

In vitro and *in vivo* correlations for prediction of human pharmacokinetics and dose of antimicrobials

Guest speakers: Mathew Njoroge & Nina Lawrence

Moderator: Greg Basarab

Host: Victor Kouassi

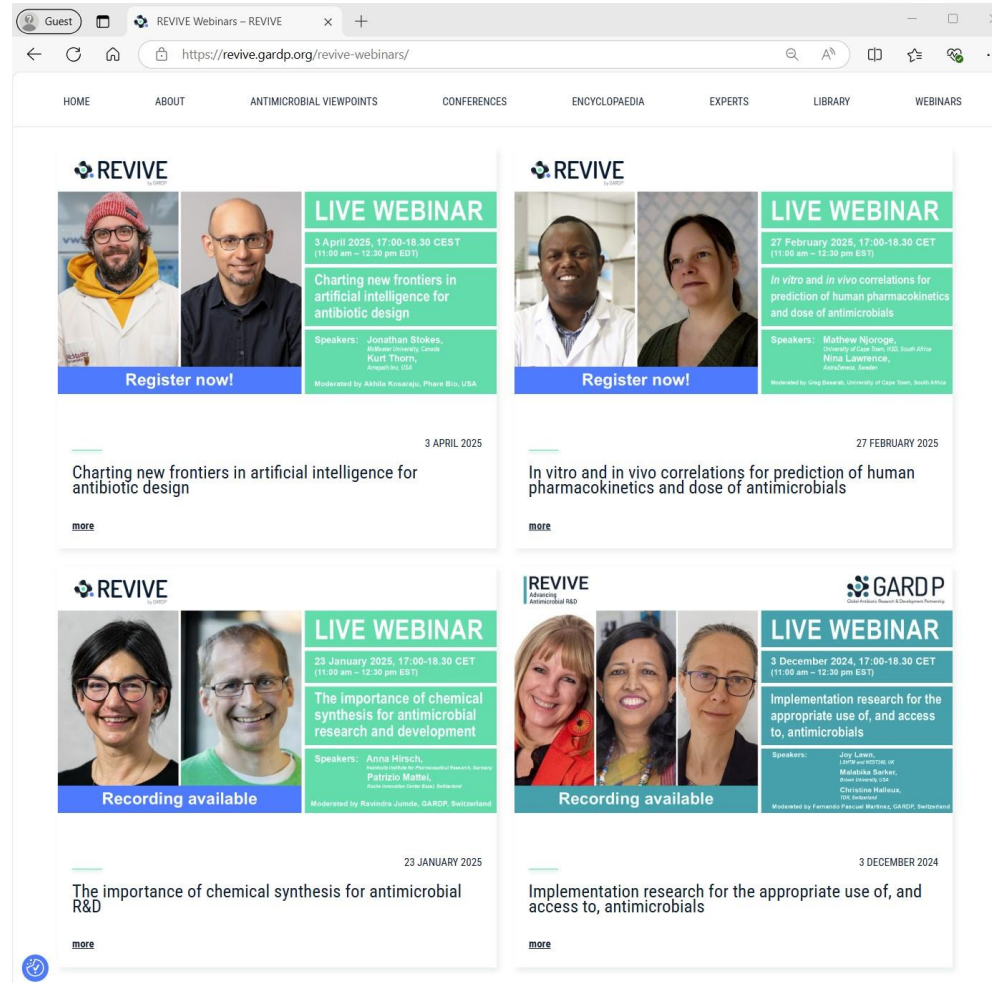
27 February 2025

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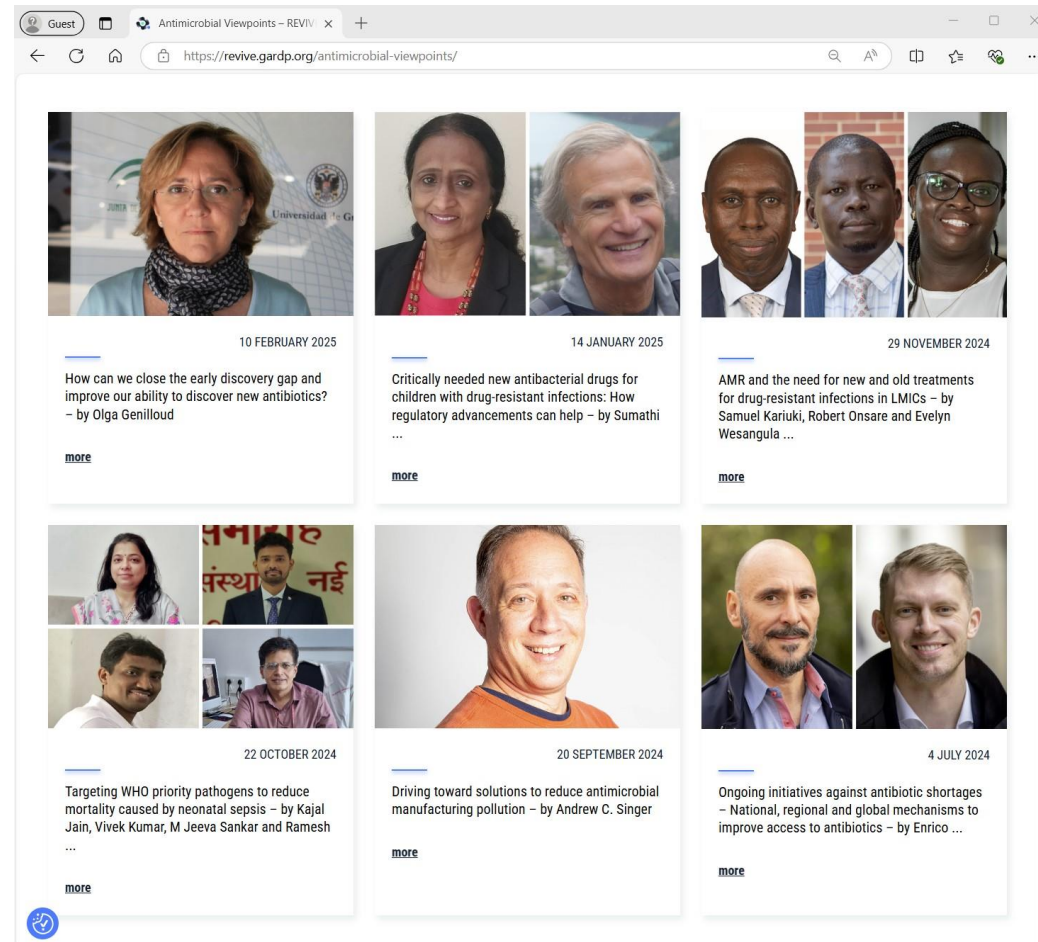
Webinar recordings



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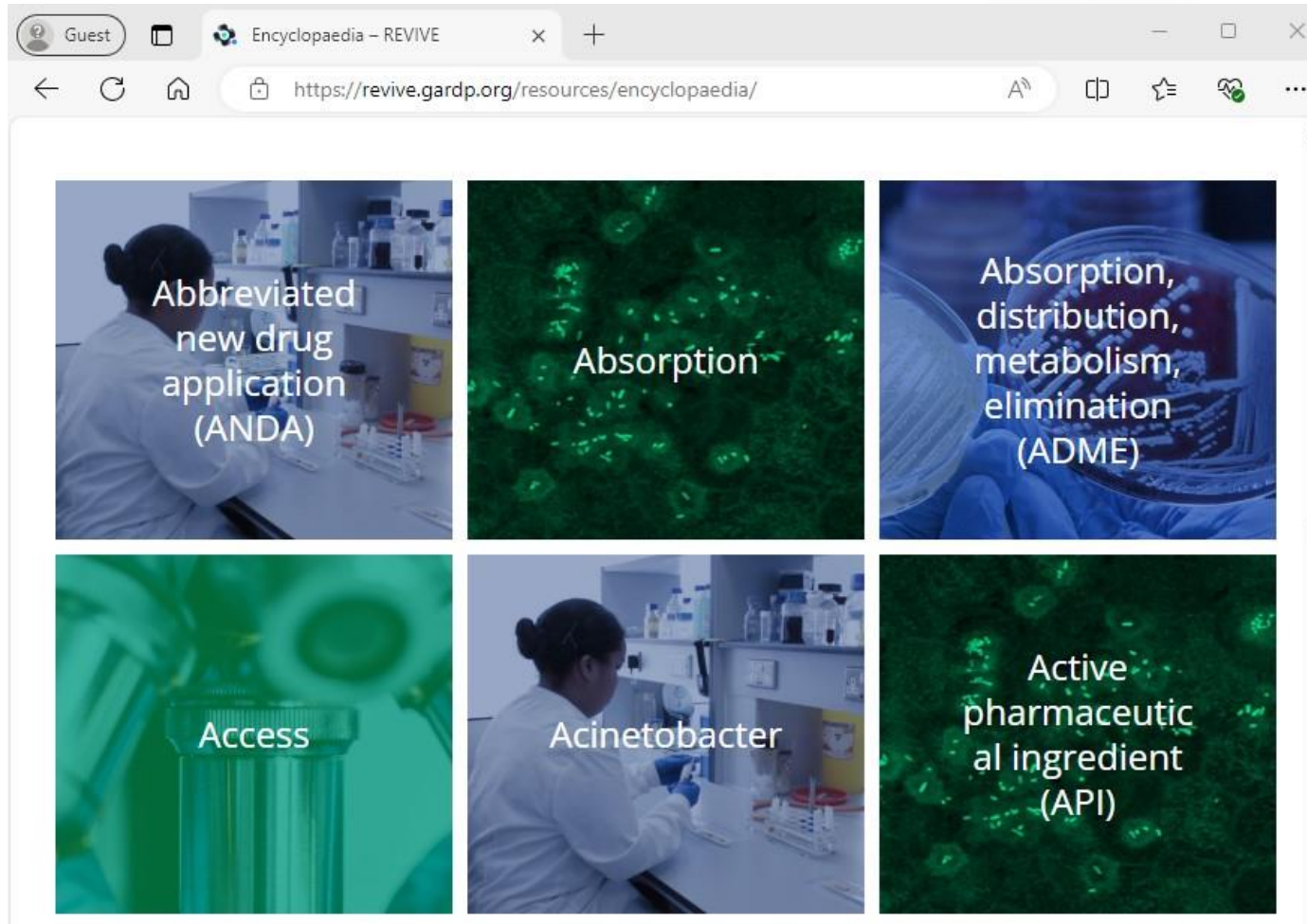
Webinar Title	Date	Speakers	Status
Charting new frontiers in artificial intelligence for antibiotic design	3 April 2025, 17:00-18:30 CET (11:00 am - 12:30 pm EDT)	Jonathan Stokes, Wake Forest University, Canada; Kurt Thorn, Amgen, USA	Register now!
In vitro and in vivo correlations for prediction of human pharmacokinetics and dose of antimicrobials	27 February 2025, 17:00-18:30 CET (11:00 am - 12:30 pm EST)	Mathew Njoroge, University of Cape Town, ZSA, South Africa; Nina Lawrence, Hoffmann-La Roche, Geneva	Register now!
The importance of chemical synthesis for antimicrobial research and development	23 January 2025, 17:00-18:30 CET (11:00 am - 12:30 pm EST)	Anna Hirsch, Hoffmann-La Roche, Switzerland; Patrizio Mattai, Hoffmann-La Roche, Switzerland	Recording available
Implementation research for the appropriate use of, and access to, antimicrobials	3 December 2024, 17:00-18:30 CET (11:00 am - 12:30 pm EST)	Joy Libero, Lilly and MSD, USA; Marilou Barker, Alkermes, USA; Christine Huetnik, TIG, Switzerland	Recording available

