Pharmacokinetics and biodistribution of rapamycin delivered as inhalable particles to mice

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Introduction
Inhalable rapamycin (RAP) particles targeting lung macrophages were prepared to investigate induction of autophagy in these cells and its role in clearance of intracellular Mycobacterium tuberculosis. RAP shows nonlinear pharmacokinetics in patients, with a plasma half-life of 57-62 hrs but only 6.4 hrs in mice. To obtain a clearer understanding of inter-species differences in pharmacokinetics and therapeutic efficacy, RAP biodistribution was established in mice following intravenous and inhalation dosing.

Material and Methods
Animals (n=3) received single doses of 0.2mg/Kg RAP either by intravenous injection or inhalation. Bronchioalveolar lavage (BAL) cells and fluid, blood, and 11 tissues were collected at indicated time-points after dosing. Drug was extracted with acetonitrile and estimated using LC-MS.

Results and Discussion
Plasma concentration profiles after intravenous injection suggested biphasic elimination. Inhalation of identical doses resulted in 1/3rd plasma concentrations, and sustained release. Concentration profiles in BAL cells revealed sustained intracellular concentration upon inhalation. Drug distribution following i.v. dosing indicated that RAP is primarily concentrated in red blood cells due to its high affinity for immunophilins. The order of distribution from highest to lowest was: plasma >blood cells >liver >lung >kidney >small intestine >pancreas >BAL cells >muscle >testis >heart >brain> urinary bladder > Spleen >BAL fluid. Following inhalation, the maximum amount of drug was recovered from BAL cells, confirming preferential targeting to alveolar macrophages. Comparing tissue to plasma ratios (Ktp) after 48 hrs of dosing by the two routes, an increase from 0.3 to 40 for BAL cells and decrease from 30.23 to 1.75, 35.26 to 1.26, 43.01 to 0.69 for Kidney, liver and spleen respectively were observed, confirming reduction in drug exposure to non-target tissues when RAP was administered as inhaled particles.

Conclusion
Inhaled RAP particles targeted lung macrophages, sustained intracellular concentrations and spared non-target tissues.

Keywords: Rapamycin, Pharmacokinetics, Tissue to plasma ratio, Pulmonary delivery.