

# Pharmacokinetics and pharmacodynamics analysis of drug candidates

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## 19.1 Introduction

Bioinformatics is increasingly becoming a key part of research in various disciplines, including pharmaceutical science, agriculture, biotechnology, and environmental science. Drug designing is a multidiscipline process, including bioinformatics, computational biology, structural biology, metabolomics, proteomics, and computer science. Bioinformatics approaches are required for exploring genomic, epigenetic, transcriptomic, proteomic, ribosome profiling, and metabolomics data generated by high-throughput experiments. The availability of complete genome sequences of human, animals, pathogens, and medicinal plants provides a new insight for novel drug designing. Bioinformatics is a data-driven discipline begins with both conceptual and practical methods for diagnoses, mechanism of disease, identification of novel drug target, and designing of suitable drug molecules for different disease. All these steps need various computational tools, algorithms, and databases.

Novel drug discovery, designing, and development all together are a complex, risk-prone, time-consuming, and highly expensive process. With the advancement of computational drug designing methodologies, both time and cost are reduced at the minimum level. There are different computational parameters for the analysis of pharmacokinetics and pharmacodynamics at different steps during the process of drug discovery and product/formulation designing of suitable candidate drug molecule (Fig. 19.1). One of the main challenging tasks of the drug designing process is gathering knowledge about the complex chemical pathways as a component of the disease so that candidate drugs can be designed to target the most significant intervention pathways and drug target molecules, leading to a desired pharmacological response.

A drug target maneuvers a key role in the molecular mechanism of a disease, and it can be targeted by a drug molecule to bring forth a desirable therapeutic effect. Examples of drug targets are various kinds of proteins (receptors, enzymes), ion channels and hormones, structural proteins, transport proteins, DNA, and RNA. Some key features of good drug targets make it a druggable molecule. Drug target must be involved in a pivotal biological pathway; it should be functionally and structurally defined and must be competent in binding to small molecules (drugs). Numerous proteins are druggable due to their structure, but their binding is not therapeutic in nature. Druggability is not the lone desirable feature to be defined as a “good” drug target. Thus a good drug target necessarily is efficacious, druggable, and harmless, and fits in medical and commercial requirements (Paananen & Fortino, 2020).

Currently, in pharmaceuticals, the dropout rate of potential lead candidate-based drug molecules is because of the selection of the wrong drug target molecule. Therefore the computational application has become a key aspect in minimizing dropout rates by facilitating the determination and validation of the most significant drug candidate. Traditionally drug target identification starts with the nonautomatic probe of scientific written material and biomedical databanks to access the significance of drug target by analyzing its molecular function in the disease under investigation and to assess its effectiveness, safety, and moneymaking perspective as a proposed drug target (Reisfeld et al., 2013).

