# 論 文 要 旨

# An inhaled phosphodiesterase 4 inhibitor E6005 suppresses pulmonary inflammation in mice

Shingo Kubota

Abstract

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease associated with significant morbidity and mortality. Although several oral phosphodiesterase 4 (PDE4) inhibitors have been developed for the treatment of COPD, their use has been restricted because of side effects including nausea and emesis. We hypothesized that delivery of a dry powdered PDE4 inhibitor by inhalation would minimize systemic absorption and enable local PDE4 inhibition to suppress inflammation within the lung. Neutrophilic pulmonary inflammation was induced in mice by intratracheal administration of lipopolysaccharide. Mice were treated intratracheally with a new dry powder PDE4 inhibitor, E6005 (methyl 4-[({3-[6,7-dimethoxy-2-(methylamino)quinazolin-4-yl]phenyl}amino) carbonyl] benzoate). The pharmacokinetics, cell profiles and levels of cytokines, chemokines, and lipid mediators in bronchoalveolar lavage fluid (BALF), and lung histology were assessed. Intratracheal administration of E6005 to mice resulted in high concentrations of the compound in the lungs. Histological analysis of E6005-treated mice demonstrated reduced inflammation of lung tissue that correlated with a decrease in BALF levels of neutrophils, proinflammatory cytokines, chemokines, and cysteinyl leukotrienes. Thus, intratracheal administration of E6005 effectively suppresses neutrophilic pulmonary inflammation, suggesting that the new inhaled dry powder PDE4 inhibitor represents an alternative to the conventional oral formulation for treating COPD.