Allometric scaling and Physiologically-Based PK Modelling (PBPK)

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The effect of body size on PK

What is the effect of body size on PK?

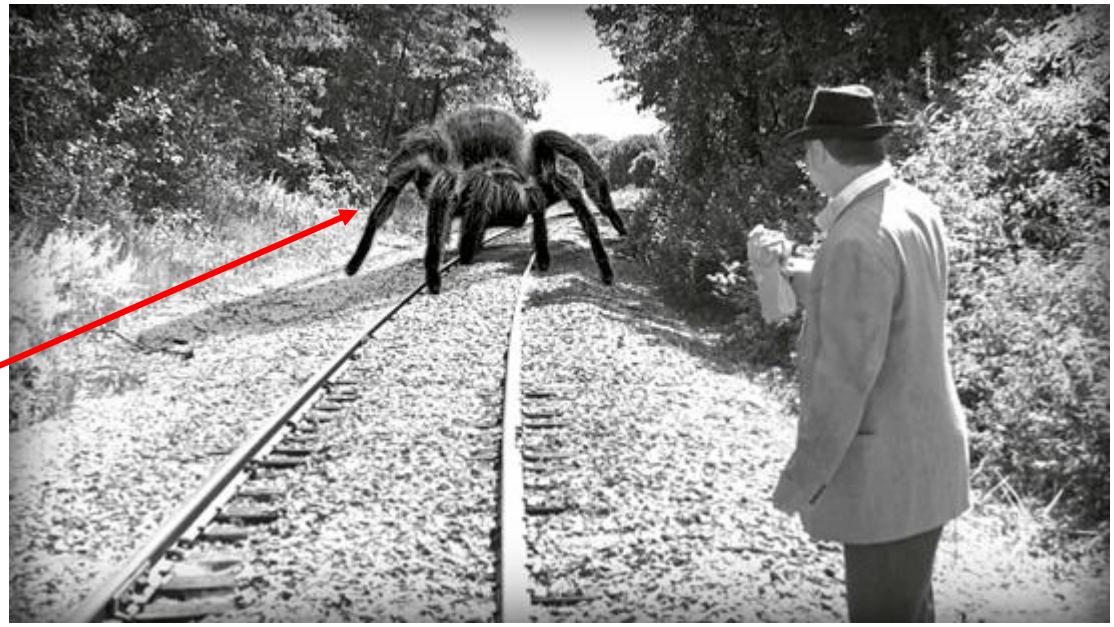
Between humans of different size?

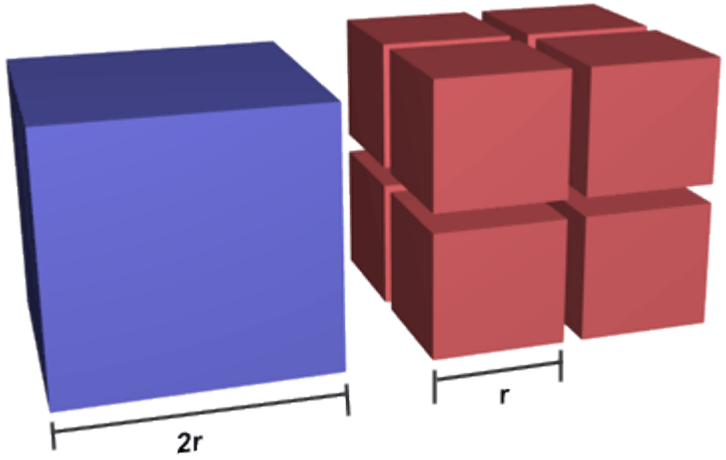
And between different species?

Allometric scaling

Why can't we just scale everything **linearly**?

For the same reason why you cannot just simply scale up a spider **to this big…** ☺





Lengths, surfaces, and volumes increase with different exponents.