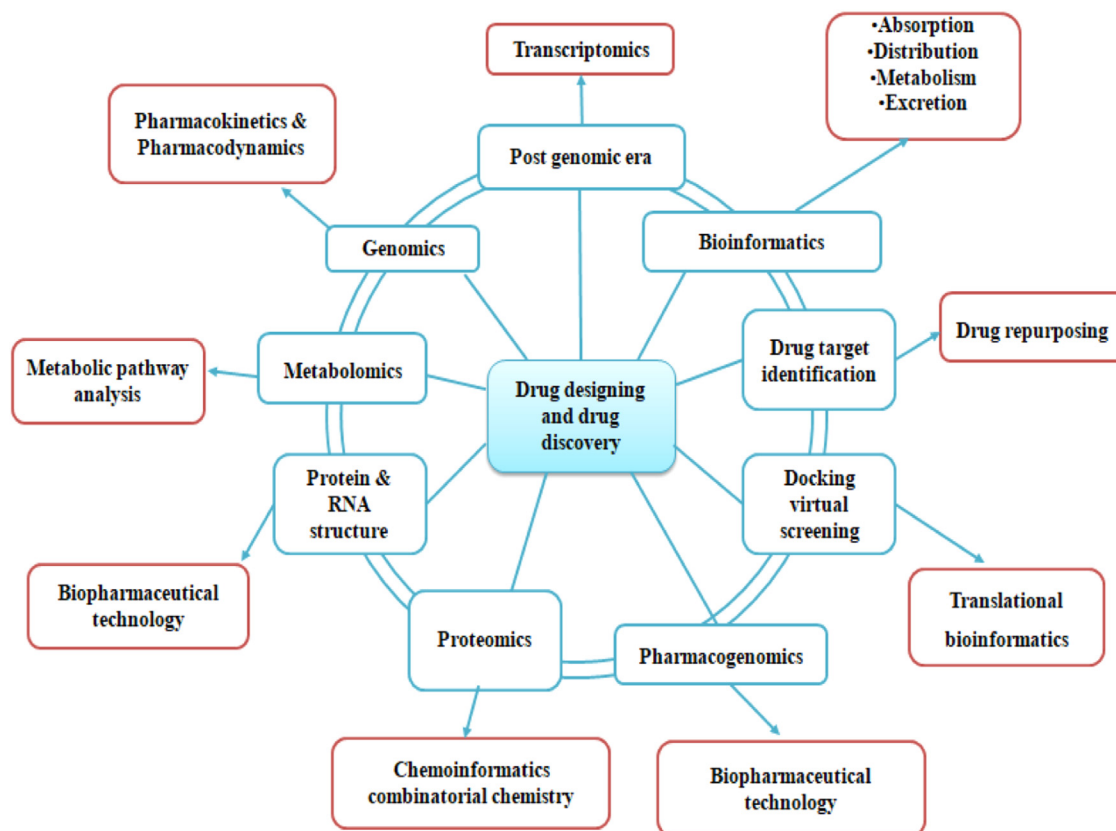


FIGURE 19.1 Different disciplines involved in drug designing and discovery.

## 19.2 Postgenomic era and drug discovery

Next-generation sequencing methods have generated a vast amount of sequencing data from many organisms. This genomic revolution has brought in the development comprehensive analytical approach to biological systems for the design and development of suitable drug molecules. The exponentially huge amount of data that is generated in the postgenomic era needed to be stored, explored, annotated, and analyzed with the help of bioinformatics and computational approaches (Table 19.1). Functional analysis of genome sequence and expression data has facilitated the finding of target genes in related disease and optimization of drug target determination process. Genome-wide data sources, such as expressed sequence tags, genomic sequences of microbes and model organisms, various polymorphisms, transcriptomics, and proteomics, can be explored using bioinformatics and computational approaches for the identification of suitable medicine candidate molecules.

The next-generation sequencing and present-day omics approaches have provided knowledge about a large number of putative targets, including proteins, enzymes, receptors, ion channels, DNA, RNA, and metabolites. Thus bioinformatics and computational method-based characteristics and ranking of disease under consideration, and putative targets will enhance the identification of most suitable drug target with desired therapeutic efficacy and minimum side effects (Bourgon, Dewey, Kan, & Li, 2018). Detailed functional analysis and annotation of human genome sequence provide an opportunity to explore human disease to gain a deep understating of disease mechanism, a pathology that can be used to improve current therapies for many human diseases. The identification of every human gene, analysis of metabolic pathway with the help of bioinformatics, and computational approaches along with functional genomics approaches can lead to pinpoint the molecular basis of every human disease and to explore appropriate intervention points, metabolic pathway, or drug target. Recent advancements in the field of genomics and proteomics will help in the successful development of drug candidates as several drugs fail due to the selection of inappropriate drug targets.