Antimicrobial Viewpoints



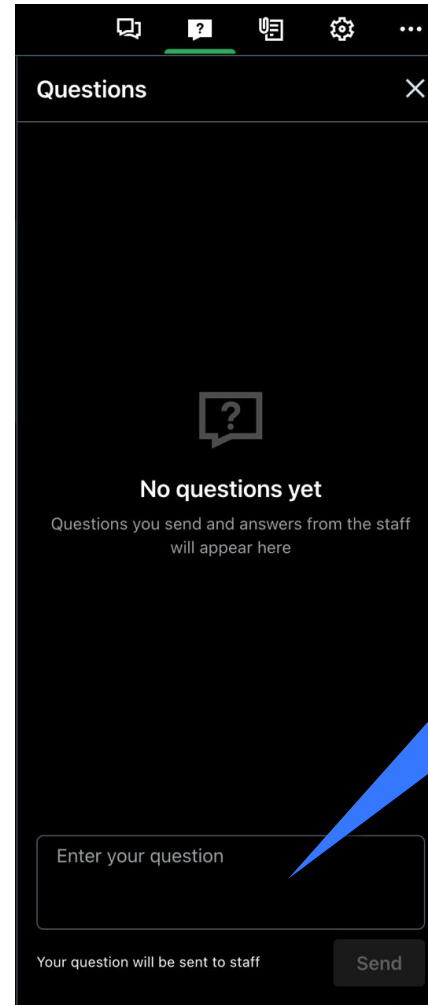
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Antimicrobial Encyclopaedia



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Today's speakers

In vitro and *in vivo* correlations for prediction of human pharmacokinetics and dose of antimicrobials



Moderator:
Greg Basarab
University of Cape
Town



Nina Lawrence
AstraZeneca



Mathew Njoroge
University of Cape
Town

Nina Lawrence



Nina Lawrence has 15 years of experience in Drug Metabolism and Pharmacokinetics (DMPK), her career spans academia and industry. She currently serves as Director and Team Lead for DMPK Design Leaders at AstraZeneca in Sweden, where she leads a team of talented scientists working on early-stage drug discovery in respiratory and immunology.

Her work focuses on modelling preclinical data toward predicting human PK and dose and contributing to the progression of new therapeutic candidates. She previously worked at the Holistic Drug Discovery and Development Centre (H3D) in South Africa, where she spearheaded in vitro ADME and African drug metabolism platforms.



In vitro-in vivo correlation for human PK and dose prediction

Nina Lawrence

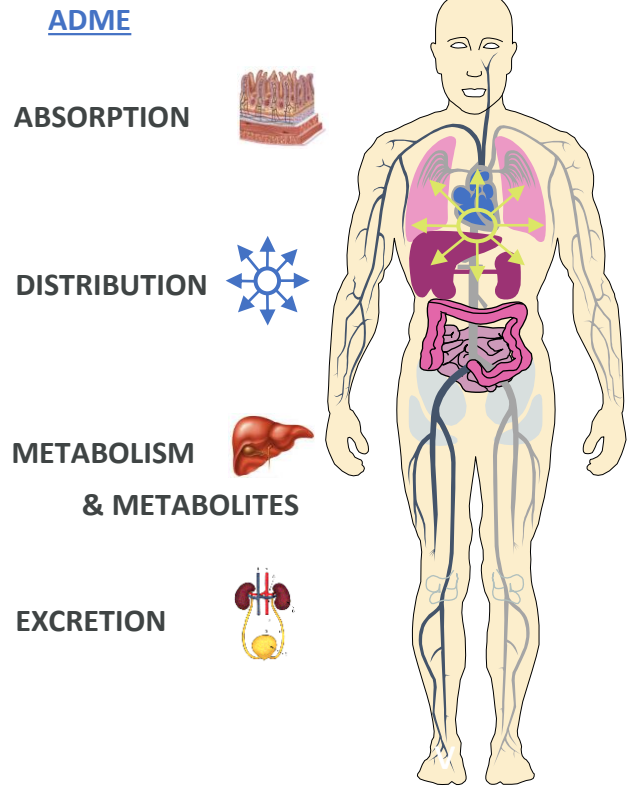
Research conducted at University of Cape Town, H3D (South Africa)

Current affiliation Director, DMPK at AstraZeneca

Outline

- DMPK & ADME
- In vitro & in vivo assays
- Predicting human PK
- PK and PD for predicting human dose
- Example

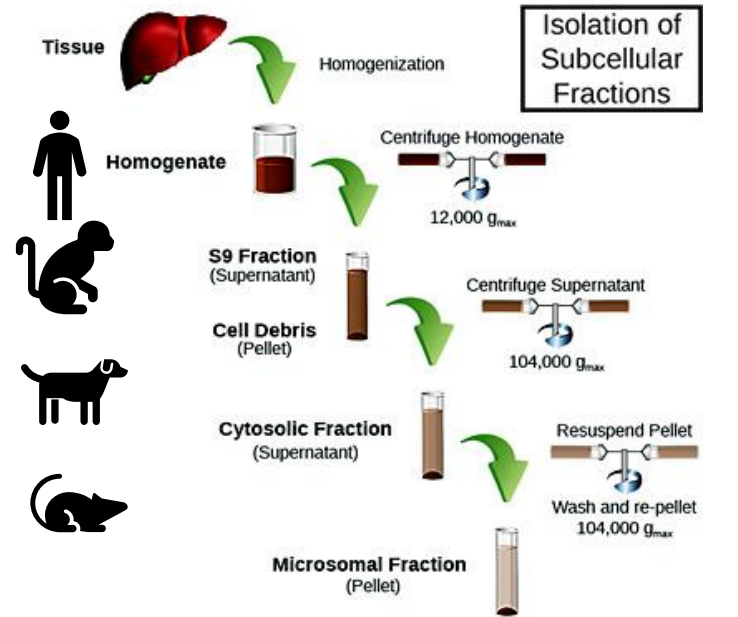
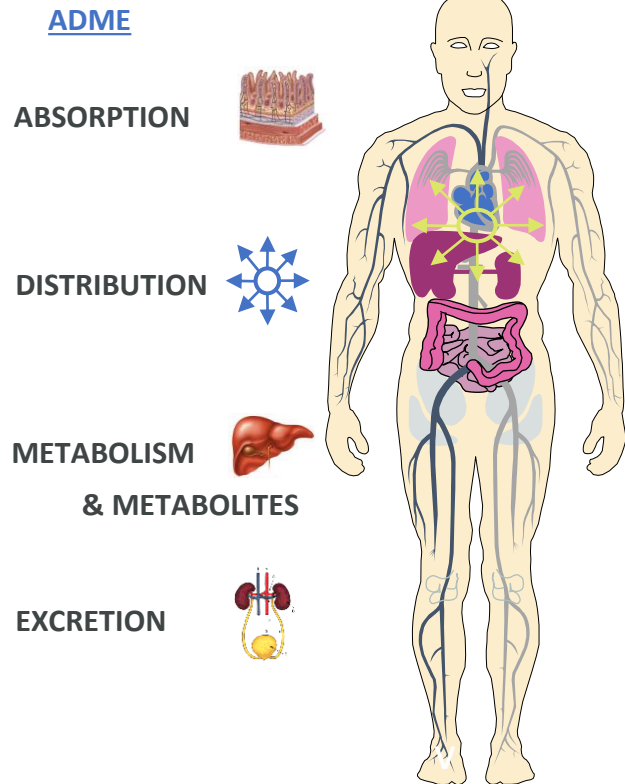
Drug Metabolism & Pharmacokinetics (DMPK)



*Pharmacokinetics (PK) – what the body does to the drug

Drug Metabolism & Pharmacokinetics (DMPK)

In vitro ADME assays & tools



CL, fu,inc, DDI, TDI, metabolites

*Pharmacokinetics (PK) – what the body does to the drug

Drug Metabolism & Pharmacokinetics (DMPK)

In vitro ADME assays & tools

ADME

ABSORPTION



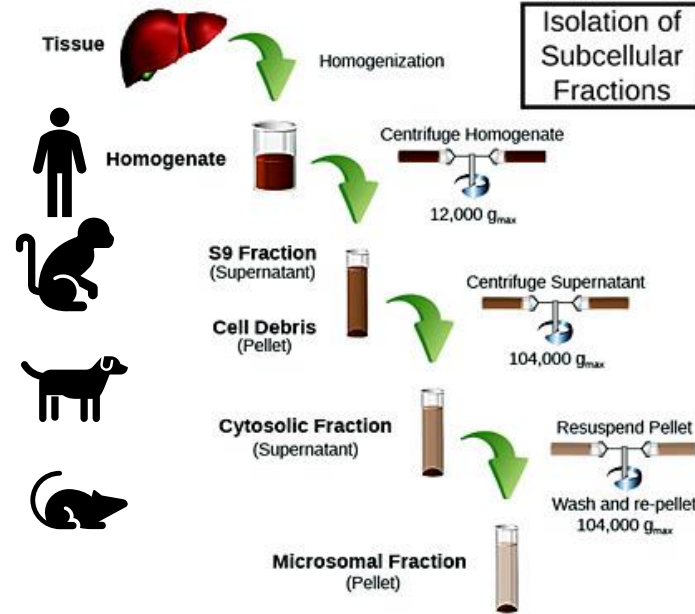
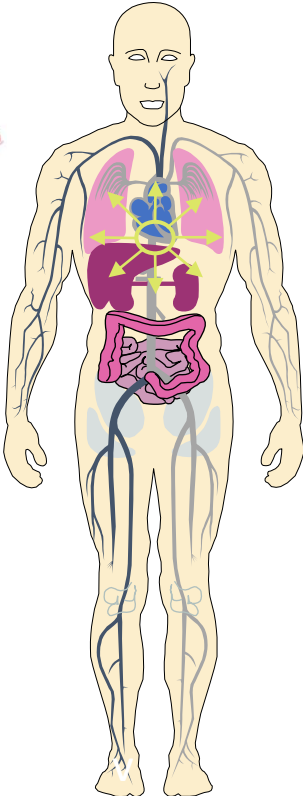
DISTRIBUTION



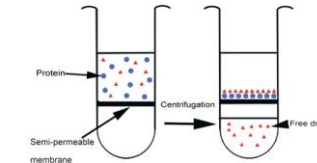
METABOLISM & METABOLITES



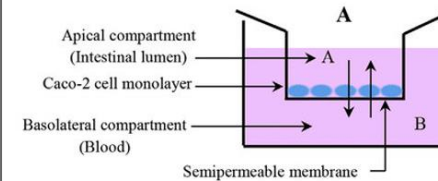
EXCRETION



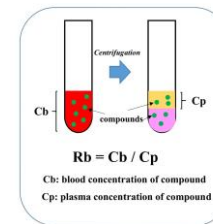
CL, f_u , inc, DDI, TDI, metabolites



Fraction unbound (f_u)



