1

The Importance of Pharmacokinetics in Early Drug Discovery

Learning Objectives

Upon completion of this chapter, you should be able to answer the following questions:

- What is the process of drug discovery?
- What is PK and what are the various roles it plays in drug discovery?
- Why is PK often used as a surrogate for efficacy?
- How is "good" PK defined for the purpose of compound screening and optimization?

Imagine! You have just been asked to participate in a brand-new drug discovery effort for an important yet unmet medical need. Many patients are depending on your team's effort to get a safe and effective drug to them as soon as possible and at an affordable price. Early basic research has already demonstrated with experimental data that intervention of a certain part of a specific pharmacological pathway could result in the desired therapeutic effect. Several potential "hits," molecules that can engage the target, have been identified. Now it is up to your team, consisting of computational and medicinal chemists, biologists, toxicologists, drug metabolism and pharmacokinetic (PK) scientists, among others, to decide how to further optimize the hits and to find the best one to take into human trial. There is excitement in the air.

1.1 PK as a Surrogate for Efficacy

Because of the huge number of compounds typically evaluated in the discovery stages, the screening process employs mostly high-throughput in vitro or in-silico assays amenable to automation, which require less (or no) synthesized material. But how does one know if the collection of compound properties measured in vitro would result in clinical efficacy in vivo? Short of testing the compounds directly in humans, the only way to demonstrate efficacy in vivo is to test it in a suitable animal model. Unfortunately, animal models are not always predictive of human effectiveness (Henderson et al., 2013; McGonigle and Ruggeri, 2014). Even for a validated animal model with demonstrated translatability to human efficacy, such in vivo studies require long durations for the pharmacological effect to manifest. The observed effect can often be highly variable and requires averaging data across many study animals in order to ascertain a reliable readout. All of these mean long study duration, hundreds of milligrams of chemical substances and involvement of many animals and personnel, not something practical to execute for the large number of compounds screened during early discovery. How else can the potential efficacy of a large number of compounds be evaluated without testing them in such labor-intensive and time-consuming animal pharmacology studies?

Putting Pharmacokinetics and Pharmacodynamics to Work in Drug Discovery: A Practical Guide for Pharmaceutical Scientists, First Edition. Emile P. Chen.

This is why human PK predicted from in vivo animal PK or in vitro ADME (absorption, distribution, metabolism, and excretion) data is often used as a surrogate for efficacy. Basic principles of pharmacology tell us that effect is elicited by the compounds that are not bound to any proteins or tissue components at the site of action. In most cases, the compound is carried to the target organ by the arterial blood that perfuses it. So, if a compound's systemic concentration in human in vivo can be predicted from in vivo or in vitro screening data, then it should be possible to use it as a gauge to determine if the compound can reach a high enough concentration and with sufficient persistence at the site of action to achieve efficacy.

Let's begin by considering the fate of a compound as it moves through the body. The focus is placed only on oral administration here, which is the most frequently used route of administration for most drugs on the market. Other dose routes will be discussed in Chapter 6.

Figure 1.1 highlights the journey a compound takes from where it is administered to reach its intended target. For example, an orally administered compound is emptied from the stomach into the small intestine, where most compounds are absorbed. As the molecules permeate across the enterocytes lining the gut wall, they could be metabolized by enzymes residing inside. The surviving molecules will then enter the portal vein, which takes them to the liver, where they may be subject to further metabolism or excretion into the bile. The molecules that escape the liver finally enter the general circulation and are carried to various organs and could be subject to further metabolism and/or excretion in the kidney or other tissues.