The postgenomic era has improved the status of drug target availability. Now there is a paradigm shift in drug designing from the identification of drug target to the validation of drug target as the number of attractive targets available is becoming too large. Therefore now bioinformatics is applied in focusing on drug target validation instead of

**TABLE 19.1** Genomics databases and their role in drug discovery.

Resources	Description	URL
HMMER	Homology searching	<a href="https://www.ebi.ac.uk/Tools/hmmer/">https://www.ebi.ac.uk/Tools/hmmer/</a>
GOLD	Genomes online database and genomic and metagenomic information	<a href="https://gold.jgi.doe.gov/">https://gold.jgi.doe.gov/</a>
DGidb	Drug–gene interactions information regarding druggable genome	<a href="https://www.dgidb.org/">https://www.dgidb.org/</a>
GWAS Catalog	Manually curated and published human GWASs	<a href="https://www.ebi.ac.uk/gwas/">https://www.ebi.ac.uk/gwas/</a>
GWAS central	Genetic association studies database	<a href="http://www.gwascentral.org/index">http://www.gwascentral.org/index</a>
dbGaP	Genotypes and phenotypes interaction database	<a href="http://www.ncbi.nlm.nih.gov/gap">http://www.ncbi.nlm.nih.gov/gap</a>
HapMap project	A haplotype map of the human genome and genes affecting health, disease, and responses to drugs and environmental factors	<a href="http://www.coriell.org">http://www.coriell.org</a>
dbSNP home Page	Database for a broad collection of simple genetic polymorphisms	<a href="https://www.ncbi.nlm.nih.gov/snp/?cmd = search">https://www.ncbi.nlm.nih.gov/snp/?cmd = search</a>
PHAROS	Database for druggable genome	<a href="http://www.pharos.nih.gov">http://www.pharos.nih.gov</a>

GWASs, Genome-wide association studies.

identification of drug target. Both experimental (in vitro/in vivo) and bioinformatics methods can be used simultaneously integrated for drug designing so that bioinformatics and computational predictions are linked and validated by performing in vitro or in vivo experiments. This will lead to the formation of in vitro/in vivo/in silico cycles where predictions are validated and further refined based on experimental results generated.

### 19.3 Pharmacokinetics

Pharmacology is simply a determination work about the impact of a drug on a biological system and the reaction of the body to it. It is basically classified into pharmacokinetic and pharmacodynamics. Pharmacokinetic and pharmacodynamics features describe the biological response of a candidate drug. Pharmacokinetics deals with the action of the body on the drug molecule while pharmacodynamics trades with the action of a drug to a body. Ideally, a drug must be potent and effective at minimum concentration with no or minimum side effect and must not give any toxic reaction. To meet this requirement, it is always essential to consider all aspects of knowledge about drug molecules (Arivazhahan, Raj, & Raveendran, 2019).

Pharmacokinetics deals with the absorption, distribution, metabolism, elimination, and toxicity related aspect of a drug. There are many physicochemical and molecular features of drug that governs concentration at the site of action, storage in different tissue, distribution, and rate of metabolism. Pharmacokinetic mainly deals with the motility of the drug in the body and the modification of the drug caused due to the body. Pharmacokinetics is a precisely crucial translational area of research, in which one mainly studies about absorption, disposal, metabolism, excretion, and transportation of a drug. Therefore for drug designing, pharmacokinetics consistently looks into the physiological and biochemical mechanisms of drugs (Moda, Torres, Carrara, & Andricopulo, 2008).

Metabolic pathways, integrated bioinformatics, and experimental approaches, along with computational pharmacology, can be used to design drug candidates with more efficacies in less time period at a comparatively low cost. There are several techniques in the postgenomic era that are well constituted in drug discovery and development (along with combinatorial chemistry and high-throughput screening). These techniques are serving well to produce an unmatched amount of prospective lead compounds (Chongyang et al., 2019).