So the section of the legs would not be large enough to support the weight of the mega spider

Allometry

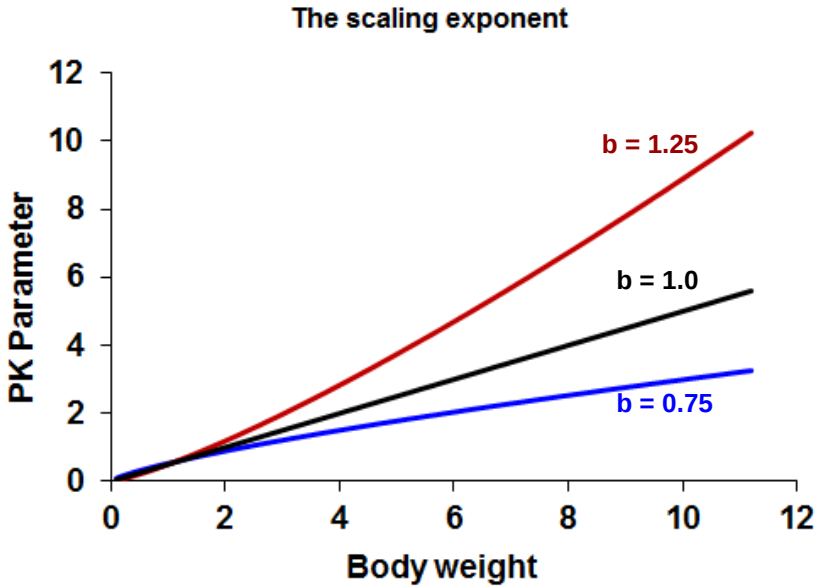
A surprising number of processes can be described using this power function:

$$Y = a \cdot BW^b$$

and after log-transformation, it becomes linear:

$$\log Y = \log(a) + b \cdot \log(BW)$$

Y → PK parameter (not weight normalized)
a → allometric coefficient (y-axis intercept of log- data)
BW → Body weight
b → allometric exponent (slope of the log line)



b=1.25
Y increase faster than BW
Positive allometry

b=1.0
Y increase proportionally with BW (isometry)

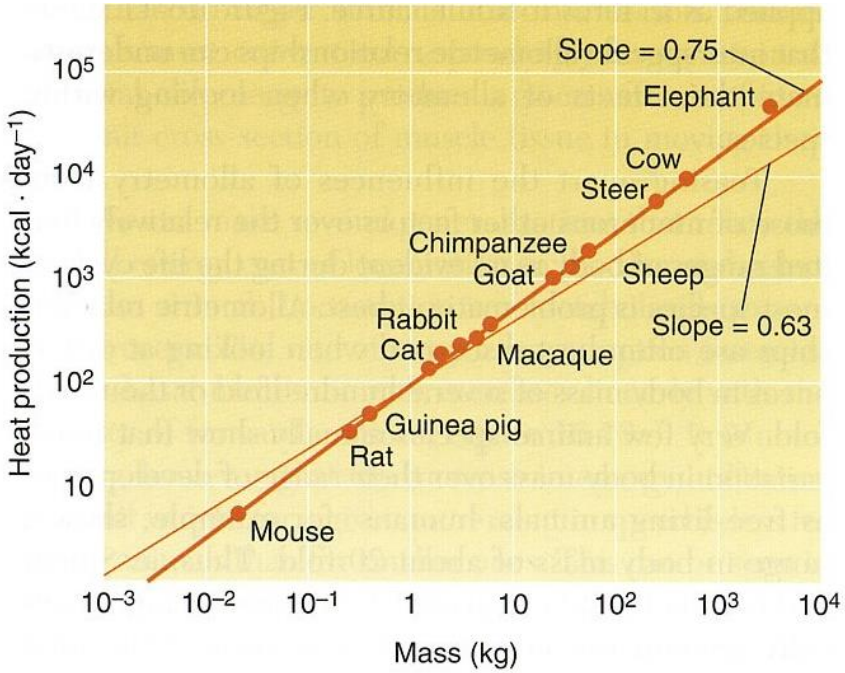
b=0.75
Y increase slower than BW
Negative allometry

Allometric Inter-Species Scaling

Studies have analysed how body size determines variation of PK parameters (also between different species)

