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Editorial:

Automated microfluidic chip system for radiosynthesis of PET imaging probes

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Positron emission tomography (PET) is a powerful non-invasive molecular imaging technique for the early detection, characterization, and "real-time" monitoring of disease, and for investigating the efficacy of drugs (Phelps, 2000; Ametamey et al., 2008). The development of molecular probes bearing short-lived positron-emitting radionuclides, such as ^{18}F (half-life 110 min) or ^{11}C (half-life 20 min), is crucial for PET imaging to collect in vivo metabolic information in a time-efficient manner (Deng et al., 2019). In this regard, one of the main challenges is rapid synthesis of radiolabeled probes by introducing the radionuclides into pharmaceuticals as soon as possible before injection for a PET scan. Although many potential PET probes have been discovered, only a handful can satisfy the demand for a highly efficient synthesis procedure that achieves radiolabeling and delivery for imaging within 1–2 radioisotope half-lives. Only a few probes, such as 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG) and [^{18}F]fluorodopa, are routinely produced on a commercial scale for daily clinical diagnosis (Grayson et al., 2018; Carollo et al., 2019).

Over the years, commonly used PET imaging probes have been prepared using large-scale automated apparatus which has several limitations. This apparatus introduces excessive dilution of radionuclides in a nanomolar scale to generate 400 mL solution for easy handling, but has a detrimental effect on reaction rates. As a result, the specific activity of the PET imaging probe decreases (dose decay), leading to a reduction of its image quality. In addition, the apparatus is optimized for a specific PET imaging probe, and cannot be frequently used to prepare other probes without significant modification. Moreover, the apparatus is bulky and expensive. For example, the model FX-FN from GE® (General Electric Company, USA) is 500 mm×480 mm×600 mm and costs more than 2 million CNY.

Microfluidic devices are capable of rapid organic synthesis and purification of target molecules based on the principles and techniques of fluid control. Together with their small size and reduced reagent consumption, these factors make them suitable for application to automated PET radiosynthesis (Arima et al., 2013). However, only a small number of them have found applications in radiopharmaceutical synthesis, since the microfluidic chips need significant modification and improvement to create an environment for rapid high-yielding radiolabel reaction and purification under digital remote control. Several groups have demonstrated that various steps of conventional batch-wise radiosynthesis can be accomplished by microfluidic devices (Lee et al., 2005; Pascali et al., 2013). Although promising results have stirred up interest in the scientific community, none of these inventions has yet been transformed into an automated microfluidic system for radiosynthesis of multiple PET probes with commercialization potential.

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After 12 years of continuous effort, we have developed the first automatic microfluidic synthesizer for PET probes (Fig. 1). This synthesizer comprises two precision syringe pumps, a multi-position selector valve, a two-position switching valve, and a set of modular microfluidic chips, which realizes a universal synthetic fluid control network system with a volume of 35 cm×28 cm×25 cm. Through the whole synthetic flow control program developed in a computer, the synthetic parameters and sequence of each module can be combined freely according to the synthetic route of the target PET probe, thereby realizing a highly flexible synthesis process. Key synthetic parameters, including reagent volume, flow rate, and temperature, can be automatically modified to set gradients, and can be quickly and automatically screened and optimized. As the core of the synthesizer, the automatic microfluidic fluid handling system enables automated operation and control of complex fluids in processes such as reagent extraction, driving, loading, adsorption and elution of radioactive reagents, and separation and purification of the product. The embedded electronic control system based on a microcontroller (MSP430F1611, Texas Instruments, Dallas, USA) was developed to control the reaction process and monitor the temperature and pressure in the synthesis. The synthesizer can run independently from the computer. The computer-based program, developed by LabVIEW (National Instruments, Austin, USA), can realize remotely the preparation of the synthetic process, control of instrument operation and parameter monitoring. The communication between the embedded control system and the personal computer (PC) program is based on the Modbus RTU (remote terminal unit) protocol.

