Fluorine-Containing Nucleic Acids with the Enhanced Cell Permeability

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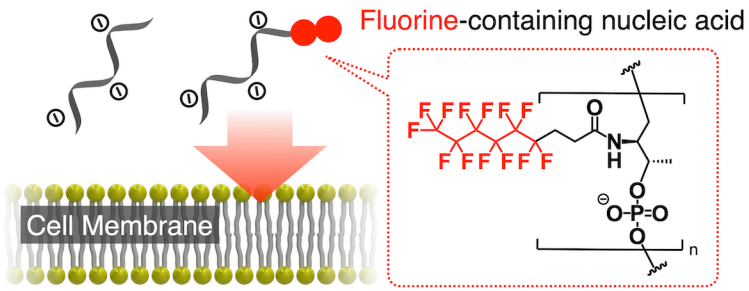
Nucleic acid drugs such as siRNA, mRNA, antisense oligos, and aptamers are expected to have high therapeutic potential for a wide range of diseases including cancer and genetic disorders. However, their practical usage is still limited by their low cell permeability. The cellular uptake efficiency of nucleic acid drugs is commonly improved by assembling with delivery carriers such as polymers, dendrimers, and lipid nanoparticles by electrostatic interactions.[1] The polycationic charge of these materials, while advantageous for their natural affinity for the anionic cell membrane, often results in severe cytotoxicity.

The conjugation of perfluoroalkyl (R_F, C_nF_{2n+1}) groups can be an alternative strategy to enhance the cellular uptake efficiency of DNAs.[2] However, the structures-activity relationship between R_F groups and cell permeation mechanism of R_F group-appended nucleic acids remain unclear.

In this study, we newly synthesized a series of perfluoro (R_F) group-append DNAs using an *a*TNA (acyclic threoninol nucleic acid)[3] backbone. When the perfluorohexyl (C_6F_{13}) group was introduced (Figure; aTNA-$(C_6F_{13})_n$, n = 2–5), the amount of DNA that internalized into cells increased by a factor of 6–8 greater than that of unmodified DNA (n = 0) according to the flow cytometric analysis. We also found that, in PBS buffer, *a*TNA-$(C_6F_{13})_n$ assembled into a micellar structure with 100 nm in hydrodynamic diameter, and internalized successfully into cancer cells via an endocytic pathway.



[1] *Nat. Rev. Drug Delivery*, **2020**, *19*, 673. [2] a) *Med. Chem. Commun.*, **2010**, *1*, 76–78. b) *Polym. Chem.*, **2016**, *7*, 4998–5003. c) *Anal. Chem.* **2018**, *90*, 6843−6850. d) *Theranostics* **2017**, *7*, 3354–3368. [3] *Chem. Eur. J.* **2013**, *19*, 14151–14158.