PK & Biotransformation Reactions - A Sampler

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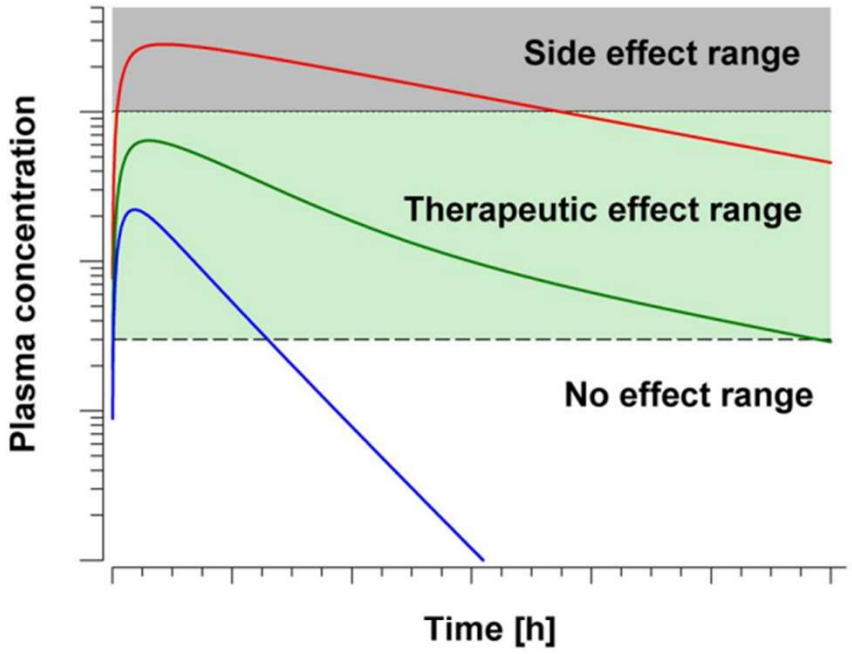
Why do we investigate the PK of drugs?

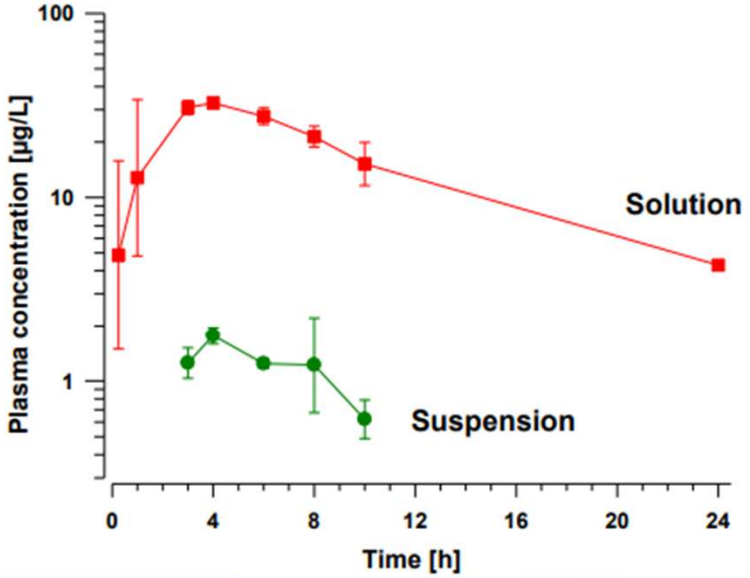


PK properties are intrinsic to molecules and need to be evaluated very early in the research phase identifying the molecule with the optimal therapeutic coverage

PK Parameters:
Exposure

- is a measure for the amount of drug that an organism has really "seen"
- is determined from the (unbound) plasma concentrations, measures are area under the curve (AUC) and C_{max}
- is dependent on dose, route, formulation and species

Plasma Concentration of Drug A After an Oral Administration of 0.5 mg/kg As a Solution and a Suspension Formulation

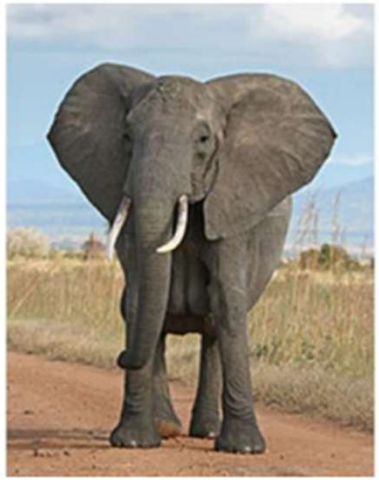


"Exposure response" is more meaningful than "dose response"!

