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August 12th, 2020

Dr. Rafaela Vasiliadou
Guest Editor, Journal of Visualized Experiments
School of Life, Health, and Chemical Sciences
Open University
UK

Dear Dr. Vasiliadou,

Please find attached our manuscript entitled "Rapid and economical optimization of radiochemical reactions using droplet arrays", which we respectfully submit for the upcoming special collection "Miniaturization of biochemical and chemical techniques" in the *Journal of Visualized Experiments*. The full author list includes: Alejandra Rios, Travis H. Holloway, Jia Wang, and R. Michael van Dam (corresponding author).

In this paper, we describe a new method for economical high-throughput synthesis optimization of positron-emission tomography (PET) radiopharmaceuticals. Due to the unique challenges in this field (radiation hazard, short half-life of radioisotopes), synthesis of these compounds is usually carried out in an automated fashion using "radiosynthesizers". These systems, however, are designed for producing large batches and can only be used on an occasional basis (i.e. typically one waits ~10 half-lives (i.e., 18 hours if using fluorine-18 with 109.8 min half-life) to allow residual radioactivity to decay to background levels before the system can be used again. As a result, optimization experiments are very costly and time-consuming, and only a tiny fraction of the available parameter space can be explored. Instead, we developed a multi-reaction microdroplet chip that contains an array of reaction sites for performing 16 simultaneous droplet-based radiochemical reactions. Each reaction uses minimal reagents and radioisotope, and the timeline and costs for optimization can be compressed 10-fold or more.

Using the synthesis of [^{18}F]Fallypride (a clinically-relevant PET tracer for visualizing D2/D3 receptors in the brain) as an example, we show how this technique is used to optimize one of several synthesis parameters, namely the precursor concentration. The ability to perform 16 reactions in 25 min allowed the optimization to be completed much more quickly than would be

possible using a conventional synthesizer. We believe this approach will be a valuable tool in the field of radiochemistry to accelerate synthesis optimization and to enable the study of reaction conditions in far greater detail than is currently practical. Moreover, the resulting optimized droplet-based reactions intrinsically leverage the advantages of microvolume radiochemistry, including reduced precursor consumption, faster process times, and compact instrumentation, and can offer these same advantages even for routine production of larger batches.

We believe that this work will be of broad interest to readers and viewers of *Journal of Visualized Experiments*, and will be of particular interest to those in the fields of radiochemistry and nuclear medicine (especially those developing new radiotracers, those developing new radiosynthesis/radiolabeling methods, and those developing, optimizing, and translating radiosynthesis protocols into the clinic).

Thank you for considering this manuscript and we look forward to your response.

Sincerely,

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Co-Associate Director, Crump Institute for Molecular Imaging
David Geffen School of Medicine at UCLA