The magnitude of response is incidental to the concentration of the drug at the acting site. The active site will depend on its pharmacokinetic features. Thus pharmacokinetic circumstances ascertain the path(s) of administration, dosage, the latency of oncoming, an instance of the prime activity, time duration of the activity, and oftenness of administration of a drug. It is not adequate for a drug molecule to bind closely to its biological target. It should also be capable to tract a place where the actual pharmacological action of the drug is required. It normally refers to cross one or more physiological barriers, such as a cell membrane and blood–brain barrier (BBB). The molecule should stay in the body for a suitable time to produce the desired outcome, but on the other hand, it should finally be abstracted from

**TABLE 19.2** ADME analysis-related resources and tools.

Resource	Description	URL/website
SwissBioisostere	Lead optimization database	<a href="http://www.swissbioisostere.ch">http://www.swissbioisostere.ch</a>
REOS	Identification of molecules with poor ADME	<a href="https://squonk.it/docs/cells/REOS%20Filter%20(RDKit)">https://squonk.it/docs/cells/REOS%20Filter%20(RDKit/</a>
SwissADME	Computes physicochemical descriptors with ADME parameters, pharmacokinetic	<a href="http://www.swissadme.ch/">http://www.swissadme.ch/</a>
PK-DB pharmacokinetics database	Pharmacokinetics information from clinical trials and preclinical research	<a href="https://pk-db.com/">https://pk-db.com/</a>
PharmGKB	Resource related to clinical information including clinical guidelines and drug labels related to a drug	<a href="http://www.pharmgkb.org">http://www.pharmgkb.org</a>

*ADME*, Absorption, distribution, metabolism, and excretion.

the body through metabolism and excretion. Furthermore, both the drug and its metabolites must not be toxic (Grzegorzewski et al., 2021).

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties are considered in the developmental state of a drug candidate, and several resources are available for analyzing the absorption, distribution, metabolism, and excretion properties of a drug candidate (Table 19.2). With the advent of bioinformatics and computational approaches, predicting ADMET properties in the early phase during drug discovery is having high priority.

### 19.3.1 Drug absorption

A drug should have a high rate of absorption to produce a better and quick therapeutic response. Absorption depends on the form in which the drug is taken, physicochemical properties, and related drug transporters present in the body (Paul, 2019). Lipophilicity is one of the important features that decides the absorption of the drug. Drugs with optimal LogP values (lipophilicity) have shown a better rate of absorption whereas drugs with very low or very high lipophilicity have shown poor absorption (Singh, 2018). High lipophilicity of a drug leads to self-aggregation as well as also increases the affinity of a drug for the plasma protein binding, which in turn reduces the effective concentration required for biological response. Compound with high lipophilicity has shown toxicity due to poor metabolism.

The genetic polymorphism alters the availability and affinity of the transporter protein to various substrates and, hence, impacts the pharmacokinetic response of drugs. Furthermore, tissue-specific drug dispersion can happen due to the existence of particular transporters in few cells. Therefore bioinformatics approaches are now being used for the analysis of genetic polymorphism in transporter protein that can modify bioavailability leading to a significant change in the proportion and level of absorption of a drug from a single dose. Computational models have been designed to predict the human oral and intestinal absorption of drug candidates based on the physicochemical features of known experimental drugs.

### 19.3.2 Drug distribution (binding/localization/storage)

As a drug enters into the blood circulation system, it diffuses to other tissues. Drug concentration gradient plays a very significant role in controlling the movement of drug from plasma to tissues. The magnitude of dispersion of a drug will depend upon several factors, including an affinity for plasma proteins and other tissue proteins, and also on the availability of transporters to the different tissues. Drugs have a physicochemical affinity for plasma proteins. Drugs that are acidic in nature often bind to plasma albumin while simple drugs bind to an acid glycoprotein. Binding with albumin is quantitatively very crucial. The conjugated portion is not accessible for activity. In the advanced level of protein–drug binding, the conjugated portion is not accessible for metabolism, or excretion till its active infusion by liver or kidney tubules takes place. There are significant clinical implications of any change in the binding of drugs to plasma proteins. It can be due to any change in the binding protein structure, change in the active site, the concentration of binding protein, etc. A drug can conjugate to numerous places on the albumin molecule. Conversely, several drugs can conjugate to the same place. During distribution, drugs can localize to a particular part of the body that may be toxic.

Computational models have been designed to predict the plasma protein binding, P-glycoprotein (Pgp) binding as substrate or inhibitor, BBB, and blockage rate to hERG channels for a drug candidate.