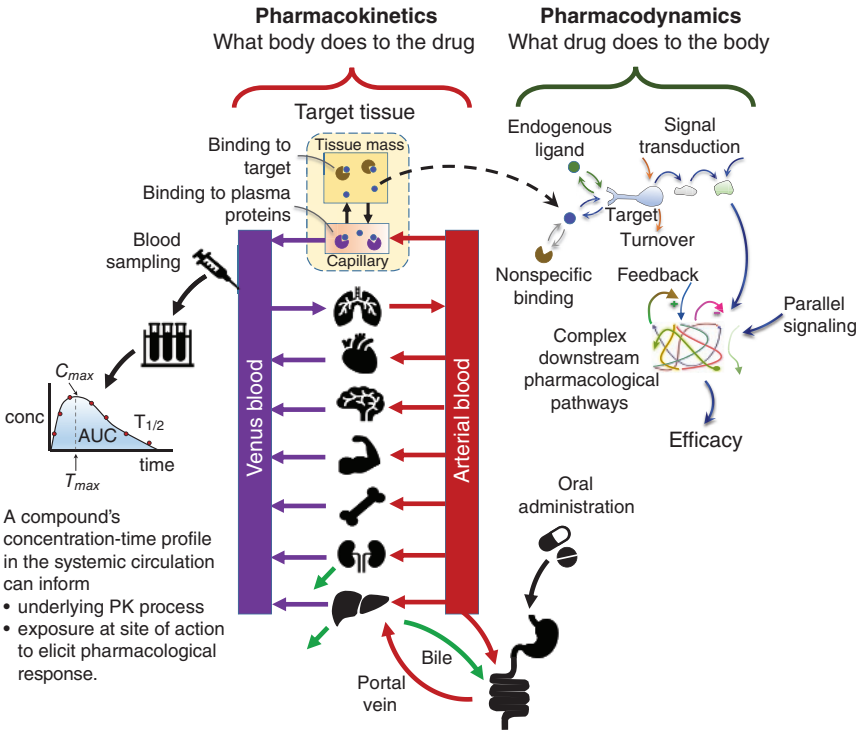

Figure 1.1 The fate of an orally administered compound as it journeys around the body and distributes into the target tissue. Only the unbound and unionized form of the compound can move between capillary blood and tissue mass, as well as between interstitial and intracellular spaces. Once inside the target tissue, unbound compound engages its intended target to trigger a cascade of pharmacological activities leading to clinical effect. Only selected organs are represented in the diagram. Red arrows represent arterial blood flow, except for portal vein blood flow that carries the absorbed compound to the liver, purple arrows represent venous blood flow, green arrows represent metabolism and excretion, and blue arrows represent pharmacological actions.

This journey is commonly summarized into four distinct processes: Absorption, distribution, metabolism, and excretion, abbreviated as ADME. These four processes collectively influence and determine the systemic and tissue level of all compounds.

1.1.1 Absorption

An orally administered compound must first be dissolved in the digestive tract and move across the intestinal mucous membrane into the portal vein before reaching the bloodstream via the liver.

1.1.2 Distribution

While in the systemic circulation, the compound could be bound to plasma proteins or be taken up into blood cells. The compound would also quickly settle into an equilibrium between the ionized and unionized form according to its acid/base characteristics and the pH in blood. The bloodstream carries the compound to various organs in the body. On reaching individual organs, only the unbound and unionized form of the compound can cross the blood vessel walls to get inside. This transit can occur either passively according to the concentration gradient on both sides of the membrane, or via active transport. Once inside the tissue, the compound could further interact nonspecifically with tissue components (i.e., tissue proteins, lipoproteins, etc.). Only the unbound and unionized portion of the compound can leave the tissue through the membranes separating the capillary blood and tissue mass.

The disposition of the compound at its site of action is governed by the same distribution process. In most cases, it must reach systemic circulation from the site of administration first, before being carried to the target tissue. Exceptions include local administration, such as inhaled drug targeting the lung, or topical applications targeting the skin, or even orally dosed drugs targeting the intestinal wall. In these cases, the administered compound reaches its intended target organ before it reaches general circulation (see section 10.6). Once reaching the target tissue, it is usually assumed that only the unbound compound in the target tissue is free to engage the intended target.

1.1.3 Metabolism

Compounds inevitably begin to break down once inside the body. Most compounds are metabolized in the liver by reduction and oxidation enzymes, called cytochrome P450 enzymes, to form metabolites that are usually pharmacologically inactive and more readily excreted. However, some metabolites may also be pharmacologically active, sometimes more so than the parent compound, and can also be toxic (Obach, 2013).

