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BETTER MEDICINE
BEST PRACTICE

PHARMACOLOGICAL ASPECTS OF CLINICAL TRIALS

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DISCLOSURES

- Alex A. Adjei has reported no conflicts of interest
- Emiliano Calvo has reported no conflicts of interest
- Anita Margulies has reported no conflicts of interest
- Ian Tannock has reported no conflicts of interest
- Joseph Tabernero has reported to have served on Advisory Boards for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Genentech, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho and Takeda

PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD)

In drug development and clinical trials

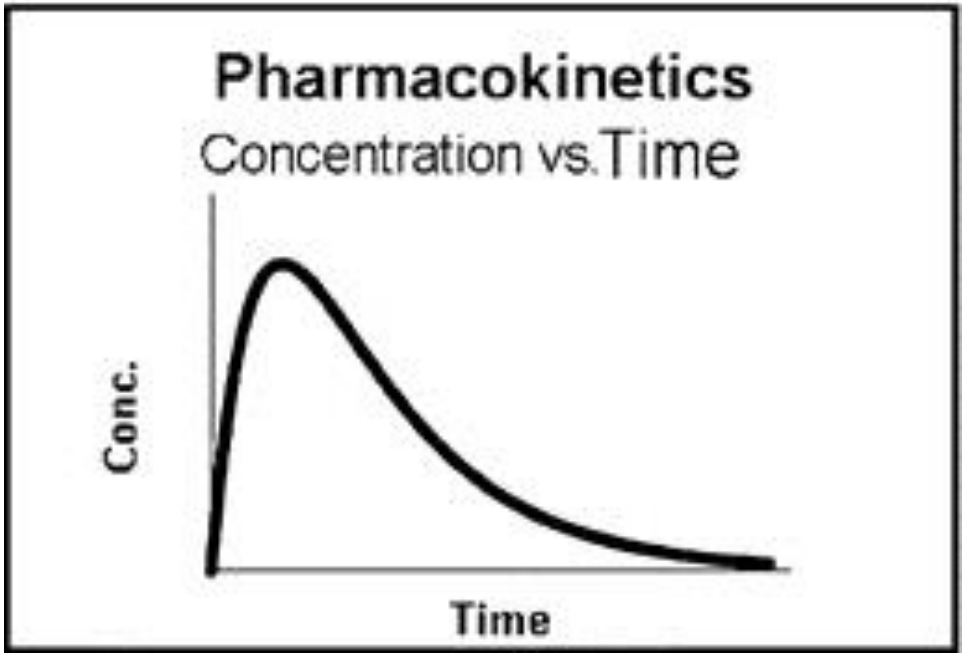
In drug development and clinical trials, what the body does to the drug (PK) is as important as what the drug does to the body (PD)

The development of targeted therapies has shifted focus to tumour biomarkers and de-emphasised the importance of PK

However, the schedule and frequency of anticancer drug administration depends on PK. This is important in drug combinations and newer drug formulations, such as nab-paclitaxel and itirinotecan

Pharmacodynamics is the study of the biochemical and physiologic effects of drugs (especially pharmaceutical drugs), and how they affect an organism, whereas **pharmacokinetics** is the study of how the organism affects the drug. Both together influence dosing, benefit, and adverse effects.

PHARMACOKINETICS (PK)