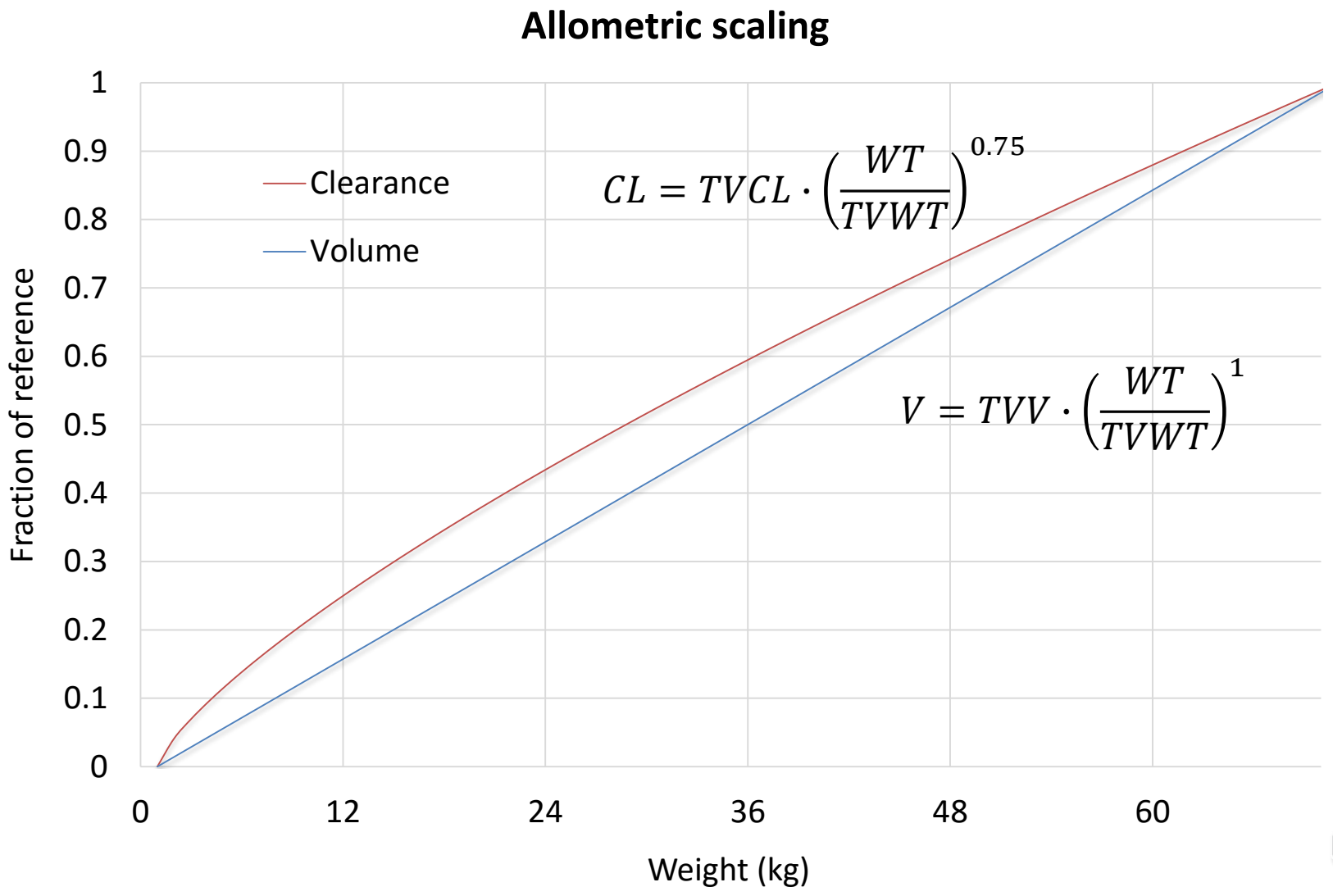
Generally accepted values for exponent b:

- b ≈ 1 for blood volume, organ size
- b ≈ 0.75 for metabolic processes (including metabolism and excretion - clearance)
- b ≈ 0.25 frequencies, $t_{1/2}$, MRT, turnover-times