1.1.4 Excretion

Compounds and their metabolites are removed from the body via excretion. The three main routes of excretions are (1) the kidney, which is the main route, where compounds and their metabolites are excreted through urine, (2) biliary excretion initiated in the liver into the gut and excreted in the feces, and to a lesser extent (3) through the lung.

Because a compound is carried to the tissue by the arterial blood that perfuses it, its concentration and persistence in the tissue is reflected by its concentration and persistence in the systemic circulation. To be sure, a compound's concentration in the target tissue would be somewhat different from that in the systemic circulation due to various physiological and compound-related properties (discussed in greater detail in Chapter 10), but concentration in the tissue is unlikely to be high and long-lasting without the same in the systemic circulation. In other words, the time course of a compound's concentration in the systemic circulation (either blood or plasma) can serve as a reasonable surrogate for efficacy.

This is a good thing, because the concentration in systemic circulation is much easier to measure than at the target site, not to mention the pharmacological effect it elicits in most cases. Instead of screening for efficacious compounds in lengthy and costly pharmacological studies in animal models, it would be far more efficient to look for compounds with reasonable concentration in the systemic circulation. The in vivo studies to characterize the compound's systemic concentration-time profile is far less resource intensive than most pharmacology studies; they involve only a few animals, small amounts of drug substance, and quick turnaround of results, typically within a few days rather than a few weeks. As we will learn in later chapters, the concentration-time profile of a compound can even be inferred with some accuracy using data from in vitro experiments or in-silico predictions, further reducing the resource requirement and making this approach very amenable as part of the screening strategy. By the same logic, PK can also serve as a surrogate for safety evaluation, as toxicology is just the expression of undesirable pharmacological effects.

1.2 The Many Faces of Pharmacokineticists

From these discussions, it is easy to see why systemic PK can play a significant role in all stages of discovery to improve drug discovery efficiency (Peck et al., 1993). Over the past few decades, the pharmaceutical industry has become increasingly adept at optimizing the PK of small molecules resulting in fewer failures at Phase I clinical trials. In 1991, PK and bioavailability were cited as the most significant cause of attrition (Kola and Landis, 2004). But by 2000, these factors had ceased to be a significant cause of attrition (Arrowsmith, 2011). Instead, by 2000, the greatest reason for drug failure was lack of efficacy and toxicity, together accounting for approximately 50% of attrition.

Five roles PK play in discovery decision making are illustrated in Figure 1.2 and also outlined in text. Applications of PK principles under each role are detailed throughout the subsequent chapters.

1.2.1 Pharmacokineticists as Observers

In vivo PK data from preclinical studies become available during the later phases of discovery, especially in lead optimization. In this role, PK is used to ***describe*** the time course of compound concentration in systemic circulation ***observed*** from in vivo preclinical animal studies to answer questions such as: how high do compound concentrations reach, how long does it take to reach the peak, how quickly or slowly does it disappear from the blood, how much does compound accumulate when it is administered repeatedly? From this information, one can infer the compound concentration and persistence in the target site. The observed concentration-time profile can then be compared to potency of the compound to determine at what dosage and dosing frequency drug concentrations would be high enough relative to the potency to elicit the desired response. This topic is covered in Chapter 2. The potency used here would either be measured in in vitro assays or be deduced from in vivo animal pharmacology studies. If potency is measured in vitro, such as using biochemical assays quantifying binding affinity or cell-based assays that measure a biological signal to more closely approximate the in vivo situation, caution must be exercised in the utilization of these in vitro data as a surrogate for in vivo potency (see Chapter 11 for more details). If potency is deduced from in vivo animal pharmacology studies, then species-differences in potency must be considered (discussed in section 16.2).

