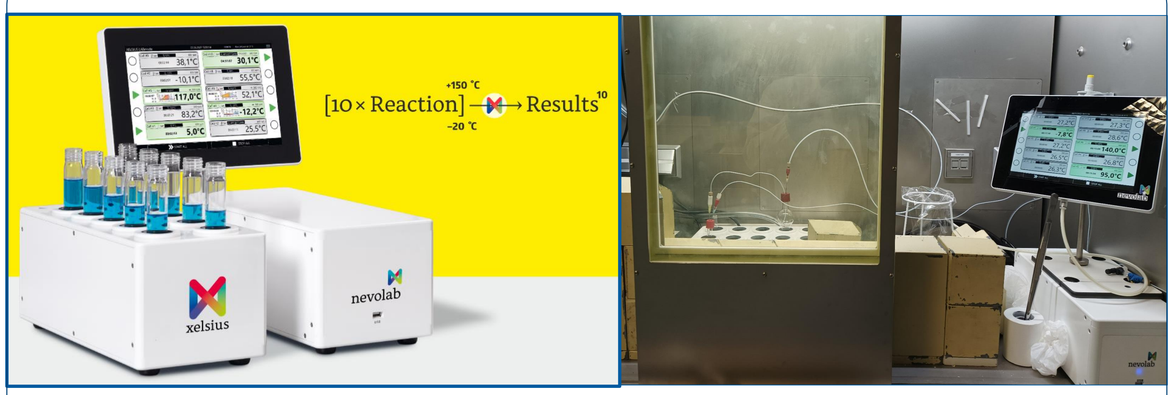

Figure 1: Nevolab's Xelsius® multi-vessel device (left) and its implementation into radionuclide hood (right)

- Preparation of ^{18}F-labeled compounds requires time-sensitive processes including azeotropic drying, ^{18}F-fluorination, deprotection, purification and formulation.
- Recent advances in late-stage ^{18}F-fluorination approaches, such as copper-mediated radiofluorination (CMRF) chemistry, have paved the way for accelerated development of structurally-diverse PET tracers.[1,2]
- CMRF reactions require particular attention with respect to reaction optimization in manual radiosyntheses.[3]
- Herein, the potential of a Xelsius® parallel reactor screening device in manual radiosyntheses and CMRF reaction optimizations is disclosed.

AIM OF THIS WORK: Radiolabeling optimization using Nevolab's Xelsius parallel synthesizer for PET tracer development

Methods

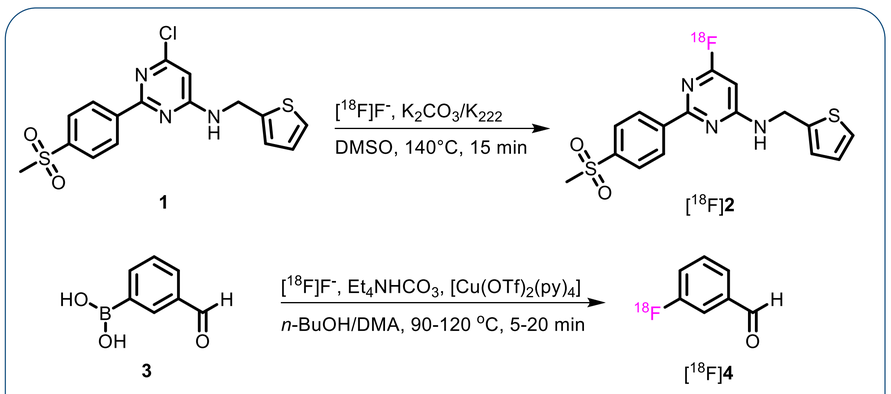

Figure 2: Radiofluorination reactions towards [^{18}F]**2** and [^{18}F]**4**

- Two approaches were tested: 1) Radiosynthesis of an ^{18}F-labeled COX-2 inhibitor [^{18}F]**2**,[4] and 2) A parallel optimization of CMRF on model compound **3** at different temperatures (Figure 2).
- Preparation of [^{18}F]**2** commenced with azeotropic drying at 95 °C, ^{18}F-fluorination at 140 °C, HPLC and SPE purification, and concentration of the final compound at 70 °C. For the radiofluorination optimization of [^{18}F]**4**; dried [^{18}F]fluoride/ Et_4NHCO_3 was reacted with precursor **3** in DMA/*n*-BuOH (4:1) under CMRF conditions in parallel with stirring for 5-20 min at 90 °C, 100 °C, 110 °C and 120 °C, respectively.
- The radiochemical conversion (RCC) values were determined by taking aliquots from the respective vessels at defined intervals and analyzing their contents by radio-UHPLC.