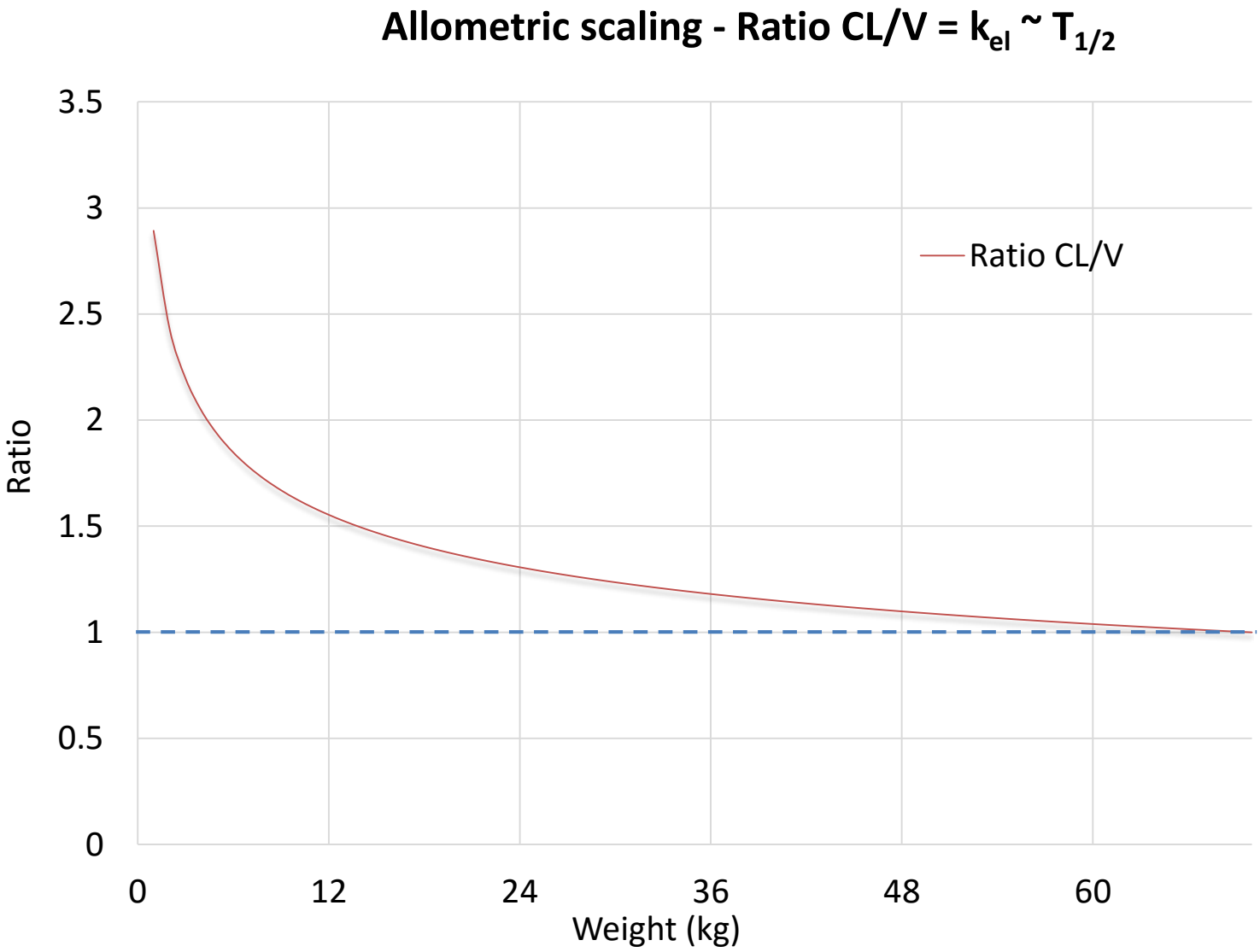
Allometric scaling

of CLs and Vs with body weight



Allometric scaling

Consequences of this for smaller kids



Incorporating even more physiology…

Allometric scaling can be used to describe the effect of body size on the PK parameters.

What if one could scale each single organ in the body?