Either way, both the PK and potency estimates would need to be suitably translated to human before comparisons are made (detailed in Part Three of this book). Another prerequisite is knowing which part of the concentration-time profile should be compared to potency. As mentioned earlier in this chapter, the PK endpoint (defined in section 2.1) driving efficacy (a.k.a. PK driver) is not generic, but highly dependent on the pharmacodynamics (PD) modulated by the interaction of a compound with its target. How to identify the PK drivers of efficacy is detailed in Part Two of the book, specifically in Chapter 12. In Chapter 2, the discussion

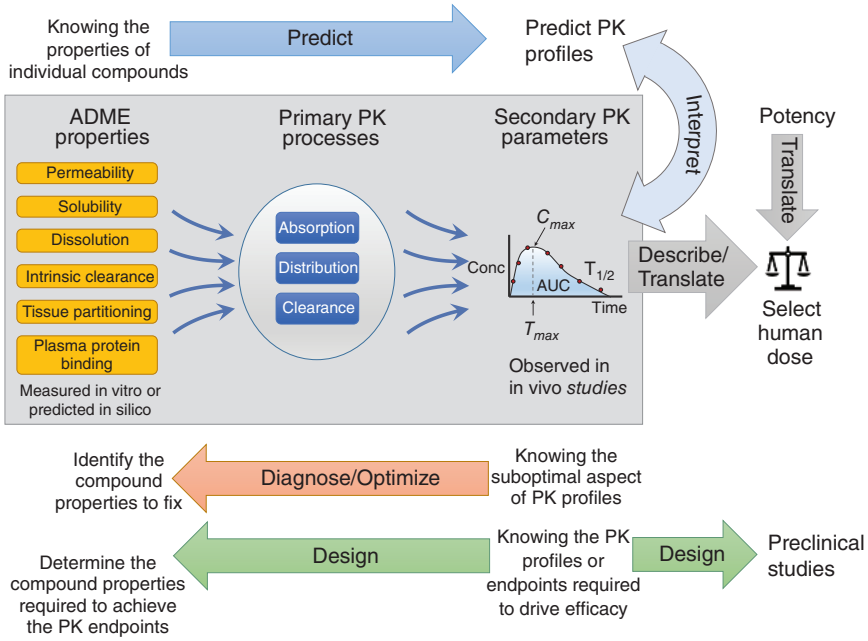

Figure 1.2 A roadmap outlining the many roles PK play in discovery decision making. The central box depicts the connections between a compound's systemic concentration-time profile (right), the underlying primary PK processes (middle), and the compound's ADME properties (left). Only representative compound properties are depicted. Block arrows depict the direction of logic flow in decision making. Secondary PK parameters are those describing the observed concentration-time profiles, while primary PK parameters characterize the underlying PK processes (see Chapter 2).

would presume PK and potency have been suitably translated and the PK endpoints most important to drive efficacy have been determined.

1.2.2 Pharmacokineticists as Predictors

At an earlier stage of discovery when only in vitro data are available, then PK principles could be used to translate the in vitro data to predict in vivo PK. The time course of a compound's concentration in the systemic circulation is the consequence of how fast it is absorbed from the site of administration, how much and how quickly it is distributed into the various body compartments, and how quickly and through which routes the compound is cleared from the body. All these rate processes are mechanistically linked to, and can be predicted from, compound properties that can be measured in vitro. Once predicted, the concentration-time profile can be compared to measures of potency to decide if the criteria for efficacy can be met when administered at a reasonable dosing regimen or not. Several steps are required to understand how such predictions are made. First, the PK profile is deconvolved into its underlying PK processes in Chapter 3. Each of the PK processes, namely distribution, clearance, and absorption, are subsequently linked mechanistically to the in vitro measured compound properties in Chapters 4 to 6. Compound selection based on the action of these ADME properties acting in concert is discussed in Chapter 7 where all the PK concepts discussed in Part One of the book are integrated.

At an even earlier discovery stage, when decisions are being made on which compounds to synthesize and to be taken into in vitro assays, the same type of analysis can still be performed by predicting the PK profiles from molecular properties using in silico quantitative-structure-property-relationship (QSPR) models (see Appendix B for more details). This topic is also covered in Chapter 7 and in various chapters for each of the ADME properties.