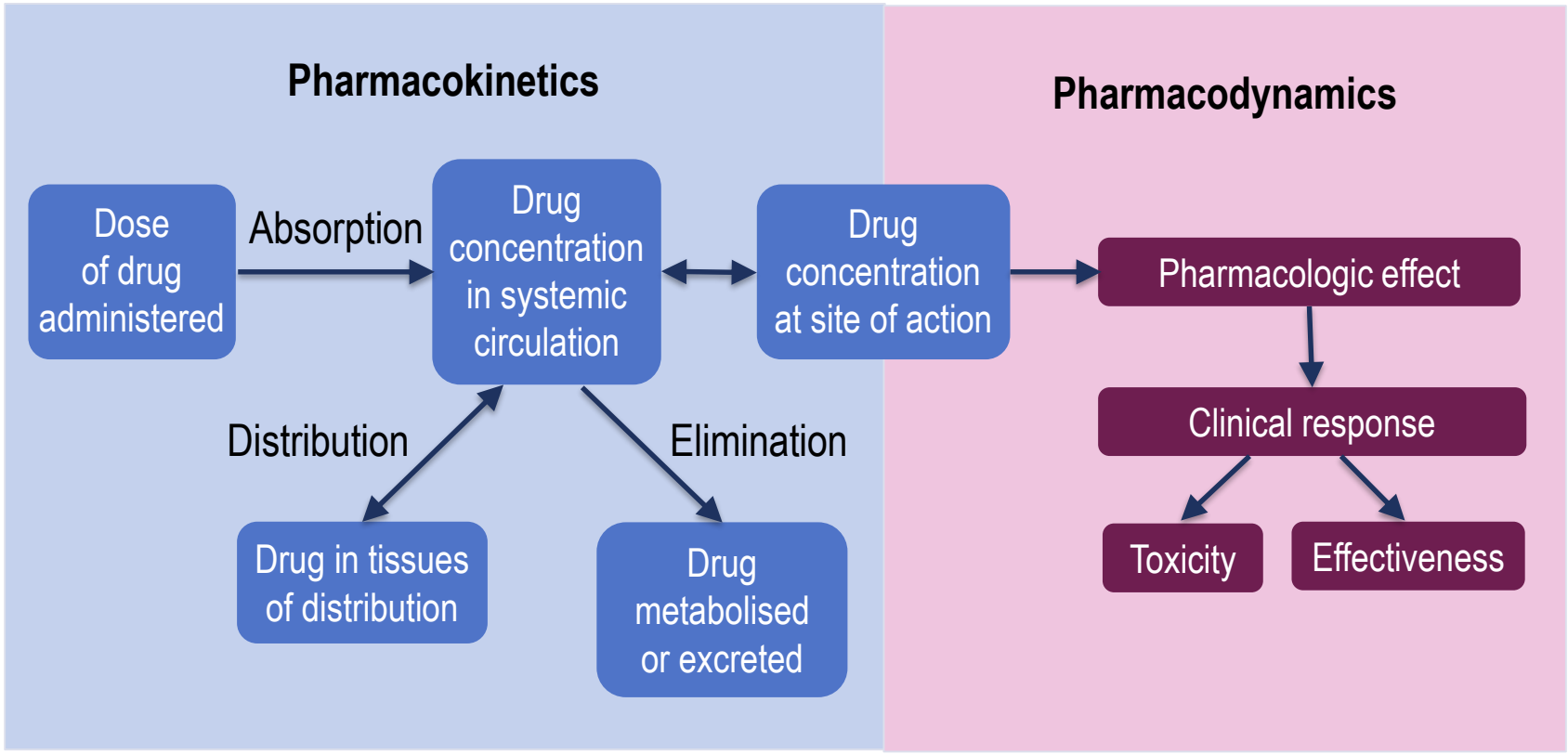


Absorption

Distribution

Metabolism

Elimination


Pharmacokinetics
Pharmacodynamics
Dose of drug administered
Absorption
Drug concentration in systemic circulation
Drug concentration at site of action
Pharmacologic effect
Clinical response
Toxicity
Effectiveness
Distribution
Elimination
Drug in tissues of distribution
Drug metabolised or excreted

SOURCES OF PK VARIABILITY

Patient-specific factors

- Genetic regulation and/or differences in absorption, metabolic and excretion pathways
- Organ function: liver, kidney
- Age
- Sex
- Race
- Weight, height (BSA)
- Circadian rhythm

Drug-related factors

- Mode of administration
- Site of administration
- Drug–drug interactions
- Incompatibilities (parenteral preparations)
- Herbal and vitamin supplements
- Food–drug interactions
- Patient adherence

