Development of PET technology for the pharmacokinetic study of siRNA medicines

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Small interfering RNA (siRNA) is a short double-stranded nucleic acid molecule which induces sequence-dependent gene silencing Gene therapy using siRNA is expected to be a novel treatment strategy. A delivery system bringing siRNA molecules to the targeted tissue is indispensable for establishing siRNA therapy. Many studies on *in vivo* applications of siRNA using drug delivery system (DDS) carriers such as liposomes and micelles have been reported.

The pharmacokinetic study of siRNA is an important stage in the development of siRNAs for use as medicine. For this purpose, we developed a novel technique for labeling siRNA with a positron emitter, ^{18}F, in which double-stranded siRNA was labeled to gain conformational accuracy in examining the pharmacokinetics of siRNA. *N*-succinimidyl 4-[fluorine-18] fluorobenzoate ([^{18}F]SFB) was used as an ^{18}F labeling reagent, and real-time analysis of siRNA trafficking was performed using positron emission tomography (PET). [^{18}F]-labeled siRNA thus prepared was identified by ESI-TOF-MS, HPLC, and autoradiography after electrophoresis. Naked [^{18}F]-labeled siRNA or cationic liposome/[^{18}F]-labeled siRNA complexes were administered to mice, and differential biodistribution of the label was imaged by PET. The former was cleared relatively quickly from the blood stream and excreted from the kidneys; in contrast, the latter tended to accumulate in the lungs. Our results indicate that PET imaging of siRNA provides important information for the development of siRNA medicines.

In conclusion, we developed a novel positron emitter-labeling methodology for siRNA and evaluated the *in vivo* trafficking of [^{18}F]-labeled siRNA by PPIS. The results of the present study suggest that siRNA is stable as a complex with liposomes and should be deliverable to specific tissues depending on the characteristics of the carrier. The designing of a DDS carrier will expand the usefulness of siRNA *in vivo*, and the technology described here may be useful in the development of such siRNA medicines.