1.2.3 Pharmacokineticists as Detectives

PK is useful not only to describe or predict the systemic concentration-time profile to aid compound selection and prioritization. If all the compounds fail the selection criteria for PK related issues (i.e., rather than for potency or safety concerns), then the above-mentioned PK concepts can be applied in reverse to find out which compound properties should be improved in future compounds. **PK can be used as a detective tool** to reveal which PK process is responsible for inadequate peak systemic compound concentration, delay in reaching the peak, or disappearing from the systemic circulation too quickly to elicit the pharmacological effect (e.g., may need to be administered at an unreasonably high dose or frequency). Through such a diagnostic process, PK can help inform computational and medicinal chemists in designing future molecules to mitigate the root causes of suboptimal PK.

The approach to identify the causes of suboptimal PK is presented in Chapter 3. Chapters 4 to 6 subsequently discuss how various compound properties contribute to the primary PK processes being the root causes of the PK endpoint not being fulfilled. Integration of these concepts, with examples of their applications in discovery scenarios, are presented in Chapter 7.

1.2.4 Pharmacokineticists as Designers

Even though PK can be an effective tool in diagnosing the causes of suboptimal PK, it would be more efficient to design a compound a priori with optimal properties rather than optimizing the properties of a compound after it has been synthesized. Beginning with an identified ideal PK driver for efficacy (Part Two of this book), the logic flow from compound properties to primary PK processes to concentration-time profile, described previously, can be applied in reverse to identify the optimal compound space required for an efficacious drug. Because compound properties work in concert to define its concentration-time profile, they can trade off for one another in complex manners. One approach is to build a physiologically based PK (PBPK) model detailed in section 7.8 that mathematically links compound properties to the concentration-time profile, and to use Monte-Carlo simulation to virtually explore the compound property space to identify the optimal space (Chen et al., 2021).

To effectively inform medicinal chemistry strategy, however, it would be necessary to map the optimal compound property space to molecular properties. For example, should we make compounds that are more lipophilic or less lipophilic, what are the optimal numbers of hydrogen bond donors and acceptors, including or excluding which functional group or molecular fragments? One can leverage QSPR models that predict compound properties from molecular descriptors to determine the optimal molecular properties to synthesize. However, because the relationship between compound properties and their molecular features are not one-to-one, this becomes a complex multidimensional optimization problem. One solution is to use virtually enumerated compounds, with compound properties predicted using QSPR models, to virtually probe PBPK models in order to identify the molecular features or functional groups most important to drive efficacy (Chen et al., 2022). These model-based virtual exploration approaches are described in more detail in Chapters 7 and 13.

PK principles can also be used to aid the design of studies, such as picking the dose levels, frequency of dosing, duration of study, number of animals, types, and timing of measurements to make. Chapter 2 illustrates how one uses PK data from existing in vivo studies to design new studies. However, the approach can be extended to design first-time in vivo PK studies using PK profiles predicted from in vitro measured or in silico predicted compound properties as well.

1.2.5 Pharmacokineticists as Interpreters

At the earliest stages of discovery, in the absence of indicative mechanistic data, PK prediction and diagnostics are usually conducted without assuming the involvement of more complex PK processes. However, as soon as in vivo PK data from preclinical species become available, one could use these data to check the validity of such

simplifying assumptions. Misprediction of in vivo PK from in vitro ADME properties could reveal the involvement of more complex mechanisms. This topic is covered in each of Chapters 4 to 6. Because of the complexity of interweaving PK processes and properties, often this is most effectively done from building and calibration of PBPK models. But for simpler situations, this can also be done using the deductive process described previously.

In fact, PK prediction and interpretation should be done in an iterative manner throughout discovery. PK prediction could indicate the need of new studies, while mismatch between prediction and the resulting data could suggest inclusion of additional PK mechanisms and the revision of prediction. One must keep in mind that all predictions are inherently uncertain in nature, and progress selected compounds with less favorable predictions along with the compounds with favorable predictions to fully explore the compound space.

PK principles also have useful applications in the interpretation of pharmacology studies in late-stage discovery. As covered in Part Two of this book, it can be used in conjunction with PD principles to understand why we get negative results despite good PK or vice versa.