APPARENT VOLUME OF DISTRIBUTION (V_D)

$$\text{Concentration} = \frac{\text{Amount of drug (dose)}}{V_d}$$

$$V_d = \frac{\text{Amount of drug (dose)}}{\text{Concentration}}$$

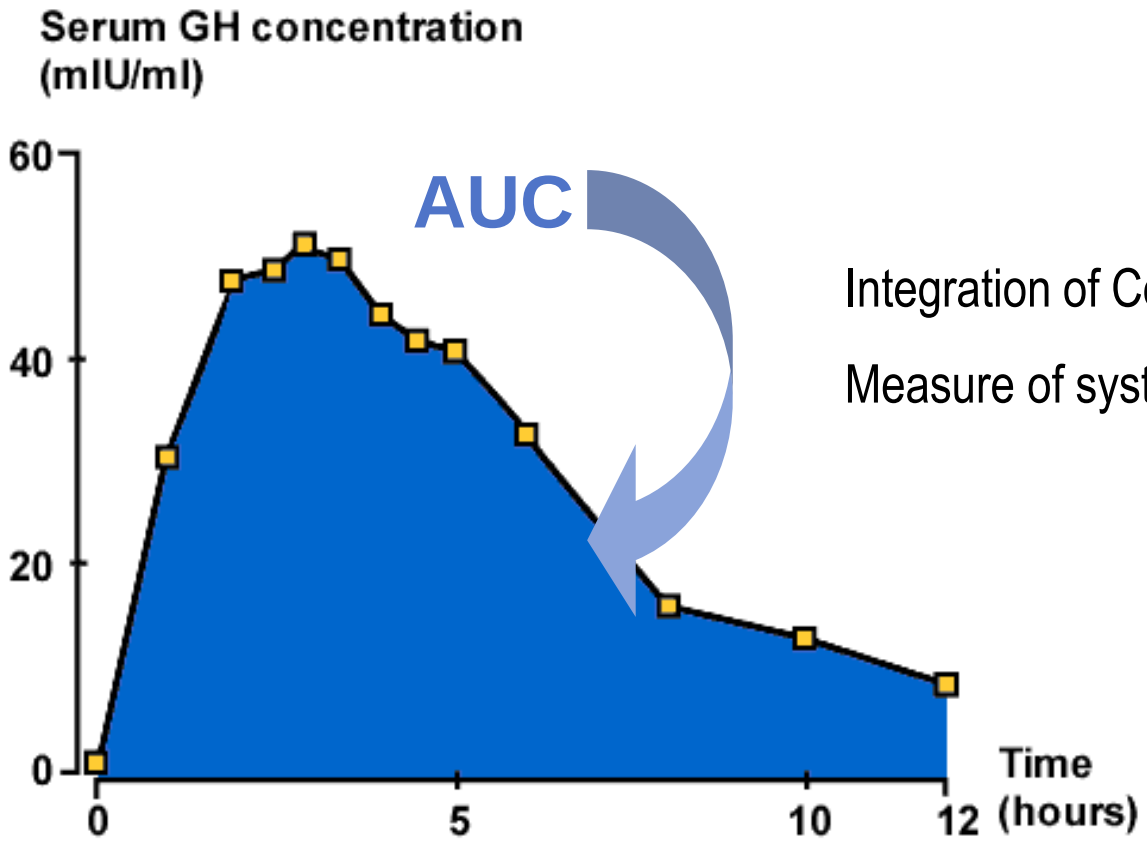
Small V_d = Low tissue binding

Large V_d Drug tightly bound

CLEARANCE (CL)