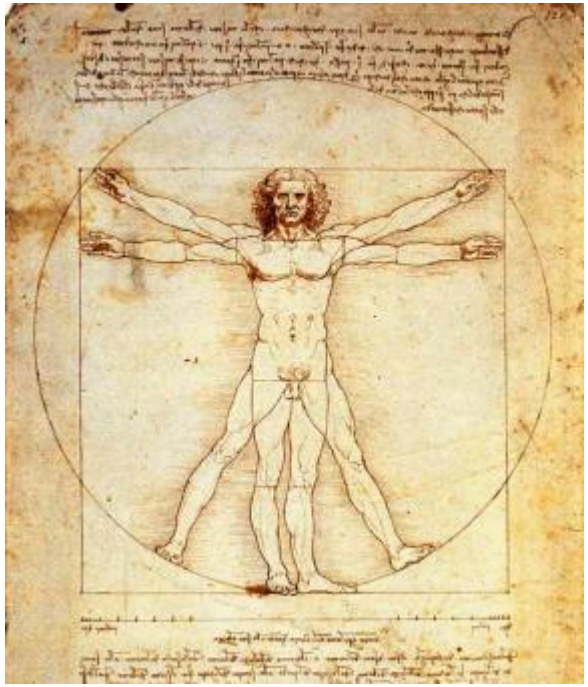
Or take into account of the chemo-physical characteristics of each drug?

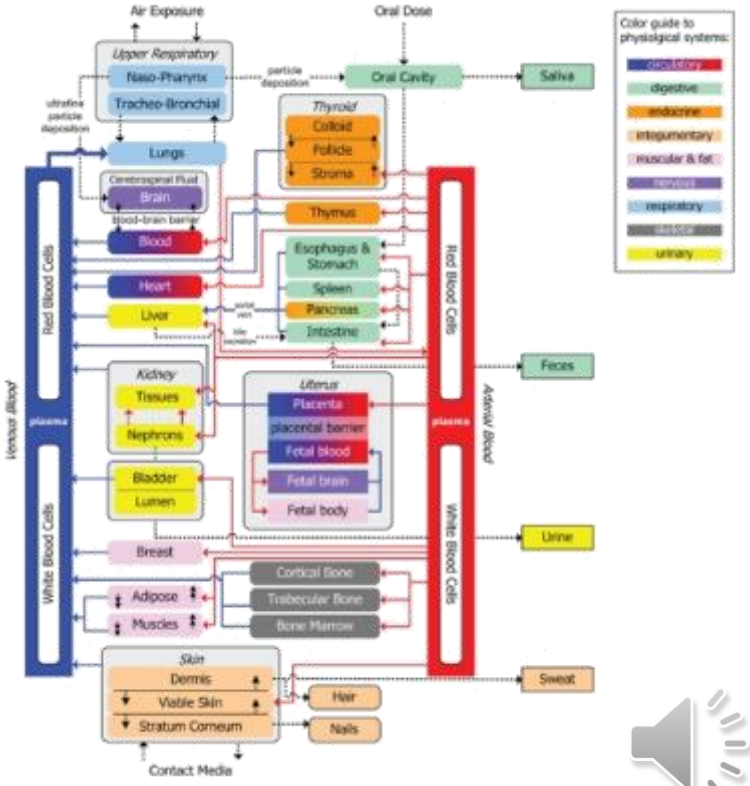
Or use results from previous experiments to inform the PK model?

This is the idea behind pharmacologically-based PK modelling.

Physiologically based PK modelling

- PBPK modelling integrates information from a wide range of sources into a complex model, used for prediction of PK
- First, a detailed model of the human body is created