1.3 The Criteria for Good PK of a Therapeutically Useful Drug

To discuss optimization of PK properties effectively, it is necessary to first define what good PK is. On the surface, the attributes of good PK seem apparent: have acceptable solubility and permeability suitable for development of formulation and ensure complete absorption (preferably via passive absorption to reduce the probability of interaction with other drugs or food or polymorphisms), have a low clearance (often defined as below 20% to 30% of liver blood flow), have long half-life, and have acceptable volume of distribution (Wan, 2013). In practice, however, the definition of a good PK profile is more complicated. Is it necessary to always have clearance below 20% to 30% of liver blood flow? Is long half-life always necessary, and if so, how long is long enough? Can some of the parameters trade off for one another? On the flip side, could a compound with perfect PK still fail to elicit the desired clinical outcome?

While safety and efficacy are paramount in our search for the right compound to develop, one criterion for a marketable drug is that the final product must be able to deliver its beneficial effects in a practical manner. For example, it must be something that can be practically manufactured in large quantity, with chemical properties amendable for development of a suitable dosage form that can be reliably given to the patient at a reasonable dosing regimen, at reasonable cost, and with minimum drug-drug interaction (DDI) potential.

Here focus will be placed only on the dosing regimen aspect. As the Swiss physician and philosopher Paracelsus once said, "The dose makes the poison." Anything can be poisonous if given at a high enough dose. The same is true for beneficial pharmacological effects; even compounds with suboptimal potency and PK can be effective if given at a high enough dose and frequent enough. But a marketable drug must achieve the desired therapeutic effect at a **reasonable dose given at a reasonable interval via a practical dose route**. While what is considered reasonable varies from case to case, it is not difficult to see as an extreme example that a drug that needs to be given at a dosage of several thousand mg would not be very practical nor desirable for the patient. It would be very challenging, if not impossible, to formulate a 10,000 mg drug while keeping the pill small enough for easily swallowing and does not cause GI irritation or interact with other drugs taken concurrently. Typically, it is aimed to keep the dosage at a few hundred milligrams or lower. For example, the guidelines for drug candidates at GSK recommend the dose for oral drugs to be below 100 mg (Bayliss et al., 2016). **Reasonable dosing frequency** is another important criterion of a practical drug. Once again, what is deemed reasonable varies from case to case. However, a drug that the patient needs to take once every hour is not a very practical one. Generally, one aims for once daily dosing, although there are efforts to make certain drugs such as anti-HIV drugs, that can be taken once monthly or even less frequently. Clearly dose route also impact this consideration, as weekly intravenous infusion at a clinic is not as convenient to the patient as monthly self-administered subcutaneous injection.

From PK and efficacy points of view, therefore, ideal compounds are those that can achieve a certain compound concentration at a reasonable dose, and with its concentration declining slowly enough that repeated dosing at a reasonable interval is enough to be maintained above the required level for a suitable duration. These two factors must be incorporated into our thinking during the early preclinical stages during the screening phase and still have the flexibility to shape the direction of medicinal chemistry, so that the final candidate for human trials will have the appropriate properties.

A prerequisite for PK optimization, therefore, is knowing what PK is needed to elicit the desired PD responses. This is highly dependent on the pharmacology targeted for therapeutic modulation. Some pharmacology requires continuously maintained compound concentration to remain efficacious, while others only require concentration to be maintained part of the time. Furthermore, some pharmacology requires the compound concentration to be far above a certain targeted level, while others have a more relaxed requirement. The approaches to analyze and elucidate the PK requirements for specific pharmacological processes are discussed in detail in Part Two. For Part One of the book, it would assume that these physiology-specific PK properties have already been identified.

Affinity is the strength of interaction between a compound and its target.
Efficacy is the maximum effect achievable by a compound.
Potency is a measure of the exposure of a compound needed to elicit the desired effect. It is a reflection of both affinity and efficacy.
Selectivity is a measure of a compound's affinity to the receptor it is designed to engage, relative to others that it is not meant to affect.

