MONASH University

CENTRE FOR DRUG CANDIDATE OPTIMISATION

# IN VIVO PHARMACOKINETICS

Pharmacokinetics (PK) characterises the absorption, distribution, metabolism and excretion (ADME) properties of a drug candidate, allowing identification of limiting features in relation to the desired route of administration. Coupled with the results from in vitro screens, in vivo ADME data enables the early identification of compound liabilities, providing a basis for structural modifications or for the early initiation of development strategies to overcome these problems.

The Centre for Drug Candidate Optimisation (CDCO) examines ADME properties for selected candidates within a chemical series after administration to small laboratory animals such as rats or mice.

A rat pharmacokinetic study for a novel compound at the CDCO typically includes the following steps:

- assessment of a number of formulation approaches to facilitate solubilisation in vehicles suitable for the intended route of delivery
- cannulation of carotid artery for blood collection (and jugular vein for intravenous administration)
- dose administration via various routes (IV, IP, SC, PO, IM and others by request)
- serial blood collection for characterisation of the plasma concentration-time profile using a Culex™ automatic blood sampling system
- LCMS bioanalysis is used for the quantitation of compounds in plasma or other biological fluids such as urine or bile, providing rapid method development and high specificity and sensitivity.
- determination of pharmacokinetic properties (including $C_{max}$, $T_{max}$, AUC, $V_d$, bioavailability)

Research platforms include:

- In vivo PK and bioavailability (rat/mouse)
- In vivo exposure to inform efficacy studies
- Formulation development for PK and early stage efficacy and toxicity studies
- Renal and biliary excretion
- Brain uptake (rat/mouse)
- Dose dependency of PK and bioavailability
- Administration of concomitant therapies or mechanistic inhibitors
- Plasma protein binding
- Whole blood-to-plasma partitioning ratio
- Stability in blood or plasma
- Assessment of in vivo metabolite formation

Early assessment of in vivo ADME properties provides critical data for the validation of in vitro screens (based on physicochemical and metabolic profiles) and establishment of in vitro / in vivo correlations.

In addition to the methods described above, the CDCO uses a number of other approaches to characterise individual processes that underpin the exposure profile, including the stability of a compound in blood or plasma, the binding of drug to plasma proteins, distribution into red blood cells and in vivo studies to determine the role of cytochrome P450-mediated metabolism using specific and non-specific enzyme inhibitors.

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NCRIS National Research Infrastructure for Australia
An Australian Government Initiative