Experimental model to investigate aerosol drug delivery and pharmacokinetics in pulmonary medicine

Guillon A[1,2], Lhommet P[2], Pardessus J[1], Boixel C[4], Montharu J[3], Schubnel V[3], Blanchard R-H[4], Battut C[4], Perrot F[4], Marchand D[1], Plante B[3], Aubert C[3], Roseau G[3], Patin F [5], Respaud R[1], Parent C[1], Bernard L[4], Dudzicki A[4], Guillot E[4], De Monte M[3], Janiak P[4] and Heuzé-Vourc'h N[1].

[1]Research Centre for Respiratory Diseases INSERM U1100, University F. Rabelais, Tours, 37032, France
[2] CHU de Tours, Services de Réanimation Polyvalente, de Chirurgie Thoracique et de Pharmacie, France
[3]PST Animaleries, Université F. Rabelais de Tours, France
[4]Sanofi, Chilly-Mazarin and Alfortville, France
[5]CHU de Tours, Laboratoire de Biochimie et de Biologie Moléculaire, France

Keywords: aerosol, aerosoltherapy, pharmacokinetics, lung microdialysis, respiratory diseases
Presenting author email: antoine.guillon@univ-tours.fr

The development of new drugs or vaccines requires regulatory preclinical studies involving the use of animal models to test the effectiveness, kinetics and toxicity of the candidate medicines. Although inhaled drug deposition and lung anatomy/physiology may be different between animals and humans, rendering extrapolation across species difficult, animal models are crucial to analyze the pharmacodynamics effects and the behavior of aerosolized drugs.

Pharmacokinetic (PK) studies aim at describing the concentration time course of pulmonary delivered drug, after their deposition within the respiratory tract. There are several methods to assess the pharmacokinetics of drug delivered through the airways, each of them with specific strength and weakness. Classically, PK parameters are estimated by monitoring drug concentrations in the systemic circulation, then computed in mathematical compartmental models to predict the behavior of both local and systemically acting drugs. For biotherapeutics, like monoclonal antibodies (mAbs) that do not diffuse passively into organ/tissue compartments, indirect estimation of lung concentrations by modeling from plasma drug profiles is limited and sometimes biased. Therefore, the objective of this project was to develop a new method to quantify the time-course exposure of inhaled mAb by direct sampling in the lung parenchyma using microdialysis.

In vivo microdialysis is an interesting and well-established semi-invasive pharmacokinetic sampling technique to determine tissue drug kinetic (Elmquist WF Pharm Res. 1997; Zeitlinger M 2005; Brunner M AAPS J. 2006; Dhanani J Int J Antimicrob Agents. 2010). Because, it does modify body fluids and blood homeostasis, it allows the repeated measurement of the unbound and/or soluble drug in the interstitial space from the same animal, which substantially reduced their number for preclinical PK studies. This method is based on the use of a probe, implanted in the tissue of interest, equipped with a semi-permeable membrane, which is continuously perfused with a physiological solution (perfusate) at a very slow flow rate (usually 1 to 10 µL/min) . The substances/drugs in the interstitial space fluid diffuse passively through the membrane pores, along their concentration gradient, and are collected at appropriate time intervals. Technically limited so far to follow the kinetic of neurotransmitters in neurosciences and to monitor small drugs in peripheral tissues, microdialysis can be used now, thanks to higher molecular cut-off membrane and push-pull methods, to monitor the behavior of larger molecules, such as proteins.

Herein, we attempted the dynamic quantification by microdialysis of mAbs in the interstitial lung space. *In vitro*, the recovery of mAbs with a 1 million Da cut-off semi-permeable membrane allowed 34% mAb recovery and sampling rate every 180 min with a flow rate of 0.3 µl/min. *In vivo*, we evaluated lung microdialysis in non-human primates (NHPs), a relevant animal model for both biotherapeutics and aerosols therapy. Immediately after delivery of mAb aerosol in conscious NHPs, a microdialysis probe was implanted into the lung by thoracic surgery and animals were thereafter maintained under prolonged anesthesia and mechanical ventilation for at least 55 hours. Microdialysate and blood were collected at time intervals for the determination of mAbs and endogenous/control markers to ascertain the permeability of the probe and determine *in vivo* mAb recovery.

Overall, we established conditions for lung microdialysis of inhaled mAbs targeting soluble-antigens, but this technique remains challenging.

This work was supported the French National Research Agency under the program "Investissements d'avenir", Grant agreement: LabEX MAbImprove ANR-10-LABX-53-01, from SANOFI and from Region Centre Grant "Micropulm" (IA 2015).

Elmquist WF et Sawchuk RJ. (1997) *Pharm Res.*14(3):267-88.

Zeitlinger M *et al.* (2005) *AAPS J.* 7(3):E600-8.

Brunner M et Langer O. (2006) *AAPS J*. 8(2):E263-71.

Dhanani J *et al.* (2010) *Int J Antimicrob Agents.* 36(6):491-500.