P_{app} , ER, transporters e.g. P-gp



B:P ratio

The free drug hypothesis assumes that the unbound drug concentration in blood is the same as that in the site of action at steady state – so only free unbound drug is available to interact with the biological target

*Pharmacokinetics (PK) – what the body does to the drug

Drug Metabolism & Pharmacokinetics (DMPK)

ADME

ABSORPTION



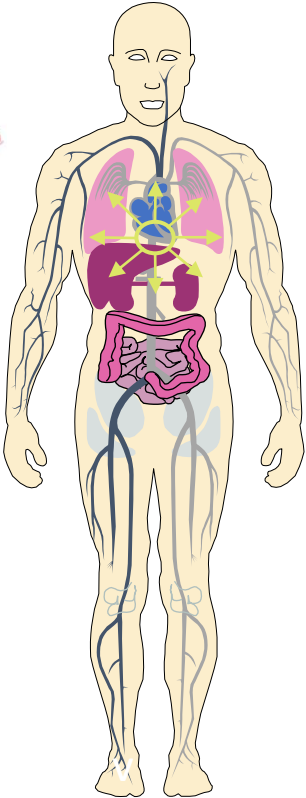
DISTRIBUTION



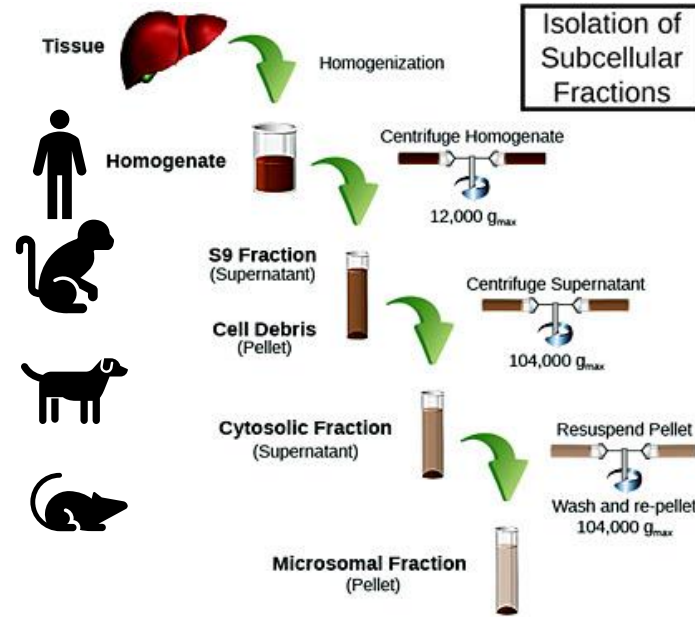
METABOLISM
& METABOLITES



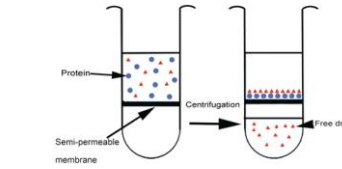
EXCRETION



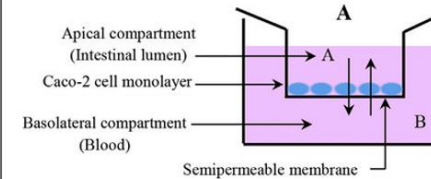
In vitro ADME assays & tools



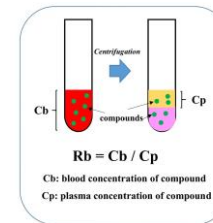
CL, f_u , inc, DDI, TDI, metabolites



Fraction unbound (f_u)



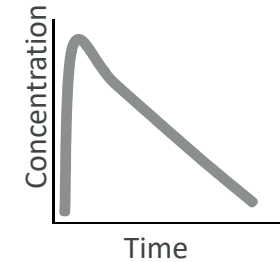
P_{app} , ER, transporters e.g. P-gp



B:P ratio

In vivo PK studies

Pharmacokinetic (PK)



Elimination pathways
BDC studies

The free drug hypothesis assumes that the unbound drug concentration in blood is the same as that in the site of action at steady state – so only free unbound drug is available to interact with the biological target

*Pharmacokinetics (PK) – what the body does to the drug

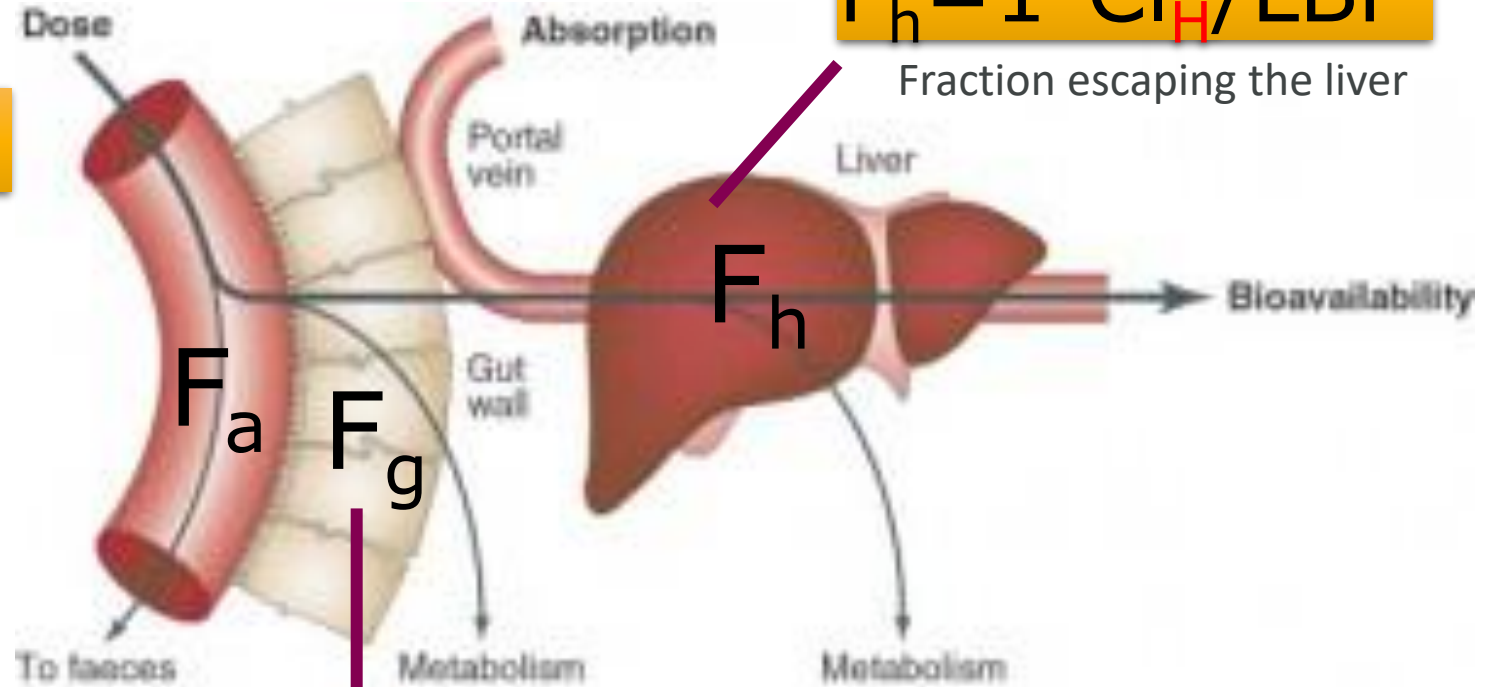
Bioavailability: a composite parameter

$$F = F_h \cdot F_g \cdot F_a$$

$$F_h = 1 - Cl_H / LBF$$

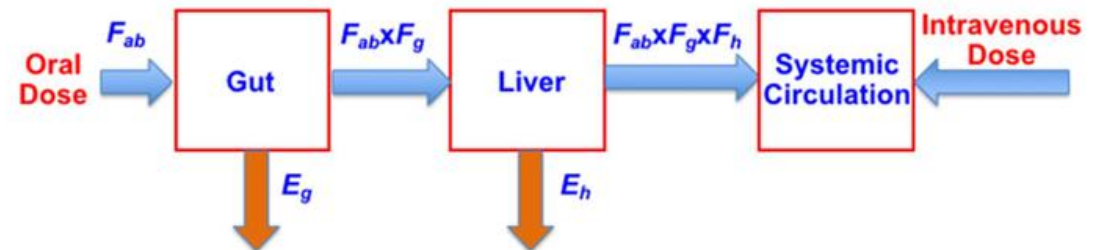
Fraction escaping the liver

F_a (Fraction absorbed)

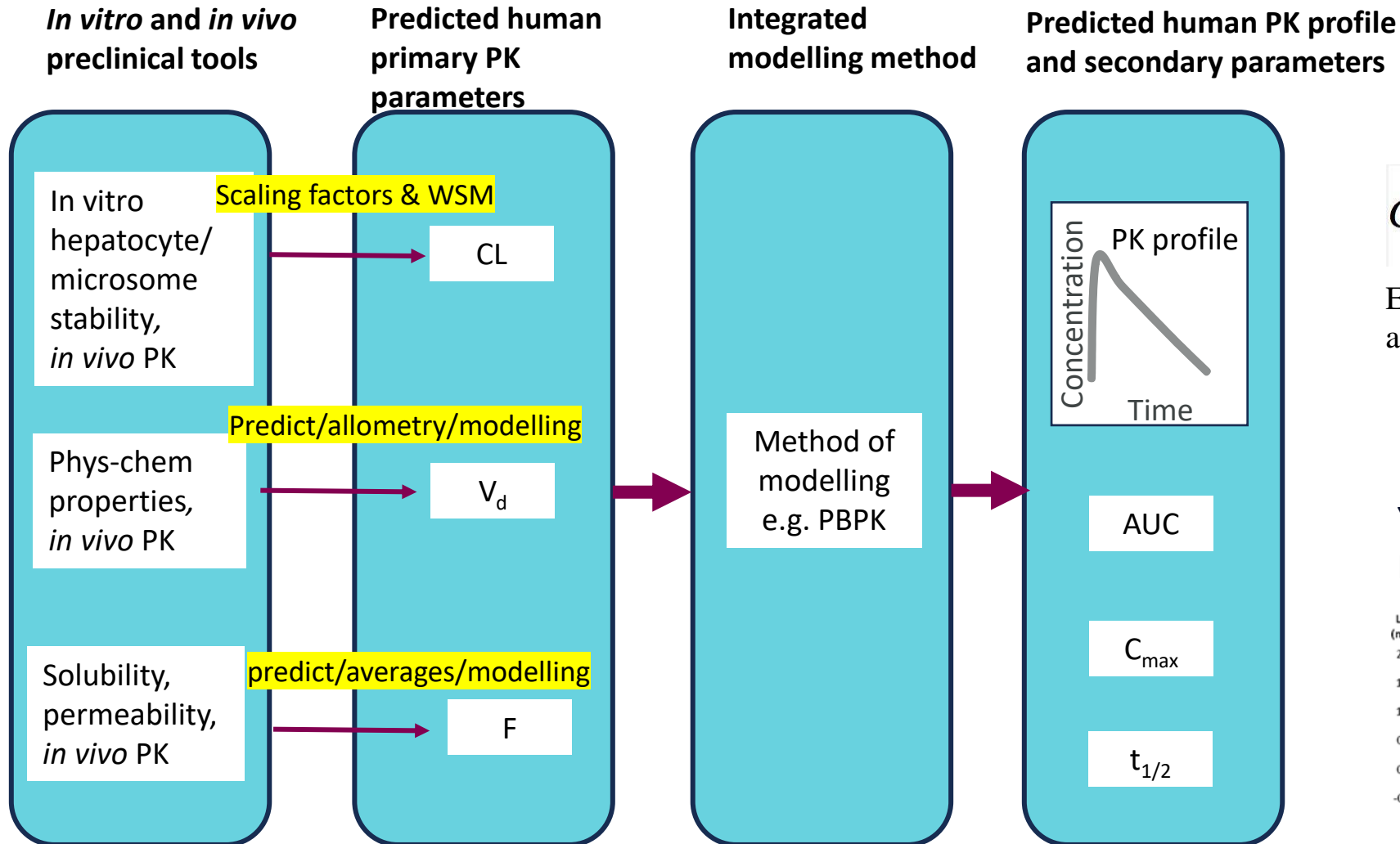
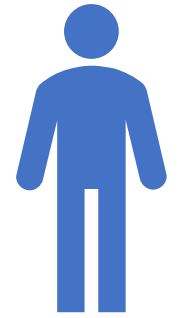


