

# DISCOVERY SERVICES

## ***In vivo* Pharmacokinetics**

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### **Background**

One of the primary reasons cited for the failure of new drug candidates in clinical trials is the lack of a suitable pharmacokinetics (PK) profile. It has been estimated that almost 40% of the attrition of all drug candidates is linked to poor PK.<sup>1</sup> Despite that valuable insight is obtained from *in vitro* ADME (absorption, metabolism, distribution and excretion) screening assays, *in vivo* drug exposure is still emphasized by drug discovery teams when making decisions about molecules within an SAR. Plasma concentration *versus* time profiles are essential for deriving a more detailed analysis of drug exposure in terms of both PK and toxicokinetics (TK). Due to recent advances in the throughput of liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods, early stage PK data is typically obtained in parallel with pharmacological testing allowing early relationships to be examined between exposure and efficacy.

In selecting lead compounds from drug discovery programs for preclinical drug development, it is essential to select those exhibiting the appropriate PK profile in order to achieve the desired pharmacological action and to minimize side-effects. For efficacy, adequate compound doses must be delivered to the target tissues so that therapeutic, yet non-toxic levels are obtained. The speed of onset of compound action, the intensity of the compounds effect and the duration of action are all controlled by the combined ADME properties of the compound in the body. Good oral bioavailability allows a lower dosage to be administered. Appropriate distribution of the compound to the site of action maximizes

efficacy. Extensive metabolism contributes to low oral bioavailability and may give rise to toxic metabolites. Renal and/or biliary excretion in addition to metabolism is generally desired for the elimination of the compound. Thus, the determination of key pharmacokinetic parameters such as oral bioavailability, plasma clearance, volume of distribution and mean residence time (or plasma half-life) are critical for selecting the best compounds to move forward into development.

### **NoAb's *In vivo* PK Studies**

At NoAb BioDiscoveries, we design and perform PK studies according to your needs. We have a government-approved vivarium which houses small rodents, including rats and mice. Our studies typically involve the use of fully conscious animals which have been appropriately cannulated for drug administration and sample collection. Our skilled scientists are trained to perform your protocols while adhering to the strict guidelines on the treatment of animals. While our studies are not performed according to GLP guidelines, they are performed under the same spirit with the proper controls.

In addition to the standard PK studies, we are currently validating two specialized techniques to be offered to our clients. These techniques are microdialysis and cerebrospinal fluid (CSF) collection.

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<sup>1</sup> Prentis, R.A., Lis, Y. and Walker, S.R. Pharmaceutical innovation by the seven UK-owned pharmaceutical companies (1964-1985). Br. J. Clin. Pharm. 25: 387-396 (1988).

## ***In vivo* ADME Studies**

- PK characterization in rats & mice
- Microdialysis
- Cerebrospinal fluid collection

### ***Microdialysis***

Drug penetration into the central nervous system (CNS) is of vital importance in characterizing a compound for potential efficacy and/or toxicity. CNS penetration is beneficial for drugs intended to treat neurological or psychiatric disorders where therapeutic targets reside mainly within the CNS, whereas it is not desirable for drugs intended to treat peripheral diseases. Presently, there are few rapid throughput *in vitro* models that can be used to test compounds for their ability to penetrate the CNS. Of the available *in vitro* assays, bovine brain endothelial cell (BBEC) cultures are the most predictive of blood brain barrier (BBB) penetration, however, the barrier is relatively leaky. *In vivo* models of CNS penetration are still the most reliable.

Microdialysis is a sampling technique allowing the *in vivo* measurement of endogenous and exogenous substances in the extracellular fluid surrounding a dialysis probe implanted into an organ or tissue. In a typical microdialysis study, two probes are implanted into an animal, one into a specific brain area of interest and the other into the jugular vein. The brain probe allows sampling of the brain interstitial fluid concentrations of a drug candidate at its predicted site of action, whereas the jugular vein probe allows sampling of the unbound concentration of the drug candidate in plasma. Brain and plasma dialysate

concentrations of the drug candidate are determined by LC-MS/MS methods. Comparison of brain to plasma concentration ratios and the corresponding areas under the concentration *versus* time curves (AUCs) allow for an evaluation of the transport characteristics of the drug candidate across the BBB. For this model, NoAb uses conscious, freely moving rats.

### ***Cerebrospinal Fluid Collection***

The CNS contains two regulated fluid compartments, the interstitial fluid that surrounds the neurons and glia and the CSF that fills the ventricles and cushions the external surfaces of the brain. In several instances, the CSF concentration of a drug candidate is indicative of its brain concentration. Since the time course of drug in the CSF and plasma following *i.v.* administration may be readily examined, we will also be offering this model.

In this model, cannulas are placed into the femoral vein and artery for drug candidate administration and blood sample collection, respectively, and a third cannula is inserted into the cisterna magna for CSF collection. CSF is collected serially up to 6 hours following drug candidate administration. Rats remain anesthetized throughout the study. Drug candidate concentrations in plasma and CSF are determined by LC-MS/MS methods.

At NoAb BioDiscoveries, we strive to provide our clients the necessary *in vivo* pharmacokinetic models in order for our clients to select their best compounds for development. Please contact us for further information.