1.4 The Goals of Early Discovery

Before discussing the industrial applications of PK and PD, lets first take a brief look at the overall drug discovery and development process of new medicines. For a more thorough treatment please refer to the excellent review of Hughes et al. (2011).

The goal of drug discovery and development is to deliver candidate compounds with high probability of being safe and therapeutically effective in humans. Broadly, the process can be divided into drug discovery, preclinical development, and clinical development stages. In the **drug discovery** stage, thousands of compounds are screened in an iterative process to find one or more with drug-like properties that can engage a target with sufficient potency and selectivity and the appropriate PK properties to deliver them to the intended site of action. In the ***preclinical development*** stage, these few drug-like molecules are subjected to even more extensive studies (usually in vivo, but also additional in vitro or *ex vivo* studies) to establish an even stronger case that at least one of these molecules will be efficacious and safe in humans. Safety is especially important, as the value of a new medicine is based on its benefit outweighing its risks (risk-benefit ratio), and regulatory agencies have stringent requirements for sufficient preclinical evidence on safety before a molecule can progress into human trials.

The output of the preclinical development stage is a drug candidate to be progressed into ***clinical development***, which is further divided broadly into three phases. ***Phase I*** is usually conducted in healthy volunteers (but can be in patients in some cases) to assess primarily PK, safety and tolerability. ***Phase II*** studies are conducted in patients with the target disease to look for preliminary evidence of efficacy and establish a dose-response relationship. The results collected in Phase II will be used to pick the optimal study design (dose level, dosing frequency, and duration of study) for the large-scale ***Phase III*** studies to confirm safety and efficacy. Clinical studies to evaluate drug-drug interaction potential (which could reduce efficacy or magnify toxicity) are also conducted during the clinical development stage. Additional preclinical safety studies are often conducted

during this stage to assess potential long-term toxicities such as carcinogenicity and effects on the developmental and reproductive systems. Preclinical studies may also be conducted as needed to further elucidate the mechanism of pharmacological or adverse effects.

This book is primarily focused on the discovery and preclinical development stages leading up to the selection of a compound to be advanced into initial human trials (Phase I). These stages are further subdivided into several important milestones: target identification and validation, hit generation, hit-to-lead optimization, lead identification and optimization, and candidate selection. The name of the stages may vary from company to company, but the general concepts are universal.

Target identification and validation usually begins with early research leading to the formation of a biological hypothesis that intervention of a certain part of biological pathways will result in the desired therapeutic effect in a disease of interest. The identified target for intervention must then be validated with experimental data.

The next step is hit identification, the process of discovering compounds, also called hits, that can reasonably interact with a fully validated target and modify its function. High throughput screening (HTS) is one of the main approaches to identify hits. It involves screening of entire compound libraries against the pharmacological target, generating approximately 30% of published clinical development candidates (Brown and Boström, 2018). Hits can also be identified through more focused or knowledge-based screening, where select subsets of chemical libraries are screened, or fragment screening where very small molecules from a compound library are screened at high concentrations. A large percentage of hits are also generated from existing compounds.

Because of the huge number of compounds typically tested at this step, the screening process employs mostly high-throughput in vitro or in silico assays amendable to automation and requiring a minimum amount of synthesized material. Compounds that are found active against the selected target are then retested to make sure that the activity is reproducible, followed by tests in a range of concentrations to establish the concentration-activity relationship. A subset of active compounds is then tested using lower throughput assays, such as functional cellular assays, that better represent the physiological conditions surrounding the target. Confirmed hits are then ranked to determine which to progress for additional in vitro testing. It is important to recognize that the ability to interact with the target is only one of the criteria in the progression selection decision. Selectivity, synthetic tractability (a compound's synthesis feasibility), and other factors such as up-scaling or cost of goods are also important aspects for consideration. Compound physicochemical properties are also taken in considerations, as they drive the in vivo properties. A compound's mode of action can also be verified using biophysical assays to rule out promiscuous binding.