F_g (Gut metabolism)

Fraction escaping gut metabolism



Predicting human PK

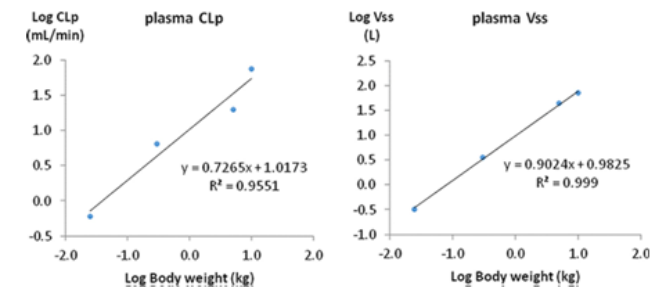


$$CL_H = Q_H \cdot \left[\frac{fu \cdot CL_{int}}{Q_H + fu \cdot CL_{int}} \right]$$

Equation for hepatic clearance according to the Well Stirred Model

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

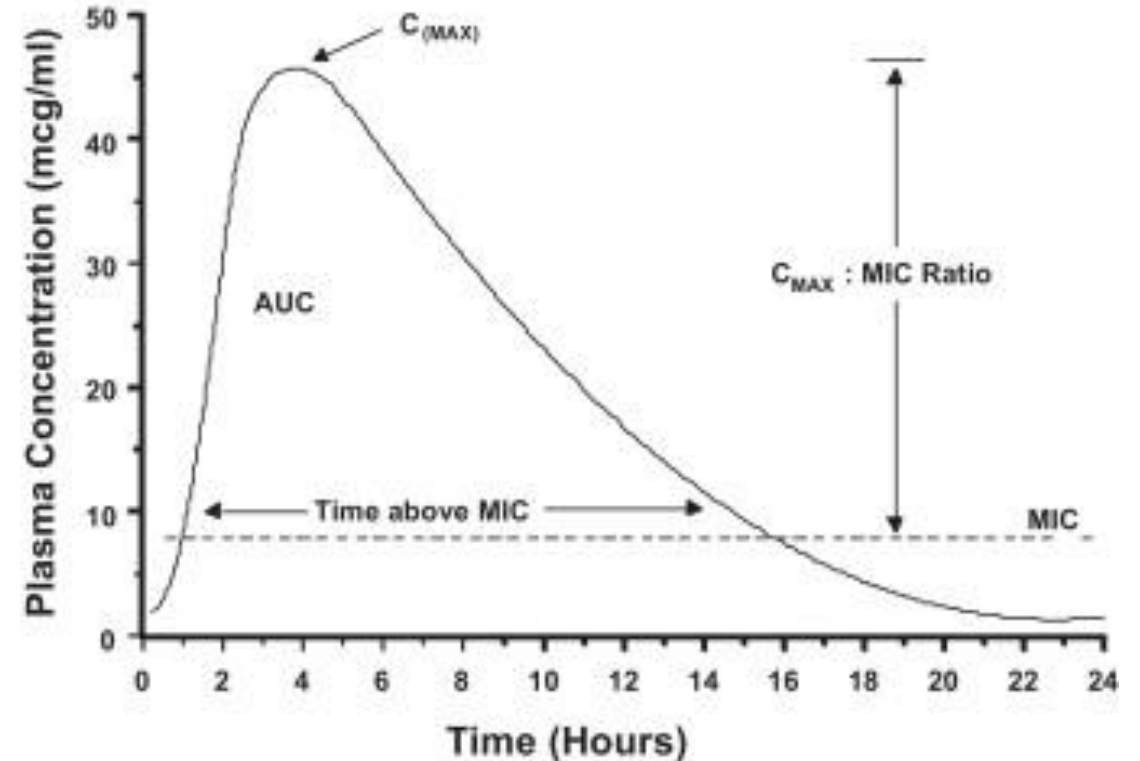
Equation for allometric scaling



Connecting PK and PD for predicting human dose



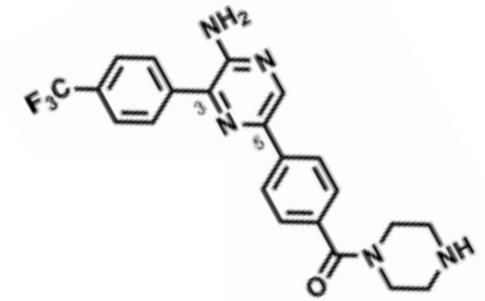
- Time above MIC (Minimum Inhibitory Concentration)
- C_{max}/MIC ratio



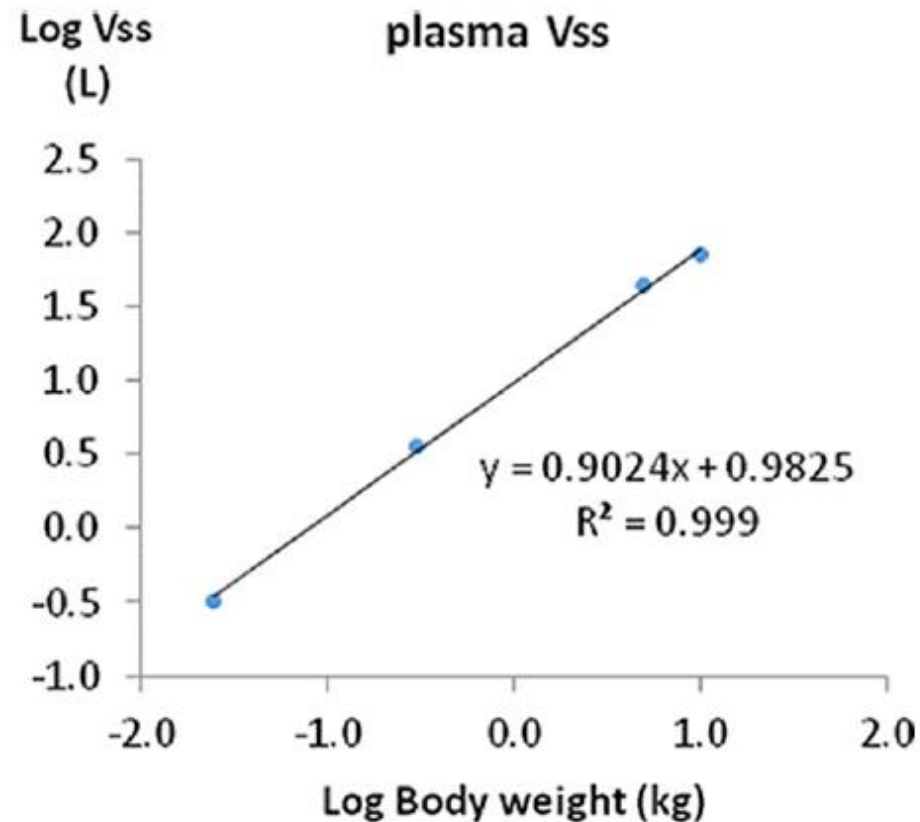
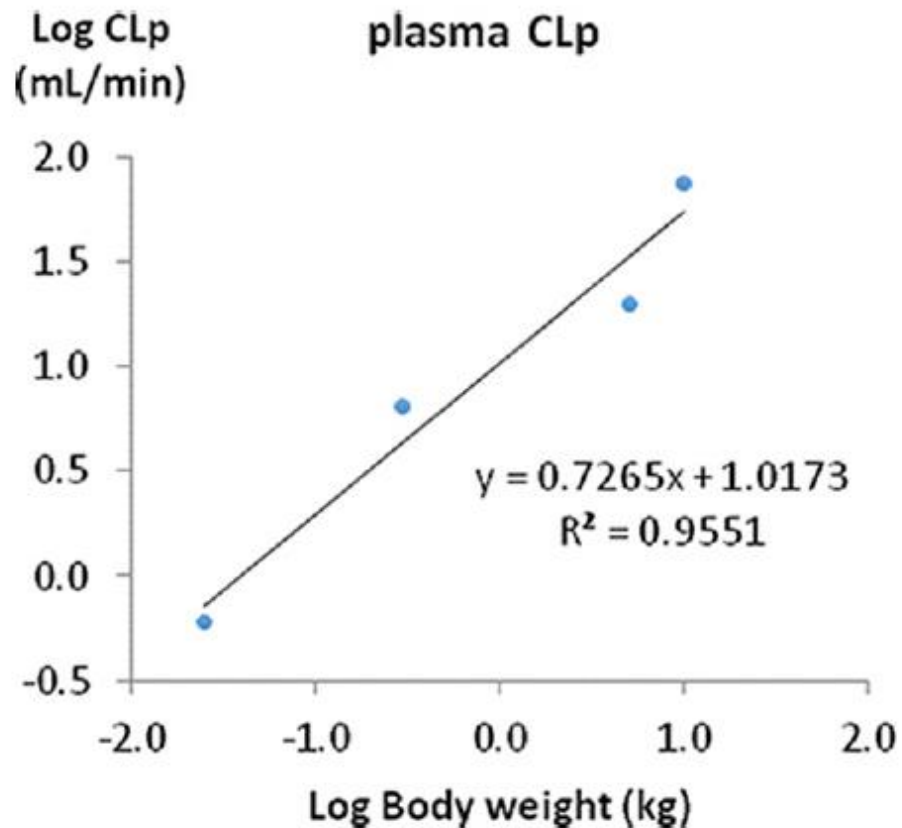
MIC: Minimum Inhibitory Concentration

Pharmacodynamics (PD) – what the drug does to the body

Example – UCT943 Preclinical Candidate for the Treatment of Malaria



Structure of UCT943



Example – UCT943 Preclinical Candidate for the Treatment of Malaria

PK prediction

- In vitro: metabolic stability in hepatocyte & microsomes (m,r,d,h), binding assays (plasma and incubation) and B:P ratio for scaling to predicted plasma clearance.
- In vivo PK studies (m,r,d,mon)