To realize automated, fast, and efficient synthesis of PET probes, we have made some innovations. Firstly, we developed a reliable "zero dead volume" interface for quartz microfluidic chips. A quartz nut is integrated into the chip and can be piped through a universal threaded head to avoid frequent leakage and damage associated with common quartz chips. Secondly, a "push-pull" liquid drive mode based on a dual syringe pump configuration is applied in the solid phase extraction (SPE) process. The ^{18}F ion concentration process based on SPE is one of the key processes in the synthesis of all ^{18}F-labeled PET probes. A conventional SPE system is based on a unidirectional process. The solution to be enriched and the eluate enter the SPE column from the upper end and then flow out from the lower end. A switching valve is required downstream of the lower end of the column to switch the flow of waste liquid and eluent. In our new synthesizer, a bidirectional design was adopted. After the ^{18}F ions are retained by the SPE column, the eluent is driven through the column reversely by another syringe pump and carries out the adsorbed ^{18}F ions. Therefore, the switching valve required in the conventional SPE process is eliminated. Thirdly, we have developed a method for rapid solvent-drying on a microfluidic chip. The microstructure of the microfluidic channel sidewall is used to capture liquid, and a dry gas through middle of the channel continuously carries away the solvent to achieve a rapid solution-drying and solvent exchange process. It breaks through the technical bottleneck of rapid drying in microfluidic organic synthesis. Fourthly, we have also developed a method for efficient mixing, heating, and pressurization in sealed microchannels. This overcomes the limitation that microfluidic synthesis cannot achieve active mixing in a sealed chip. Finally, based on this microfluidic modular integrated synthesis system, we have established a rapid synthesis method for ^{18}F-FDG and ^{18}F-octreotide. Through multidisciplinary joint research, and exploiting the advantages of microfluidic chip synthesis technology at the micro scale, such as high mass and heat transfer, we have achieved the rapid synthesis of ultra-micro molecular imaging probes. The FDG synthesis time has been shortened from 40 min (conventional synthesizers) to 25 min. The ability to synthesize different molecular imaging probes is also achieved using different synthetic procedures on the same synthesizer.

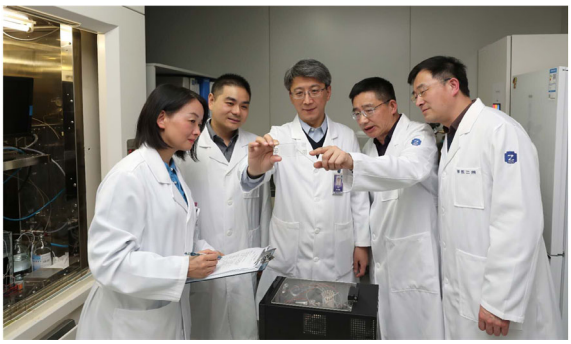

Fig. 1 Group discussion on the automatic microfluidic synthesizer for PET probes

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Compliance with ethics guidelines

Ming LEI, Jian-zhang PAN, Guang-ming XU, Pei-zhen DU, Mei TIAN, and Hong ZHANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：PET 分子影像探针微流控芯片自动合成系统

概　要：放射性核素标记的分子影像探针是支撑正电子发射断层成像（PET）分子影像和核医学诊断应用的关键。微流控芯片自动合成系统可以根据各种不同 PET 分子影像探针的合成工艺，灵活组合微流控芯片模块，微量且高效地合成不同类型的 PET 分子影像探针。这种自动合成系统的成功研制对发展现代 PET 分子影像技术具有重要意义。

关键词：PET 分子影像探针；微流控芯片；模块化；自动合成仪

Introducing editorial board member:

Prof. Hong ZHANG is a distinguished professor specializing in nuclear medicine and molecular imaging. He serves as Chair of the Department of Nuclear Medicine at the Second Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China), Director of the Institute of Nuclear Medicine and Molecular Imaging of Zhejiang University. Prof. ZHANG is also a Distinguished Young Scholar of the National Natural Science Foundation of China (NSFC) and Principal Investigator of the National Key Research and Development Program of China. He has studied and worked in the National Institute of Radiological Sciences in Japan and at London University in UK for ten years. He is the recipient of awards from the Japanese Society of Nuclear Medicine (JSNM), Academy of Molecular Imaging (AMI), American Association for Cancer Research (AACR), American Society of Clinical Oncology (ASCO), and Ministry of Science and Technology of China (MOST). He serves as a member of the Editorial Board of the *Journal of Nuclear Medicine*, *European Journal of Nuclear Medicine and Molecular Imaging*, *Nuclear Medicine Communications*, *Annals of Nuclear Medicine*, and *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)*.