Development of novel amphiphilic PET probes for in vivo imaging of functional lipidic particles

Hiroyuki NEMOTO

Department of Synthetic Organic Chemistry, Graduate School of Pharmaceutical Sciences

Nanocarriers such as liposomes are widely used in the field of drug delivery system (DDS) to improve the pharmacokinetics, the pharmacodynamics and the pharmacotoxics of small drug molecules or nucleic acid medicines. Comprehensive evaluation of their disposition accelerates the development of novel liposomal DDS drugs. Recently, we have developed a new ^{18}F-labeled amphiphilic compound **1** that enables simple and rapid labeling of liposomes. This method allowed noninvasive and real time monitoring of the liposomal behavior in a living body by the PET imaging.

In this study, I have applied our method to labeling red blood cell to monitor its behavior in a living body. However, the incorporation of **1** into the red blood cell membrane was not satisfactory. Therefore, I planned to construct a library of candidates for ^{18}F-probes to label various functional lipidic particles including the red blood cell. I designed phospholipid-mimetic amphiphilic molecules **2** comprising a glycerin moiety as a core, terminally-fluorinated polyethylene glycol as a hydrophilic component, and a long alkyl chain as a hydrophobic one. At first, three compounds with different length of the chain were synthesized each for the hydrophilic and hydrophobic components, and then they were combined to give a set of the candidates. I also devised an effective method to prepare the desired length of the hydrophilic components with high purity.

Rapid and high-yielding introduction of ^{18}F on their precursors was another important issue in this study because fluorine is a weak nucleophile and may cause side reactions due to its high basicity. By applying a reported method (Kim, D. W. et al. *J. Org. Chem.* 2008) to my substrates, I developed an effective fluorination reaction to give **2** in about 60% yields within 45 minutes. The evaluation of efficiency of the synthesized compounds as ^{18}F-probes for in vivo imaging of functional lipidic particles is under investigation, which is believed to contribute to the development of novel liposomal DDS drugs.