	Predicted plasma clearance (ml/min/kg)			
	mouse	rat	dog	human
Mics	15.8	23.8	24.1	9.4
Heps	10.5	13.1	13.6	3.3
mics:hps	2	2	2	3

	Plasma CL (ml/min/kg)		
	mouse	rat	dog
Mics	15.8	23.8	24.1
Heps	10.5	13.1	13.6
obs in vvo	13.0	10.0	7.5
Fold diff (mics)	1	2	3
Fold diff (hps)	1	1	2

- From allometry:
 - Predicted human plasma CL: 3.33ml/min/kg – in line with in vitro data
 - Predicted Vss: 6.3 L/kg

Example – UCT943 Preclinical Candidate for the Treatment of Malaria

PK prediction

- In vitro: metabolic stability in hepatocyte & microsomes (m,r,d,h), binding assays (plasma and incubation) and B:P ratio for scaling to predicted plasma clearance.
- In vivo PK studies (m,r,d,mon)

	Predicted free plasma clearance (ml/min/kg)			
	mouse	rat	dog	human
Mics	15.8	23.8	24.1	9.4
Heps	10.5	13.1	13.6	3.3
mics:heps	2	2	2	3

	Plasma CL (ml/min/kg)		
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- From allometry:
 - Predicted human plasma CL: 3.33ml/min/kg – in line with in vitro hepatocyte data
 - Predicted Vss: 6.3 L/kg

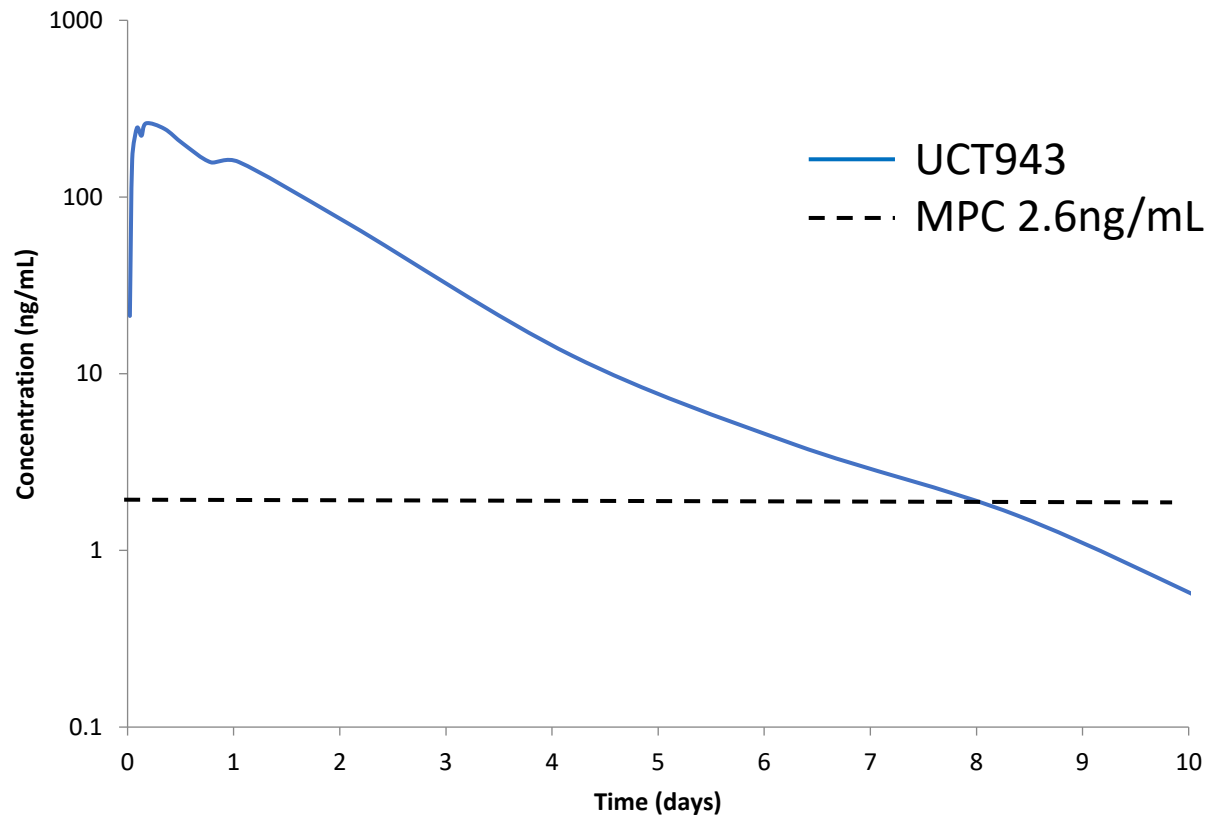
Exposure requirement:

- MPC of 2.6 ng/ml maintained for 8 days (i.e. four asexual parasite cycles)

MPC: minimum parasitidal concentration

50-80mg of UCT943 predicted to cover MPC for 8 days

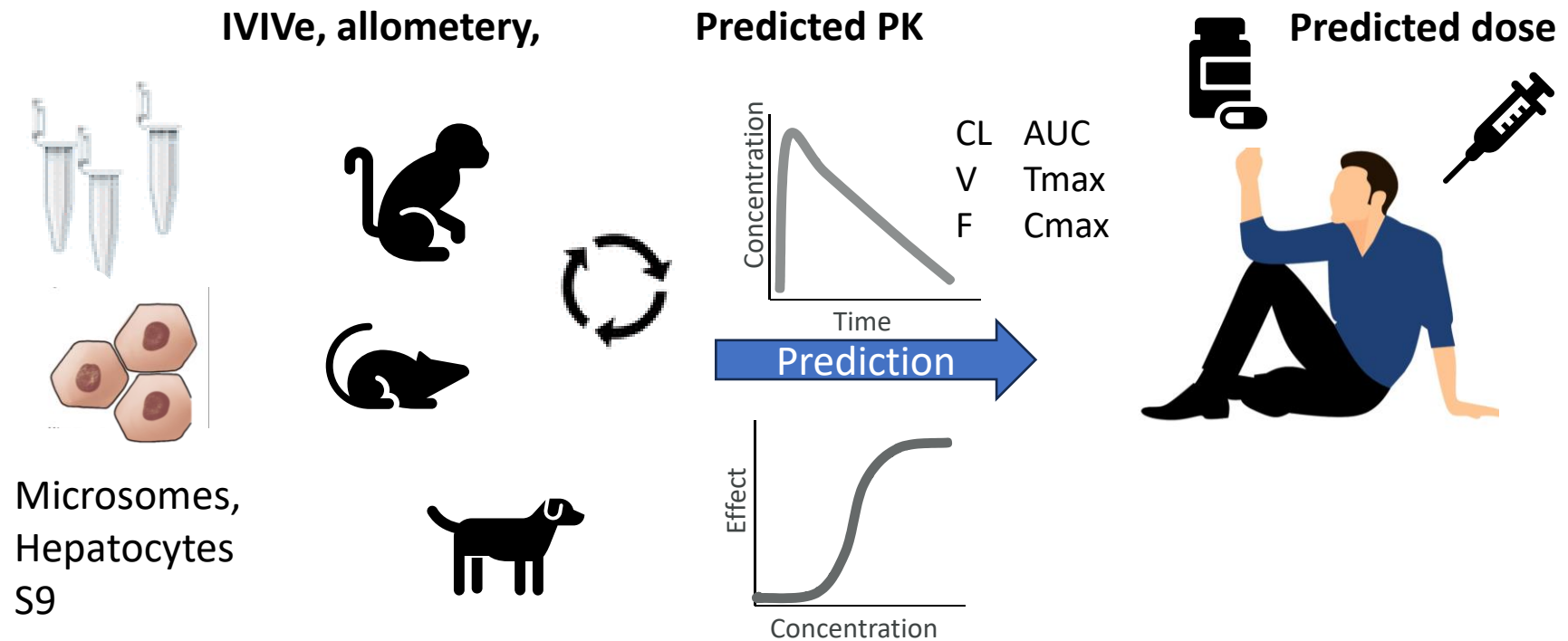
simulated human PK at 50mg dose



Cmax (ng/mL)	234
AUC (ng.h/mL)	4,213
Bioavailability (%)	80
T1/2 (h)	27

Normalisation & Wajima transformation

Conclusion



Thank you



Mathew Njoroge



Mathew Njoroge is a senior drug metabolism and pharmacokinetics scientist at the University of Cape Town (UCT)'s Holistic Drug Discovery and Development Centre (H3D) in South Africa where he works as part of a multidisciplinary team to advance preclinical drug discovery projects.

His research focuses on understanding the metabolism and pharmacokinetics of compounds with a view to translating in vitro data to human exposure – efficacy relationships, as part of drug discovery projects in malaria, tuberculosis and antimicrobial resistance. This work, combined with H3D's mission to build Africa-specific models, has led to research interests in drug metabolism and disposition in the African population – more specifically in considering the impact of pharmacogenetic variability on the pharmacokinetics of drugs in African populations.



In vitro and In vivo correlation for prediction of human pharmacokinetics and dose of antimicrobials:

Impact of genetic variability on Pharmacokinetics and Dose

Mathew Njoroge

REVIVE webinar, 27th February 2025



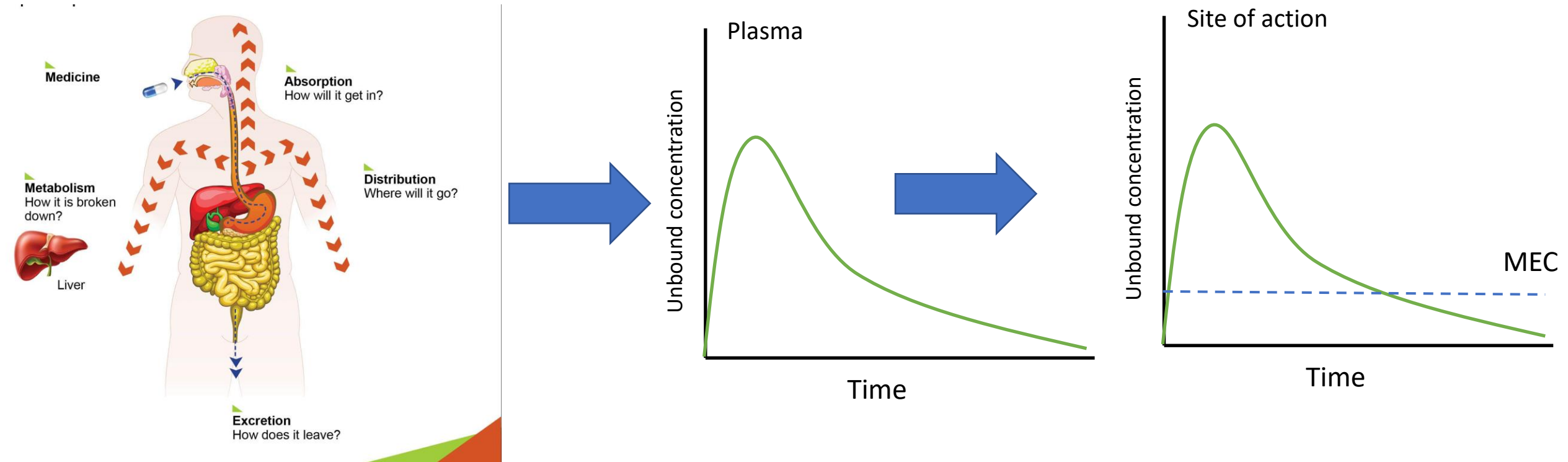
PIONEERING WORLD-CLASS
DRUG DISCOVERY IN AFRICA



UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA - UNIVERSITEIT VAN KAAPSTAD

