Objective
The present study aimed to clarify the pulmonary disposition of a cyclosporine derivative, IMM 125 (IMM), inhaled as a dry powder consisting of micronized particles for the treatment of asthma. The physiological mechanism of pulmonary accumulation of IMM, as well as the relative exposure of such an immunosuppressive drug between systemic and local (target) sites, were particularly investigated in order to assess the advantages of the inhalation route in comparison with a systemic one.

Method
In vitro study: Alveolar macrophages (mp) were collected by Bronchoalveolar Lavage (BAL) from golden hamsters, washed and incubated with microparticles to measure in vitro uptake.

In vivo study: The microparticles were inhaled to male rats by nose only exposure for 15 min. At various time post-dose, animals were sacrificed and the lung lumenal content by BAL as well as various organs were collected. Drug concentrations in BAL fluid (supernatant and pellet by centrifugation, i.e., dissolved+crystal and mp), blood and various organs were measured by HPLC. The same design of experiment was performed after an intratracheal (i.t.) administration of the drug solution.

PBPK modeling: Presystemic drug disposition was modeled as shown in the scheme below, where fractions of inhalation dose are either deposited in the lung lumen or swallowed into the digestive organs. The microparticles in the lung are considered either to be incorporated to tissue, to exist in the lumen, or to be associated with mp. Both pulmonary and intestinal absorptions are considered. The systemic drug disposition is fixed with a formerly developed PBPK model.27

Results and Discussion
The suspended IMM particles were progressively incorporated into the mp in vitro. An ultrastructural microscopic observation using a stereological method suggested phagocytosis as the uptake mechanism. This mp loaded IMM was stable; mp/medium ratio was 70% after 6 days of incubation. The uptake dynamics is not far different from the inert insoluble reference (latex) but a dose-dependent tendency was observed for IMM (Fig. 1), due presumably to the difference in structural (crystalline vs. spherical) or physicochemical properties (hydrophilicity, etc.).

In vivo study in rats consisted of inhalation (powder) and i.t. (solution) administrations; the latter was for evaluating and modeling the PK process of drugs which were dissolved from the lumenal microparticles. Elimination of Lt. dose from the lung was fairly rapid, suggesting a rapid pulmonary absorption or mucus transfer, while that after inhalation was substantially slow. The result indicates that dissolution or mp retention of microparticles is the rate-determining process of the lung clearance after inhalation. Indeed, a progressive microparticle uptake into mp was similarly observed in vivo as in the in vitro system (Fig. 2). All the in vivo data were integrated and analyzed
simultaneously by a hybrid PBPK model (scheme); the optimized model was justified by its reproducibility of the *in vivo* data as shown in Fig. 2. According to the best fit model parameters, the half-life of *in vivo* drug uptake into *mp* was 8 h, while the disappearance rate of this *mp*-retained drug from lung was even slower (t<sub>1/2</sub> = 3 days). A 1st-order kinetics was assumed to describe this biological process; while inconsistent with the *in vitro* finding, a good agreement between predicted and measured *mp* drug level after 2 weeks suggested that the assumption approximates this *in vivo* kinetics. The recovered drug amount in *mp* fraction accounted for only 1/5 of total lung level, therefore *mp*’s existing in the interstitial space (lung-tissue-associated *mp*) were considered to play an important role in lung accumulation of dry powder drug. The model, reflecting the lung accumulation PK for 2 weeks, also predicted fairly well the lung measurement of 26-week multiple inhalation, suggesting that this lung retention performance is unchanged during such a long period.

Absorption of IMM occurs from both pulmonary and intestinal route with comparable contributions at steady state according to the best fit parameters, despite more than 85% swallowed into intestinal route, perhaps due to the slow dissolution rate, thus low bioavailability, of crystals from intestinal route. The fact seems to justify the advantage of inhalation. The model was then scaled-up to the larger mammals. Prediction and comparison with toxicokinetic data in dogs demonstrated that predictability of inhalation PK is successful with reasonable adjustment of model parameters taking into account the apparent interspecies difference. Human PK was predicted accordingly (Fig. 3); both blood and lung concentrations increased progressively along with the daily multiple treatment. Fraction of lung exposure which is accounted for by direct lung delivery (i.e., inhalation) reaches 50-60% and the rest is systemic exposure via blood perfusion. Considering that systemically delivered drug distributes to the whole tissue while inhalation target the drug to efficacy site (bronchiolar surface), the actual targeting efficiency by inhalation seems more than shown in Fig. 3. The PBPK model also predicted such PK profiles in different physiological conditions, such as inspiration skill by patient, effect of food consumption (gastric emptying), systemic clearance, etc., which were helpful to optimize the clinical study program.

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**References**

2) I. Maye et al., Cell Biol. Toxicol. submitted 1997