$$CL = \frac{\text{Dose}}{\text{AUC}}$$

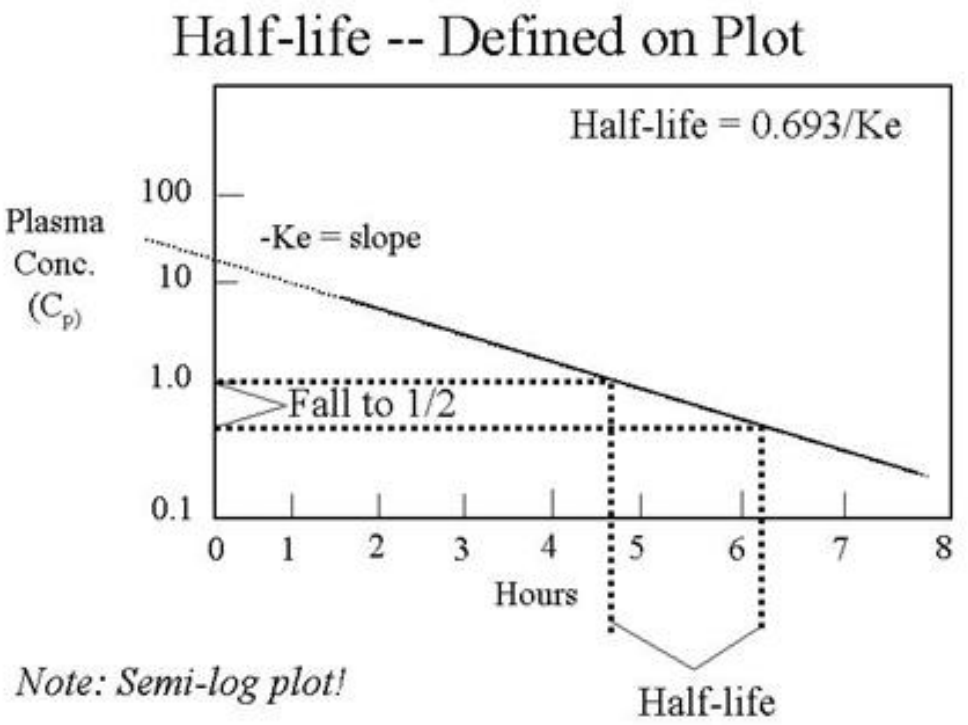
AREA UNDER THE CURVE (AUC)



Integration of Concentration *vs.* Time

Measure of systemic exposure

HALF-LIFE ($T_{½}$)



- Time required to clear 50% of drug
- Depends on Volume of Distribution (V_d) and Clearance (CL)
- Multiphasic (if you can capture the distribution phase)
- **Rule of thumb:** Drug is cleared in 5 half-lives