PK Species Scaling
Background of Allometric Scaling (1)

- Although the body weight of mammals varies over a very wide range the body temperature is almost the same

Etruscan shrew
body weight about 0.002 kg



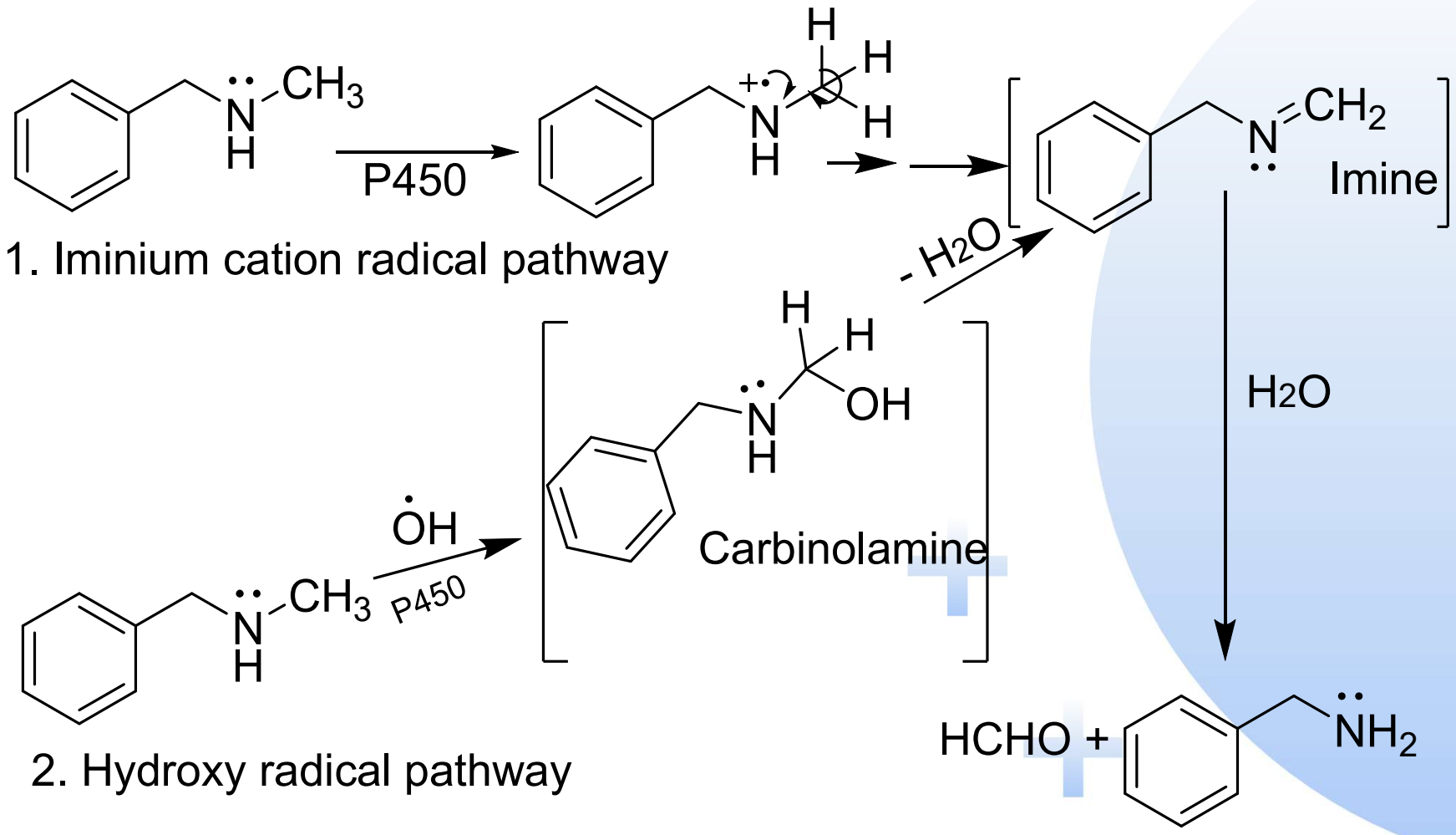
African elephant
body weight about 11 000 kg

- Increase in size leads to a smaller ratio of surface area / body weight.