- Radiosyntheses were performed manually using the Xelsius® parallel synthesis reactor (Nevolab, Figure 3) offering ten separately controllable positions to perform reactions between -20 °C and 150 °C.
- Heating steps were performed at separate positions of the device while one position was cooled at -10 °C to trap contaminated distillates.

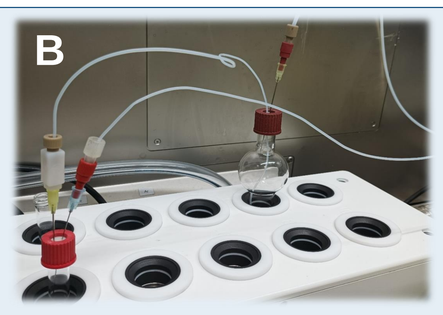

Figure 3 A & B: Xelsius® reaction setup for optimization (left) and azeotropic drying (right)

Results

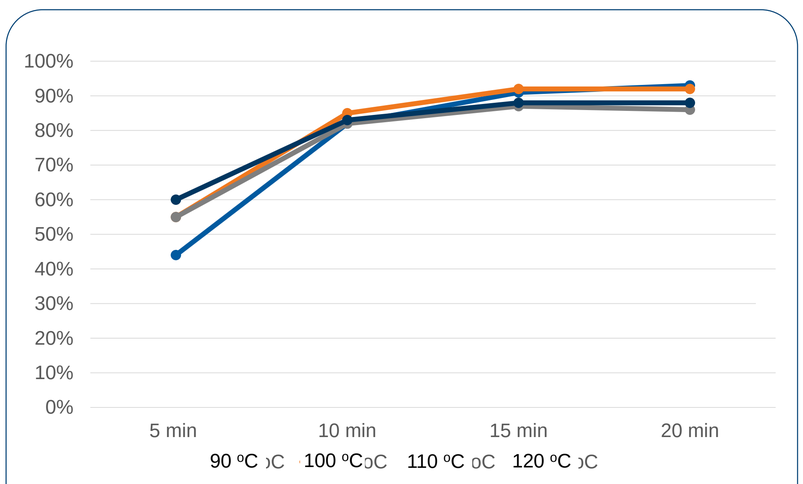

Figure 4: Optimization results of ^{18}F-fluorination of [^{18}F]**4**.

- For both approaches, the radiosyntheses were translated to the parallel synthesis reactor.
- The different heating steps in the multi-step radiosynthesis of [^{18}F]**2** were performed at different positions in the device without the need to wait between the single reaction steps for temperature equilibration.
- Radiofluorination rates for [^{18}F]**4** (Figure 4) at the respective timepoints and temperatures ranged between 44-93% RCC.
- The overall duration for the series of four ^{18}F-fluorination reactions took 1 hour. The use of a reaction vessel as a cooling trap to facilitate the evaporation of MeOH was carried out upon attachment of a cooler.

Conclusions & Outlook

- ✓ Using a parallel synthesis reactor can facilitate multi-step radiosyntheses and optimizations in radiochemistry taking into consideration the space-saving construction of the device and the ability to investigate different temperature conditions at a time as well as the ability to fastly switch between different temperatures.
- ✓ The ^{18}F-labeling results were comparable to previous reports in the literature, and facilitated rapid screening of [^{18}F]**4** preparation via CMRF.
- ✓ Notably, for our initial screening only four vessels were simultaneously used; however, it is anticipated that the use of the six additional vessels would further accelerate ^{18}F-fluorination reaction optimization.
- ✓ The automation of the radiolabeling screening method would be an outlook of this project.

References

[1] B. D. Zlatopolskiy et al. Chem. Eur. J. 2015, 21, 5972-5979. [2] C. Hoffmann et al. Chem. Eur. J. 2023, 29, e202202965. [3] G. D. Bowden et al. Sci. Rep. 2019, 9, 11370. [4] M. Y. Cortes-Salva et al. Molecules 2018, 23, 2850.

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Institute of Radiopharmaceutical Cancer Research

Dr. Austin Craig · a.craig@hzdr.de · www.hzdr.de