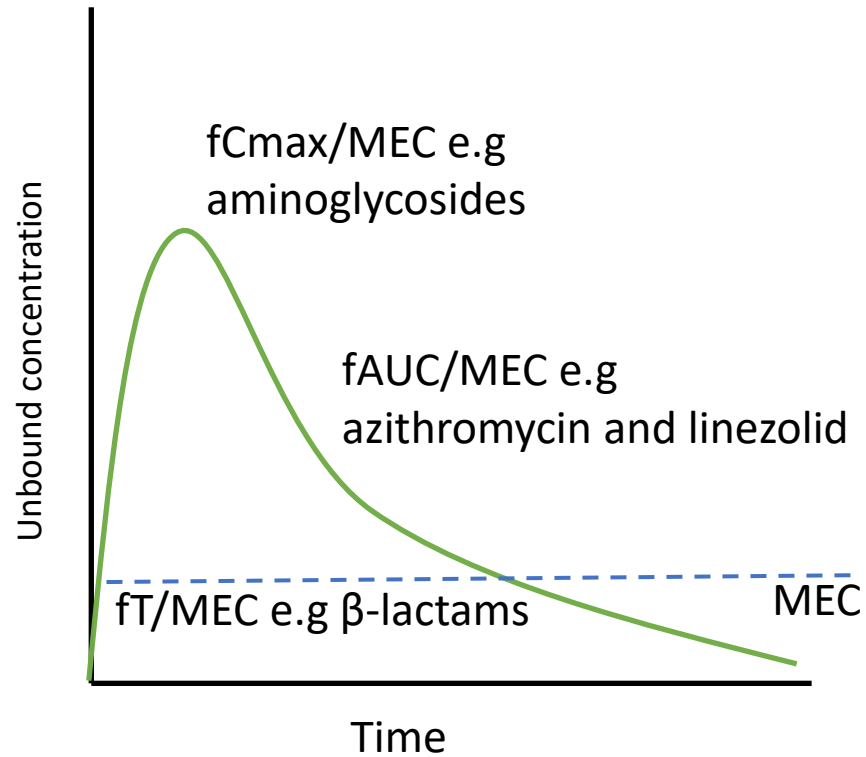
Pharmacodynamics and Pharmacokinetics

- For a drug to show biological activity *in vivo*, it needs to get to its site of action at sufficient concentrations and stay there for long enough to trigger and maintain the required activity
- The concentration vs time profile of a compound is defined by its **A**bsorption **D**istribution **M**etabolism and **E**xcretion

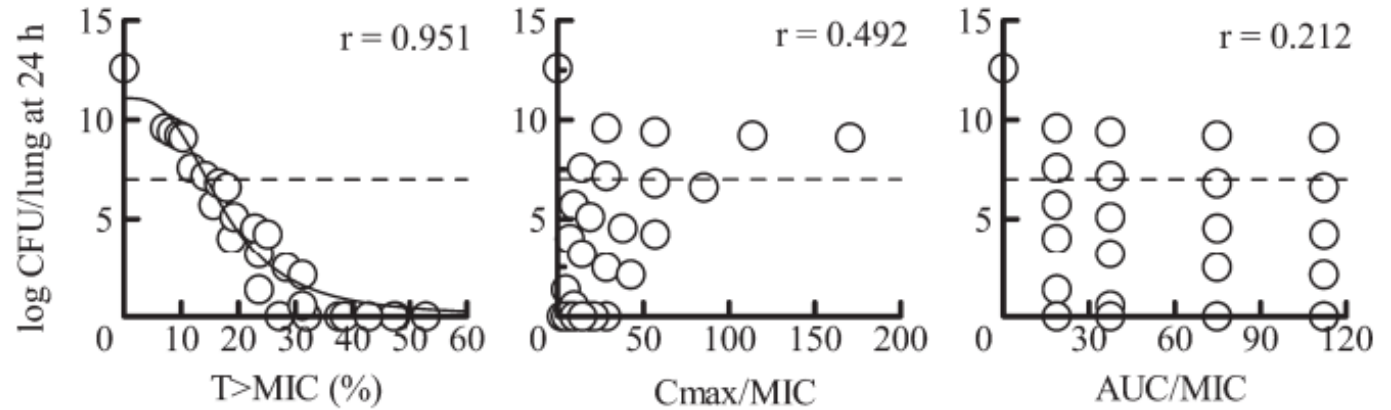


*MEC – minimum effective concentration

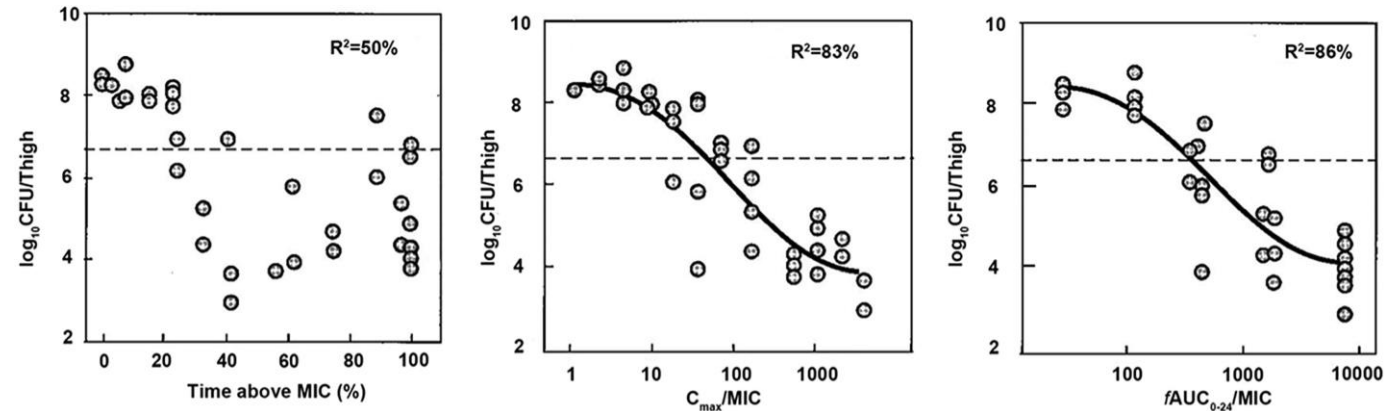
Linking PK and PD



PK/PD of meropenem/cilastatin in mouse lung infection model



PK/PD of daptomycin in mouse thigh infection model

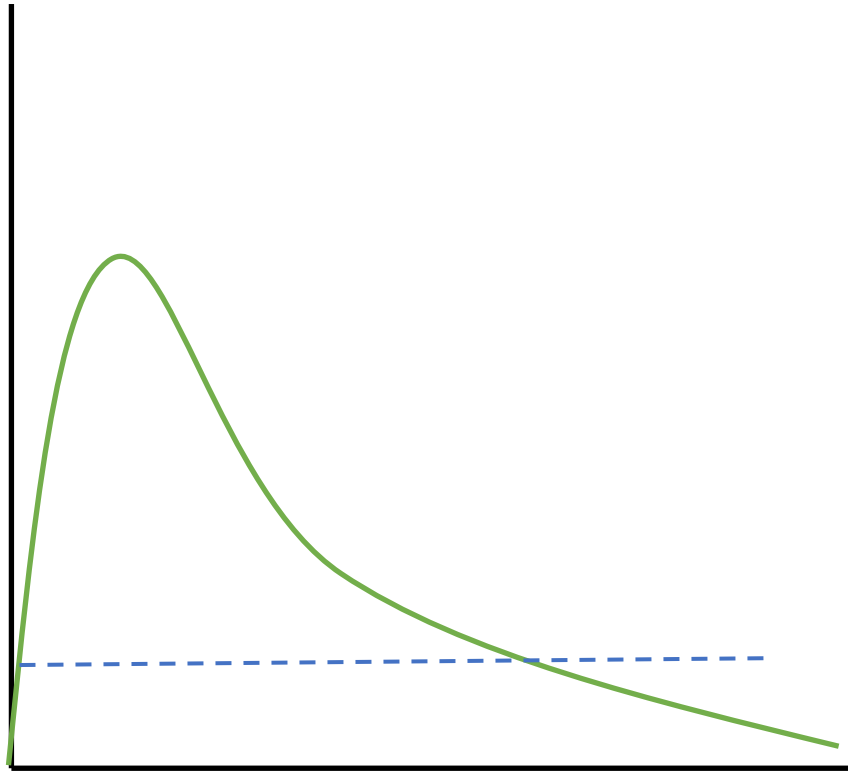


From PK/PD to human dose

$$Dose = \frac{C_{avg,ss} \cdot CL_{int} \cdot \tau}{f_{abs}}$$

C_{avg} – average unbound concentration at steady state,
 CL_{int} = Intrinsic clearance,
 τ = duration
 f_{abs} = fraction absorbed

Unbound concentration



Time

C_{av} – the average unbound concentration

- Improving **biological activity** (MEC) will mean that a lower C_{av} can produce the required biological activity leading to a lower dose

CL_{int} (Intrinsic clearance)

- Improving the **intrinsic clearance (CL_{int})** of the compound will increase the fraction of compound escaping gut and hepatic metabolism leading to a lower dose

Fraction absorbed

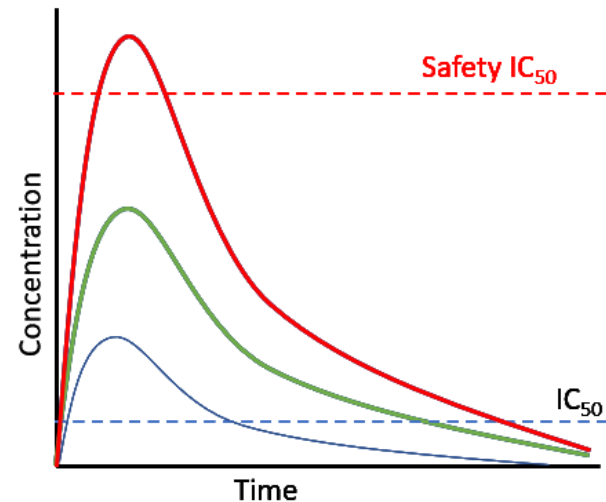
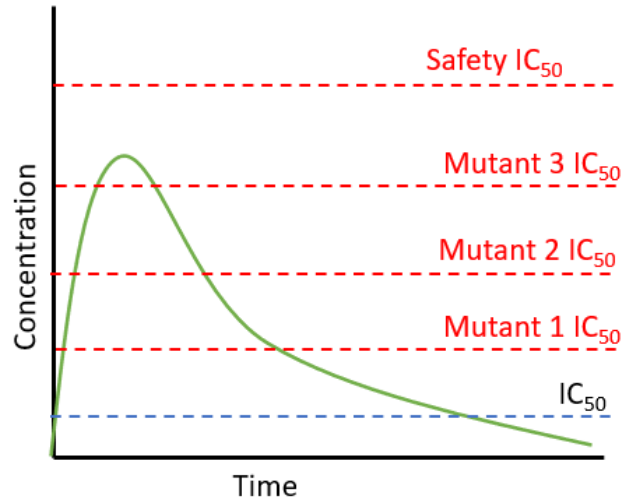
- Improving **solubility** and **permeability** will increase the fraction of compound absorbed leading to a lower dose.