PK Species Scaling
Background of Allometric Scaling (2)

- With the smaller ratio of surface area / body weight in larger mammals, an adaptation was needed to keep the body temperature constant.
- Evolution has adopted the **metabolic rate** to cope with that, the physiological setup and biochemical processes remained the same.
- Same as for the surface area, the correlation of metabolic rate to body weight follows an allometric equation: **metabolic rate $= a \times BW^{b}$**
- The correct value for the **exponent b** is still under debate; while there are many papers supporting a value of **0.75**, there are also a lot of data supporting a value between 0.67 and 0.75

N-Dealkylation



In Vitro Metabolic Systems

Drug Metabolizing Enzymes (**DMEs**) In Various Liver Fractions

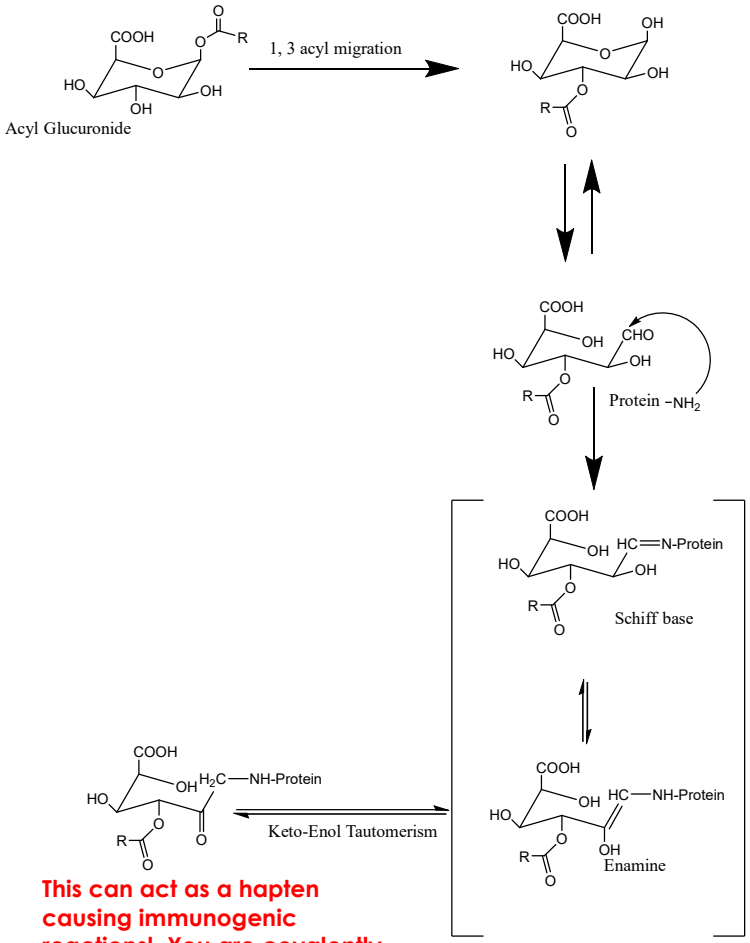
in vitro System	Functional Enzymes	Co-factors to be supplemented	Prediction of clearance by in vitro-in vivo scale-up
Microsomes	CYP450s, reductases	NADPH	yes
	Flavin Monooxygenases (FMO)	NADPH	yes
	Amidases, Esterases	no	no
	microsomal epoxide hydrolases (mEHs)	no	no
	UDP-Glucuronosyltransferases (UGTs)	UDPGA and detergent	no
	Sulfotransferases (ST)	PAPS	no
	Glutathione S-transferases (GST)	GSH	no
	Xanthine oxygenases (XO)	NAD	no
	Esterases and amidases	no	no
S-9	CYP450s, reductases	NADPH	uncertain
	FMOs	NADPH	uncertain
	UGTs	UDPGA and detergent	uncertain
	STs	PAPS	no
	GSTs	GSH	no
	N-acetaltransferases (NATs)	CoA	no
	AO, XO, esterases, amidases, mEHs	NAD	no
Mitochondria	e.g. Monoamine oxidases (MAO)	no	no
Hepatocytes	all enzymes activities	no	yes

Only two of these *in vitro* systems are amenable to scaling

(*In vitro* to *In Vivo* Extrapolation/Scaling;abbreviated as "IVIVE")

Metabolism is <u>not</u> always synonymous with detoxification ! Bioactivation should not be overlooked

Acyl Glucuronides-Why are they a Liability in Drug Development "Amadori Rearrangement"



This can act as a hapten causing immunogenic reactions! You are covalently modifying native proteins

History. The Amadori rearrangement was discovered by the organic chemist Mario Amadori (1886–1941), who in 1925 reported this reaction while studying the Maillard reaction.

Mario Amadori

ADME in a Nutshell