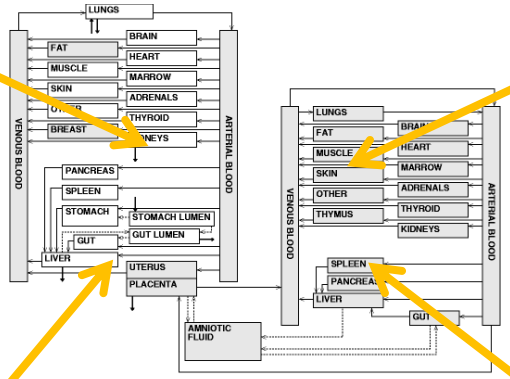


PBPK modelling

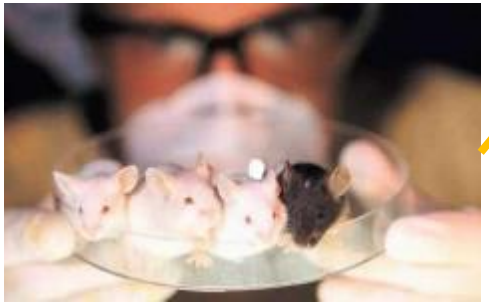
Such a model is too complex for parameter estimation. The parameters must be fixed to reasonable values

In vitro results

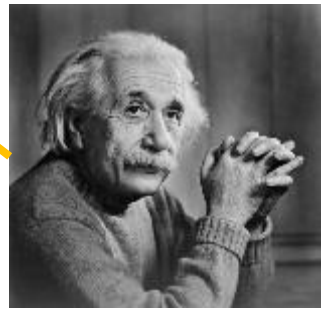
Drug specific information



In vivo results



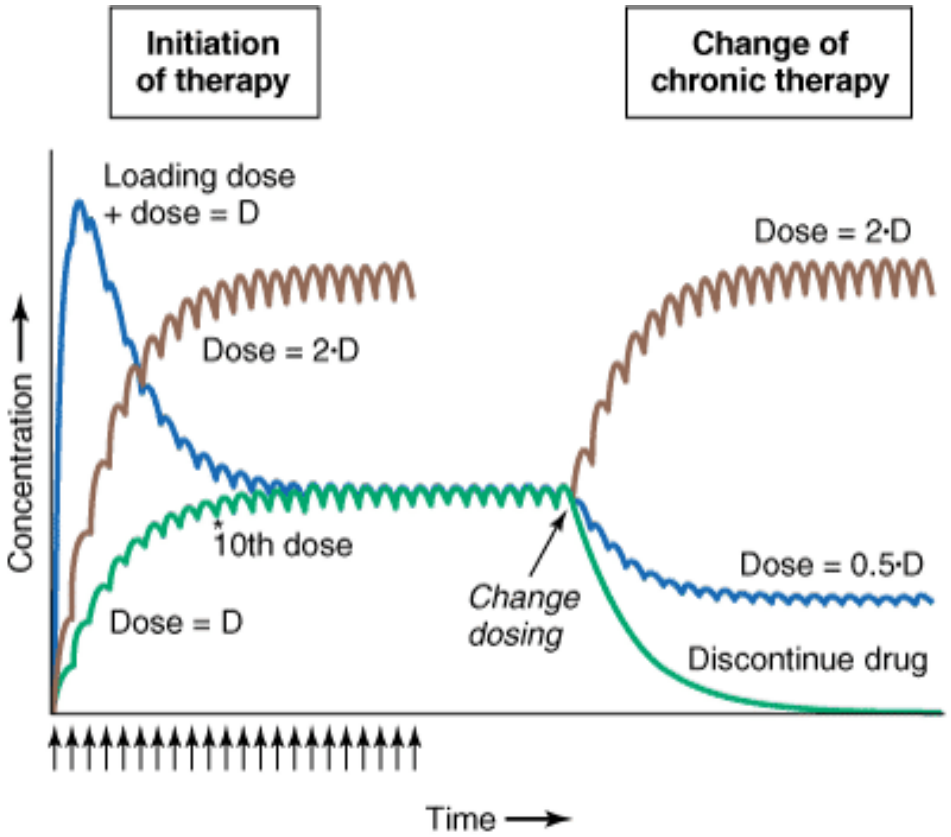
Other scientific knowledge



PBPK modelling

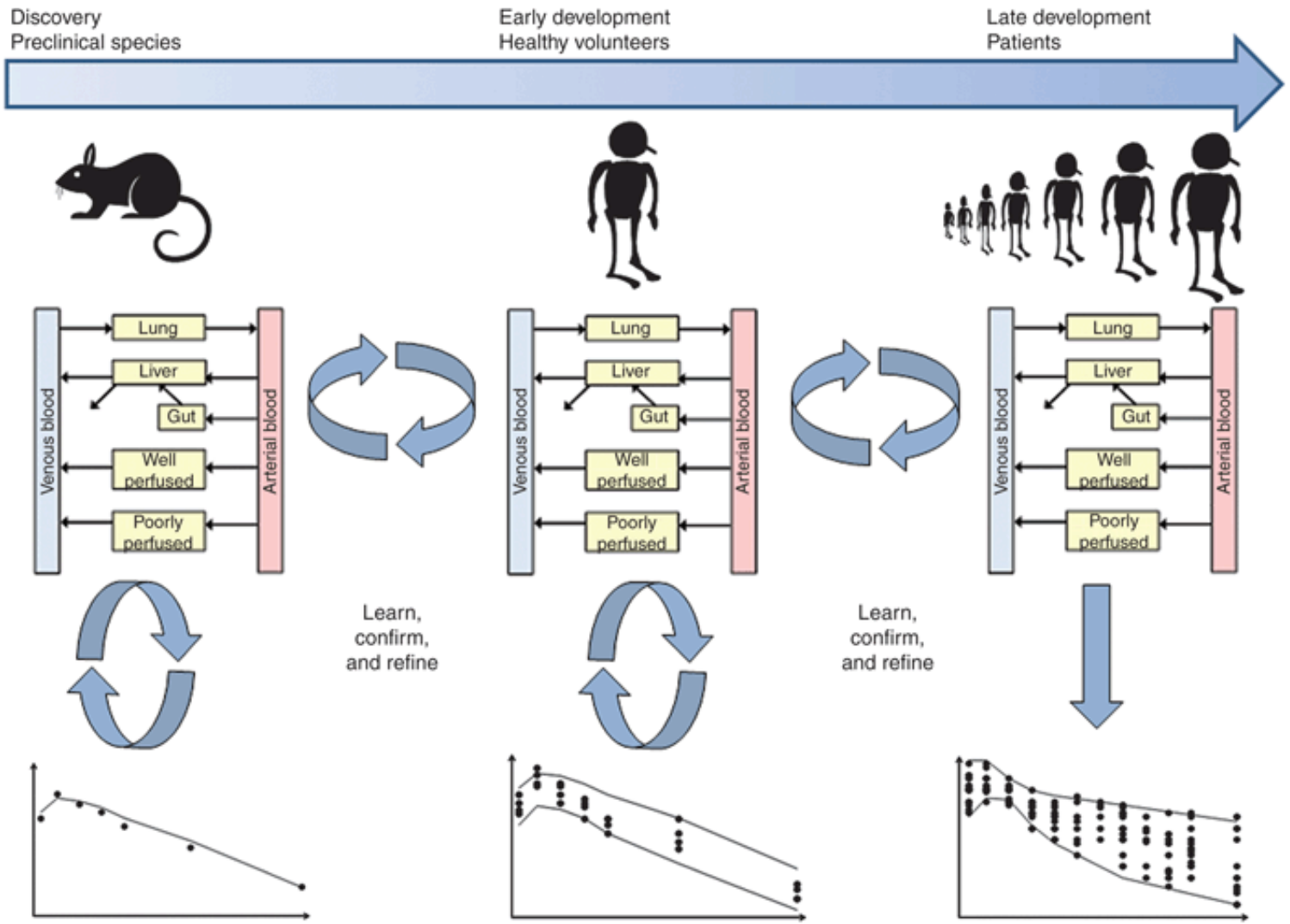
Once a candidate model has been obtained, it can be used for simulation

(always tend to make conservative choices and apply safety factors)



Fauci et al.

PBPK modelling



Jones and Rowland-Yeo, 2013

PBPK modelling

Pros

- All the parameters in the model are automatically scaled to body organs, and ideally they interact with each other in a physiologically plausible way.
- It provides a versatile platform to integrate knowledge from different sources

Cons

- Complicated to implement
- It relies on a large number of assumptions, so the robustness of the results needs to be critically evaluated