$$dose = \frac{C_{max} V_{ss} (k_a - k_{el})}{F k_a} \left(\frac{e^{-k_{el} T_{max,ss}}}{1 - e^{-k_{el} \tau}} - \frac{e^{-k_a T_{max,ss}}}{1 - e^{-k_a \tau}} \right)^{-1}$$

dose for C_{min}

$$dose = \frac{C_{min} V_{ss} (k_a - k_{el})}{F k_a} \left(\frac{1}{1 - e^{-k_{el} \tau}} - \frac{1}{1 - e^{-k_a \tau}} \right)^{-1}$$

PK and PD variability



$$Dose = \frac{C_{avg, ss} \cdot CL_{int} \cdot \tau}{f_{abs}}$$

C_{avg} – average unbound concentration at steady state,
 CL_{int} = Intrinsic clearance,
 τ = duration
 f_{abs} = fraction absorbed

C_{av} – the average unbound concentration

- Improving **biological activity** (MEC) will mean that a lower C_{av} can produce the required biological activity leading to a lower dose

CL_{int} (Intrinsic clearance)

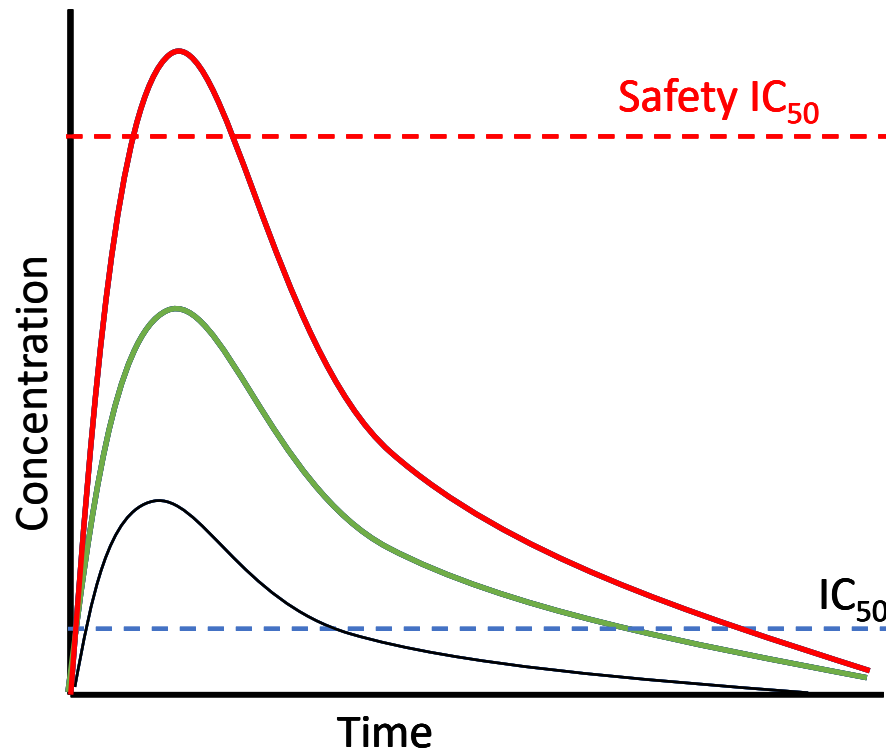
- Improving the **intrinsic clearance** (**CL_{int}**) of the compound will increase the fraction of compound escaping gut and hepatic metabolism leading to a lower dose

F_{abs} - Fraction absorbed

- Improving **solubility** and **permeability** will increase the fraction of compound absorbed leading to a lower dose.

Variation in drug metabolism

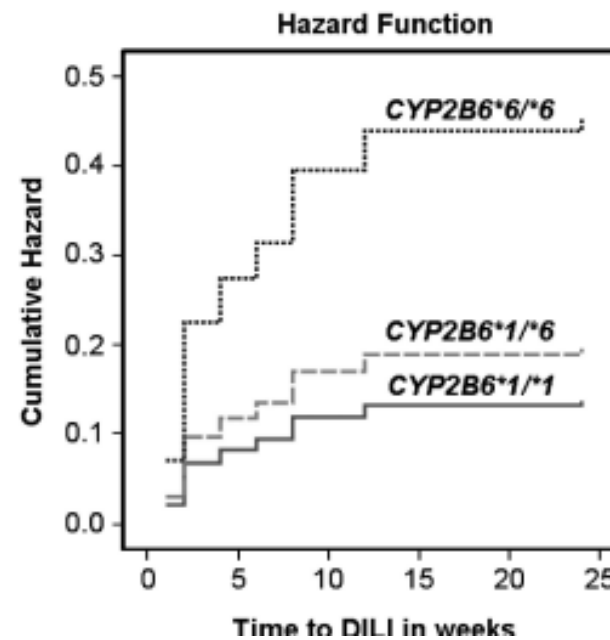
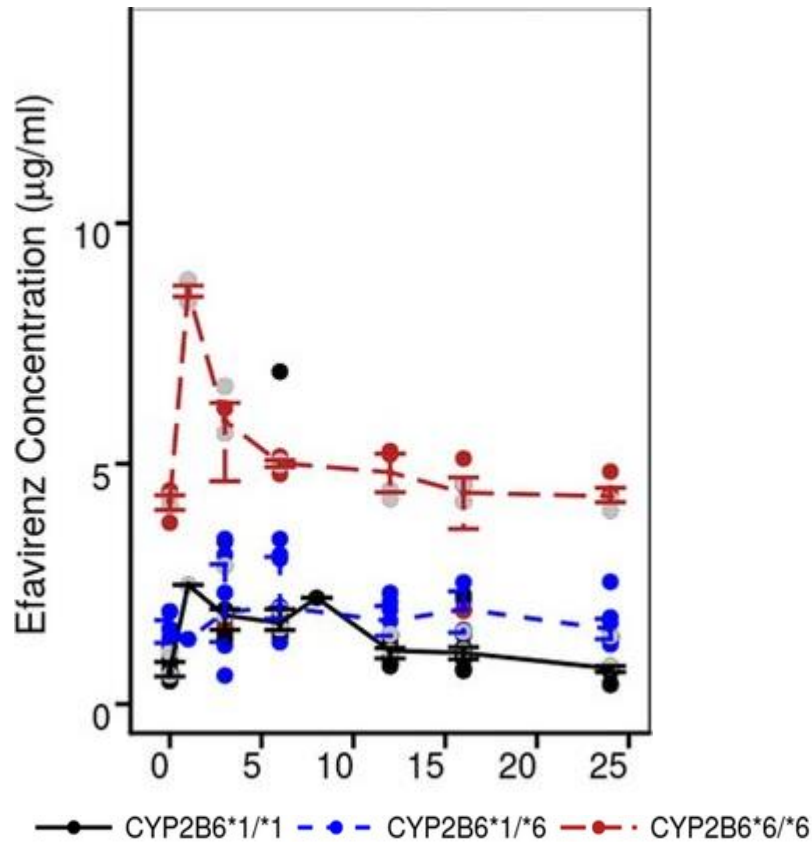
- Mutations in the genes encoding for drug metabolizing enzymes may result in significant differences in the expression and activity of the enzymes leading to different *in vivo* exposure



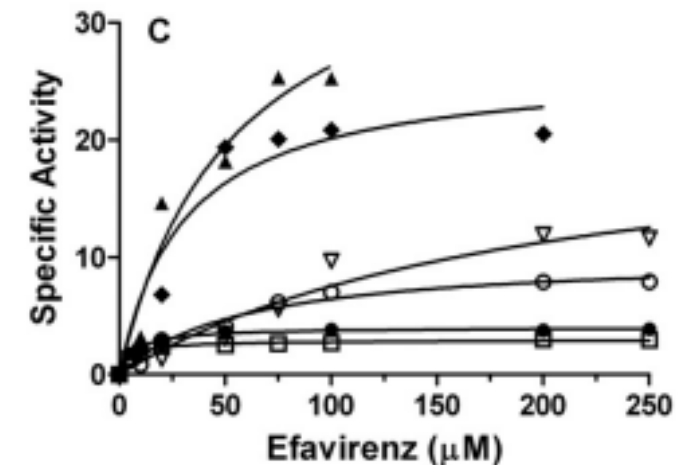
- **Slow metabolizers** (drug concentrations too high – toxicity)
- **Fast metabolizers** (drug concentrations too low – lack of efficacy, resistance?)

Efavirenz

Efavirenz metabolism is primarily through the polymorphic CYP2B6.
Slower metabolism is associated with increased risk of adverse effects