$$t_{½} = V_d \times \ln(2) / CL$$

OTHER IMPORTANT PARAMETERS

Peak plasma concentration

Bioavailability

Duration above a threshold concentration

Free drug *vs*. Total drug

Cumulative dose

Bioactivation to active metabolite

Plasma protein binding

Variations in drug concentration within a tumour

MOLECULARLY-TARGETED DRUGS

SHIFT TOWARDS TARGET-BASED *VS.* COMPOUND-BASED DEVELOPMENT

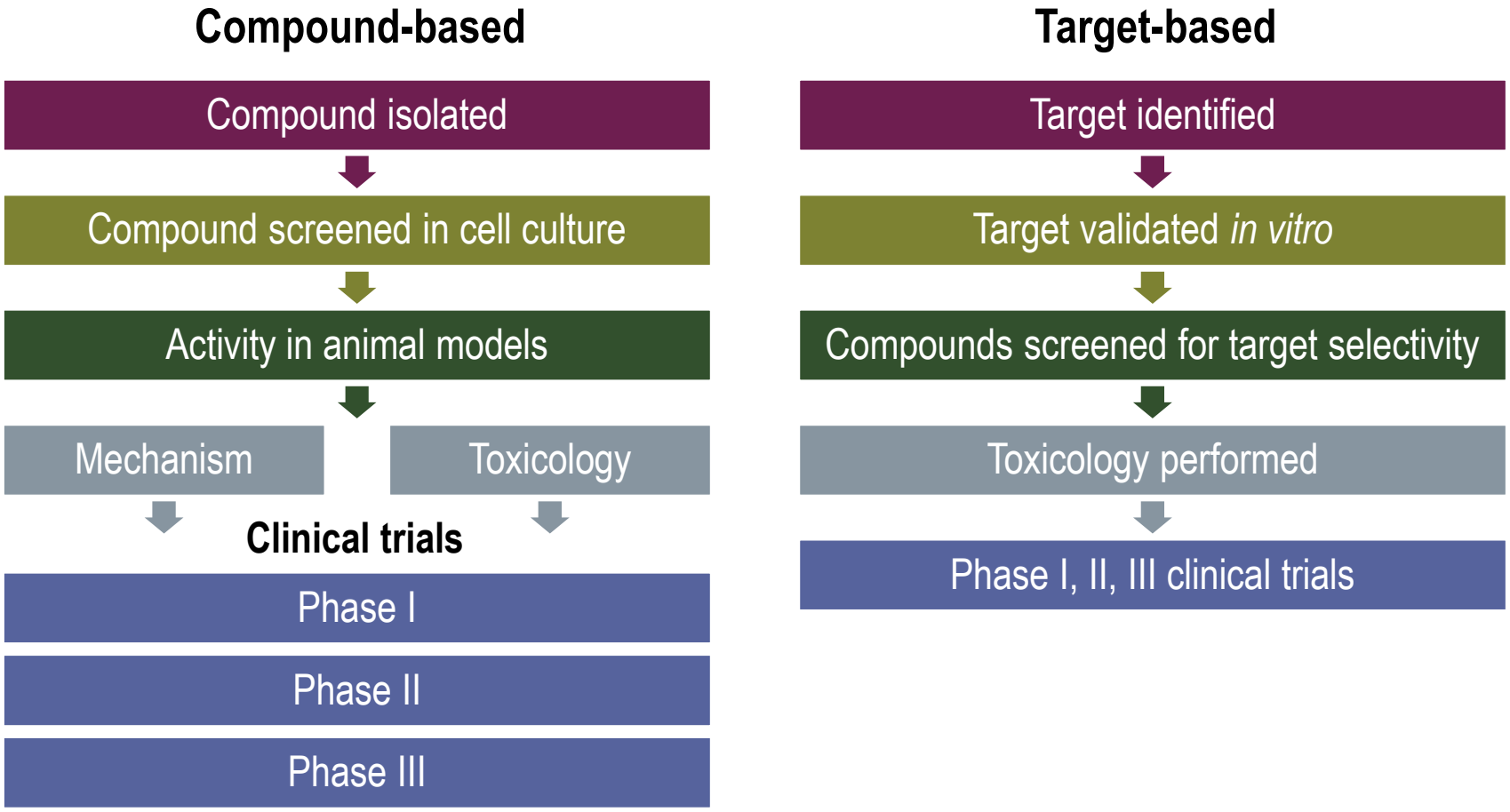
Compound-based **(backward)**

- Interesting compound discovered with activity in *in vitro* models

Target-based **(forward)**

- Protein or gene targets identified on carcinogenesis pathway
- Drugs designed to interfere with these specific targets
- Immunotherapy agents – antibodies, vaccines, etc., are developed against specific proteins

COMPOUND-BASED *VS.* TARGET-BASED DRUG DEVELOPMENT



PERSONALISED MEDICINE AND CLINICAL PHARMACOLOGY

Drugs are developed against specific targets in patient tumours

It is important in this context to also consider variations in drug exposure due to differences in drug transport, metabolism and elimination

Right drug – right patient – **right exposure** – whatever the dose

CLINICAL RATIONALE FOR DOSE MANAGEMENT

TOO HIGH

- Toxicity
- Premature treatment termination
- Higher treatment costs

TOO LOW

- Lack of therapeutic response
- Continued growth of cancer
- Higher cost of recurrence

THERAPEUTIC DRUG MONITORING (TDM): ONCOLOGY

Anticancer drugs

- Busulfan
- 5-fluorouracil
- Taxanes
- Imatinib

Consideration may have to be given to TDM in order to truly personalise therapy and truly achieve effective anticancer drugs

Therapeutic drug monitoring is the measurement of specific drugs at intervals in order to maintain an optimal concentration and benefit to the patient with minimal toxic side effects. Therapeutic drug monitoring is common in other fields of medicine, especially the use of antiepileptic medicines, some antibiotics, and immunosuppressants. In oncology, therapeutic drug monitoring has been used primarily with vancomycin, methotrexate, and carboplatin.

CLINICAL PHARMACOLOGY: CONCLUSIONS

Critical part of the clinical development of new anticancer drugs

PK data can give important information as to mechanisms responsible for distribution, metabolism, and elimination

Allows assessment of degree of intra- and inter-patient PK variability

PD correlations between drug exposure and drug toxicity can be made

Provides insights into optimal dose and schedule for subsequent Phase II studies

THANK YOU!

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