NOVEL NANOCRYSTAL SOLID DISPERSION OF TRANILAST FOR INHALATION THERAPY: BIOMARKER-BASED PHARMACODYNAMIC AND PHARMACOKINETIC CHARACTERIZATIONS
Yosuke Aoki, Takuya Matsui, Yohei Kawabata, Kiyoshi Yamamoto, Hideyuki Sato, Satomi Onoue and Shizuo Yamada
Department of Pharmacokinetics and Pharmacodynamics and Global Center of Excellence (COE) Program, School of Pharmaceutical Science, University of Shizuoka, 52-1 Yada, Suruga-ku Shizuoka 422-8526, Japan

[Purpose] Tranilast (TL) has been clinically used for asthma therapy, although orally-taken TL at high dose sometimes cause hepatic dysfunctions. In the present study, for reducing toxic potential and enhancing topical effect for asthma, dry powder inhaler (DPI) formulation of TL using nanocrystal solid dispersion (NC/TL) was developed.

[Methods] For development of NC/TL-DPI, NC/TL, prepared with wet-milling technology, was micronized with jet-mill, and mixed with lactose carrier. Physicochemical properties of NC/TL-DPI were characterized with focus on crystallinity, surface morphology, thermal behavior, dissolution, and inhalation properties. In vivo pharmacodynamics of NC/TL-DPI was assessed using ovalbumin (OVA)-based experimental asthma/COPD model rats, and pharmacokinetic behavior of TL after oral and intratracheal administration in rats was also evaluated by UPLC/ESI-MS.

[Results and Discussion] NC/TL-DPI exhibited rapid dissolution in water and suitable powder properties for inhalation therapy. Although severe airway inflammation was observed in experimental asthma/COPD model rats, pre-treatment with NC/TL-DPI resulted in marked reduction of inflammatory biomarkers (MPO and EPO) and LDH level in plasma and lung. Airway granulocyte infiltration in response to OVA challenge was markedly attenuated in rats treated with NC/TL-DPI, but not with jet-milled powder of crystalline TL. According to pharmacokinetic data, inhaled DPI at pharmacologically effective dose (0.1 mg/kg) was much lower in C_{max} and AUC values of plasma TL than the oral form at clinical dose (1.7 mg/kg).

[Conclusions] DPI formulation of NC/TL would be efficacious dosage form for clinical treatment of airway inflammations with minimal systemic side effects.

CELL SURFACE MODIFICATION OF MESENCHYMAL STEM CELL MAMBRANE BY LIPID DERIVATIVE
Atsushi Muro, Yuriko Higuchi, Shigeru Kawakami, Fumiyoshi Yamashita, and Mitsuru Hashida
1Department of Drug Delivery Research, Graduate School of Pharmaceutical Science, Kyoto University, Kyoto 606-8501, Japan. 2Institute for Innovative NanoBio Drug Discovery and Development, Graduate School of Pharmaceutical Sciences, Kyoto University Kyoto 606-8501, 3Institute for Integrated Cell-Material Science(ICeMS),Kyoto University, Kyoto 606-8302, Japan.

[Purpose] Mesenchymal stem cells (MSCs) have a great potential in cell-based regenerative therapy. However, because of low adhesion of MSC for targeted inflammatory sight make it difficult to apply MSC by intravenous injection. Hence cell surface modification with ligand for targeting should improve cell based therapy. The purpose of this study was to decorate cell surface of MSC with DSPE derivative.

[Methods] DSPE-PEG_{2000} was conjugated with FITC in pyridine, and dialyzed in distilled water. Human mesenchymal stem cell line, UE7T-13 was given by RIKEN. UE7T-13 was treated with each doses of DSPE-PEG-FITC in each time. The fluorescent was verified by fluorescent microscopy and flow cytometry. ATP was depleted by pre-treatment of sodium azide and 2-deoxyglucose.

[Results and Discussion] The intensity of fluorescent on MSC was increased depending on dose or treated time of DSPE-PEG_{2000}-FITC. Under the ATP depleted condition by sodium azide, DSPE-PEG_{2000}-FITC was observed on cell membrane of MSC. It suggests that lipid derivatives are induced to cell membrane not by active transeptor but passive transport. After incubation DSPE-PEG_{2000}-FITC modified MSC with 10% serum, the intensity of fluorescent on MSC was evaluated by FACS. Cell surface modification was maintained at least 6 hours. The same result was observed by fluorescent microscopy. [Conclusion] Cell membrane of MSC can be stably modified by DSPE-PEG_{2000}-FITC for 6 h.