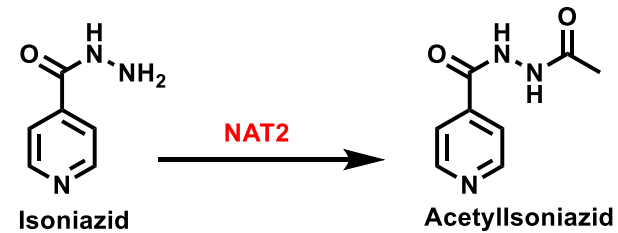


In vitro efavirenz metabolism by different variants of CYP2B6

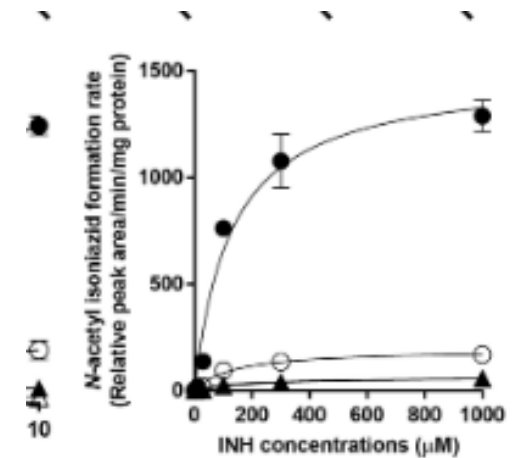
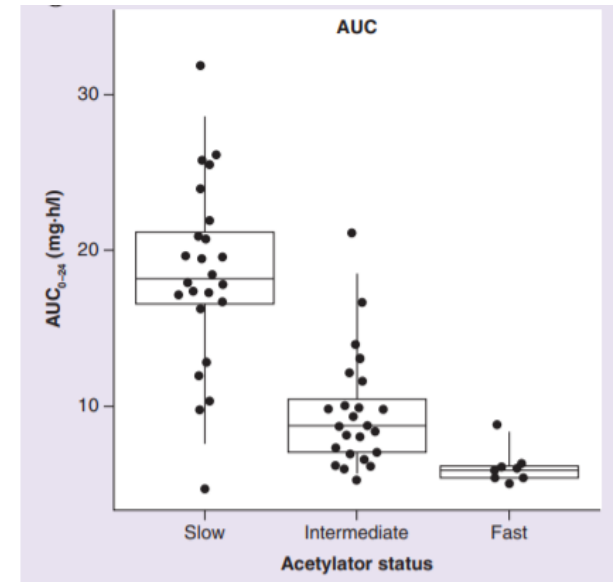
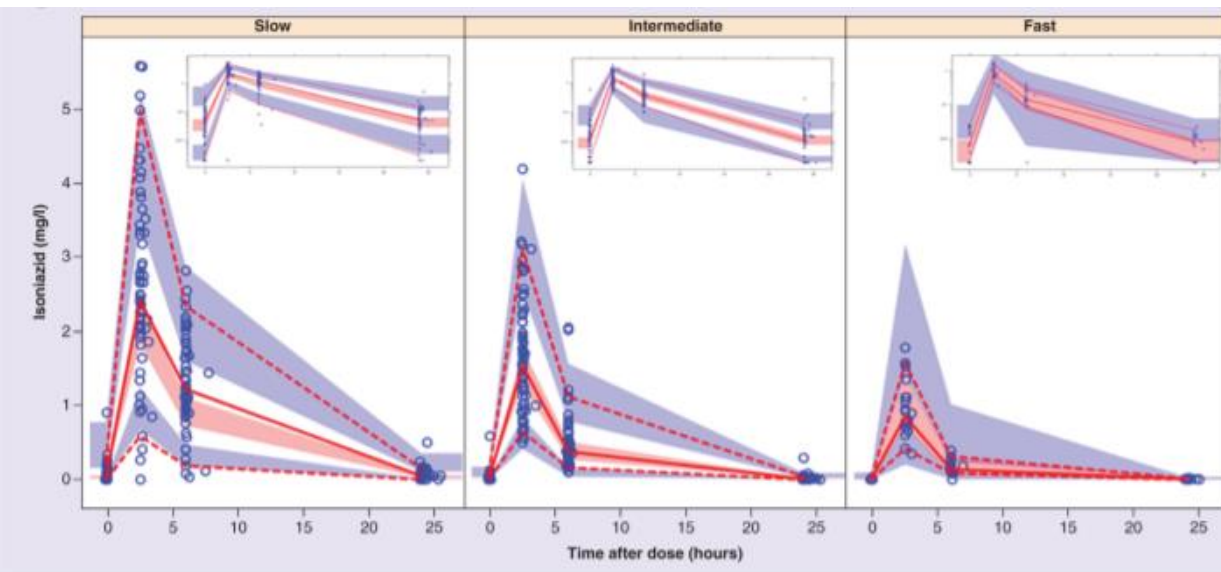


Isoniazid

- Isoniazid is primarily metabolized by acetylation through a polymorphic enzyme, *N*-acetyltransferase

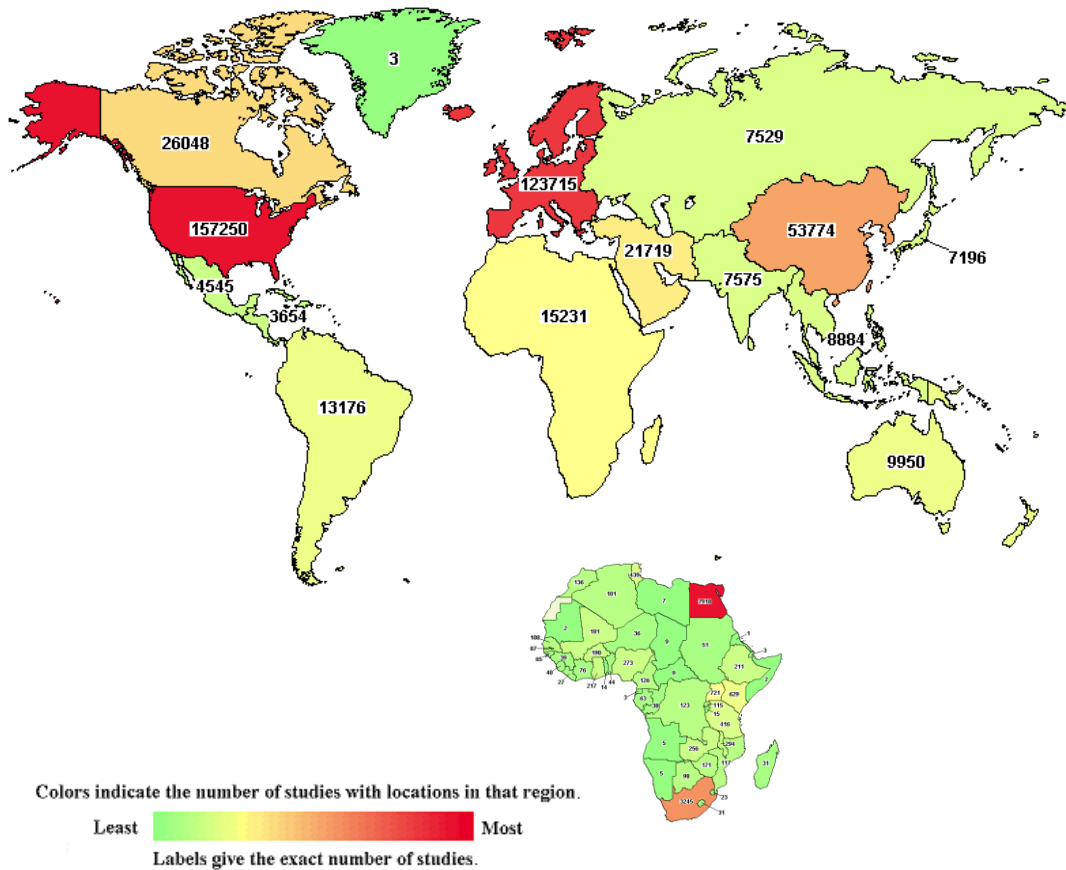


In vitro isoniazid metabolism by different variants of NAT2

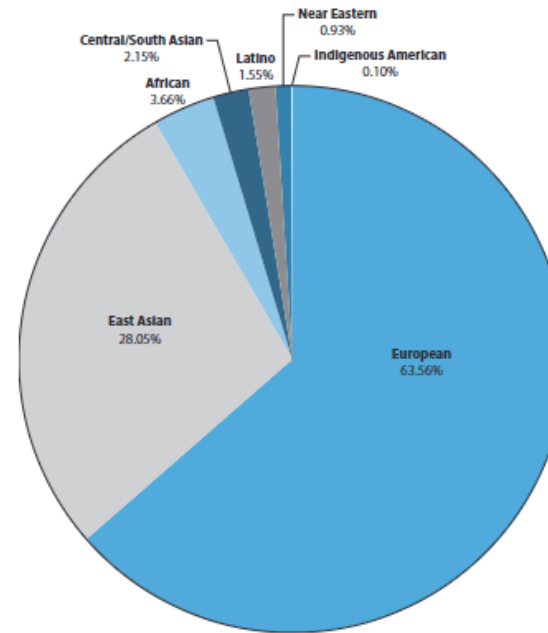


Gaps in considering genetic variability in dose prediction/optimization

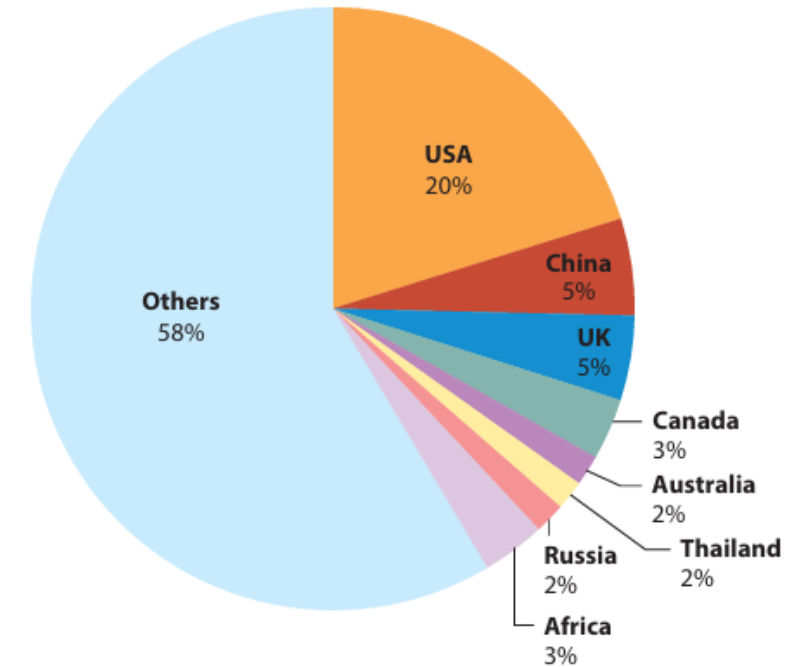
Clinical trials by region on clinicaltrials.gov



Genetic data in PharmGKB



Origin of bacterial data in PATRIC



Summary

$$Dose = \frac{C_{avg,ss} \cdot CL_{int} \cdot \tau}{f_{abs}}$$

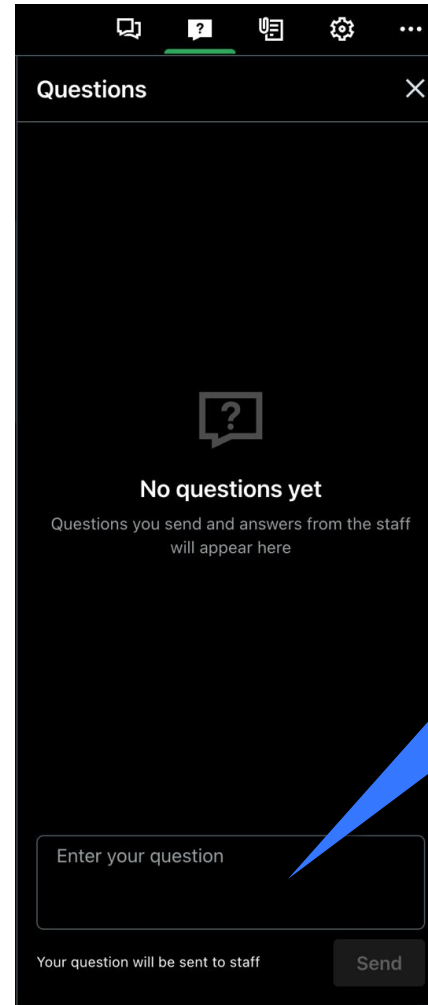
- Variability in drug metabolism contributes to interindividual variation in the efficacy and safety of drugs
- Key gaps in genomic data, clinical trials and preclinical systems need to be filled.

THANK YOU



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Questions

No questions yet

Questions you send and answers from the staff will appear here

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Greg Basarab
University of Cape
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Nina Lawrence
AstraZeneca



Mathew Njoroge
University of Cape
Town

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artificial intelligence for
antibiotic design

Speakers: **Jonathan Stokes**,
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Moderated by Akhila Kosaraju, Phare Bio, USA

Charting new frontiers in artificial intelligence for antibiotic design

With Jonathan Stokes & Kurt Thorn

- 3 April 2025, 17:00-18:30 CEST

**Thank you for
joining us**