Of course, activity alone is not enough to assure a compound's efficacy. It also needs to have adequate PK properties to ensure that high compound concentrations reach the site of action and persist there long enough to engage the target. This is why the confirmed hits from the previous step are further tested in addition to in vitro assays to evaluate their PK properties. Usually, the screening is done through a cascade (tiers) of progressively more resource-intensive and accurate assays from in silico, to in vitro, and eventually to in vivo as illustrated in Figure 1.3. The PK properties screened vary from project to project, and can include binding to human plasma proteins, chemical and metabolic stability, cell membrane permeability, water solubility (above 10 μM), potential interference with cytochrome P450 enzymes and P-glycoproteins, and cytotoxicity (Bowes et al., 2012; Valentin et al., 2018; Dragovich et al., 2022).

The discovery team will usually select a few (e.g., between three and six) compound series to be further explored and to establish quantitative structure-activity relationships (QSAR). ***Hit to lead*** (H2L), also known as ***lead generation***, is a stage in early drug discovery where hits from a high throughput screen are evaluated and undergo limited optimization to identify promising lead compounds. These lead compounds undergo more extensive optimization in a subsequent step of drug discovery called ***lead optimization*** (LO).

Taken together, the overall goal of discovery is to reduce the millions of molecules screened to a few compounds that are safe and effective to progress into human trials. The challenge is how to accomplish this goal efficiently (Waring et al., 2015). The balance between PK and activity cannot be overemphasized. In fact, less

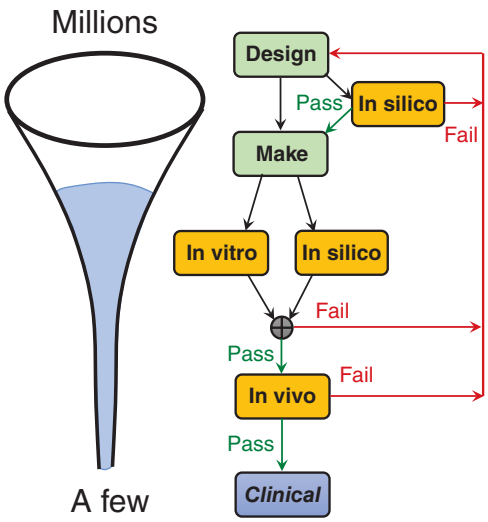

Figure 1.3 Iterative screening of compounds in drug discovery. The boxes in yellow denote screening steps. In silico in the flow chart refers to in silico screening of compounds. It does not exclude the use of in silico modeling in the design step, possibly based on multiparameter optimization (Nicolaou and Brown, 2013) using generative models (Ciepliński et al., 2023).

potent compounds with excellent PK properties could be more efficacious than highly potent compounds with poor PK properties. If compounds are screened for potency first before evaluating their PK, it risks potentially eliminating less potent compounds with exceptional PK. That is why in recent years there is a trend to move away from the linear process of compound optimization toward a parallel strategy in which the profile of chemical entities is shaped in a multidimensional manner allowing the properties of a molecule to be appropriately balanced in a rapid, iterative fashion (Bleicher et al., 2003).

Take-Home Messages

1. PK can often (but not always) be used as a surrogate for efficacy because in most cases the compound is carried to the target organ by the arterial blood that perfuses it.
2. A compound's concentration at the site of action is not identical to that in the systemic circulation due to various physiological and compound-related properties. The difference can be significant for some compounds and in some tissues.
3. Absorption, distribution, metabolism, and excretion are the four processes that collectively determine the systemic and tissue level of all compounds.
4. PK can be utilized to describe the concentration-time profile of a compound in systemic circulation and tissues. Additionally, its principles can be applied to predict human PK from in vitro PK or in vivo PK of preclinical species, assist in the design of future compounds, plan and interpret studies, and diagnose causes of suboptimal PK.
5. The definition of "optimal" PK is not universal. The PK to optimize toward is one that enables the exposure at the site of action required to elicit the desired pharmacological response to be achieved at a reasonable dose given at a reasonable interval via a practical dose route. It is highly specific to pharmacology and therapeutic areas in question.

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