

P026 An oligoarginine-based cargo-transporter system for improving drug intestinal absorption: utilization of self-cleavable peptide linkers

Kentaro Takayama^{1,3}, Yoshio Hayashi², Yuka Suehisa¹, Takuya Fujita¹, Akira Yamamoto¹, Shiroh Futaki^{3,4} and Yoshiaki Kiso²

¹Department of Biopharmaceutics and ²Department of Medicinal Chemistry, Kyoto Pharmaceutical University, Kyoto 607-8412, Japan; ³Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan; ⁴SORST, JST, Kawaguchi, Saitama 332-0012, Japan

Conjugation with oligoarginine is expected to increase penetration of low permeable drugs through the intestinal epithelial cell layer into blood. Our preliminary experiments showed that conjugation with heptaarginine only slightly increased permeability of the model drugs. A novel self-cleavable linker strategy may be a solution to this problem. FITC-ethanolamine (FE) was chosen as a drug-model with low intestinal permeability. FE-heptaarginines conjugated with a series of self-cleavable linkers having different half lives ($t_{1/2}$ =9-100 min) were developed for efficient intracellular release of FE after cellular uptake. Caco-2 monolayer permeation assay using FE-heptaarginine conjugates showed that the conjugate having a $t_{1/2}$ value of 9 min yielded a basolateral permeation of FE three times higher than FE alone. Other conjugates with longer half lives exhibited slightly increased or similar permeation to FE, suggesting that shorter half lives might be important for improving permeability. These novel peptidic self-cleavable linkers are promising for the development of effective oligoarginine-based cargo-transporter (OACT) systems to enhance intestinal absorption of drugs.