### 19.3.3 Drug metabolism

Drug metabolism (biotransformation) produces metabolites with different physicochemical and pharmacological properties from the parent drug molecule. The safety and efficacy of drug metabolism can be predicted and analyzed with the help of bioinformatics and experimental methods. Molecular modeling and data modeling are often used in the prediction of drug metabolism. Thus it is often applied in drug designing, pharmacokinetics, pharmacodynamics, and toxicology, which in turn helps in the structural characterization of metabolites.

Different metabolism enzymes (liver enzymes) in the human body bring chemical modification of drugs and convert them into other metabolites. The chemical composition of drug molecules significantly changes after drug metabolism and sometimes produced metabolite can have a toxic response. It can lead to the constitution of progressive metabolites from active drugs and also the constitution of progressive metabolites from prodrugs and inactive metabolites and toxic metabolites. These metabolites could either suppress metabolic pathways or will have physicochemical properties that are very much different from the parent drug molecule (Lakshmanan, 2019).

Drugs are metabolism in two steps: phase I (nonsynthetic reactions) and phase II (synthetic reactions). In phase I, oxidation, reduction, and hydrolysis reactions take place leading to the loss of pharmacological activity. Based on the chemical properties of the parent drug molecule, active and chemically reactive intermediate products could also be produced. In phase II (biosynthetic), a functional group on the parent compound (or on a phase I metabolite) is covalently bonded to glucuronic acid, sulfate, glutathione, amino acids, or acetate, which are produced endogenously. The conjugates produced are extremely polar in nature and are quickly excreted through urination and feces. Drug metabolism primarily occurs through the liver.

Drug metabolism is carried out with the help of specific enzymes, such as monooxygenases and cytochrome P 450 (CYP). Several CYP isoenzymes have a varied affinity toward different drugs. The CYP isoenzymes are categorized into different families and subfamilies represented by numerals (1, 2, 3, and 4, and A, B, C, and D). Key CYP enzymes causing biotransformation of drugs are CYP3A4/5 (responsible for nearly 50% drugs), CYP2D6 (around 20% drugs), CYP2C8/9, CYP2C19, and CYP1A1/2. Microsomal epoxide hydrolase enzyme hydrolyzes extremely activated arene oxides (product of CYP oxidation) to unreactive, water-soluble trans-dihydrodiol metabolites. The most crucial conjugation enzymes are uridine diphosphate glucuronosyltransferases, which catalyze the transportation of glucuronic acid to molecular compounds. Bioinformatics resources for metabolite, xenobiotic prediction, and metabolism enzymes are listed in Table 19.3.

**TABLE 19.3** Database and tools for metabolite, xenobiotic prediction, and metabolism enzymes.

Tool	Description	URL
plantiSMASH	Database for plant secondary metabolite	<a href="http://plantismash.secondarymetabolites.org/">http://plantismash.secondarymetabolites.org/</a>
AntiSMASH	Database for analysis of secondary metabolite biosynthesis	<a href="https://antismash.secondarymetabolites.org#!/start">https://antismash.secondarymetabolites.org#!/start</a>
HMDB (Human Metabolome Database)	A database containing detailed information about small molecule metabolites	<a href="https://hmdb.ca/">https://hmdb.ca/</a>
Metabolights	Database for metabolomics experiments	<a href="https://www.ebi.ac.uk/metabolights/">https://www.ebi.ac.uk/metabolights/</a>
MDL Databases	Database of metabolic transformations of xenobiotic compounds	<a href="http://www.akosgmbh.de">http://www.akosgmbh.de</a>
MetaPrint2D	Predicts xenobiotic metabolism	<a href="https://pharmb.io/tool/metaprint2d/">https://pharmb.io/tool/metaprint2d/</a>
MetabolExpert	Prediction of the metabolic fate of a compound	<a href="https://www.compudrug.com/metabolexpert">https://www.compudrug.com/metabolexpert</a>
Madison Metabolomics database	Database for small molecules of biological significance	<a href="http://mmcd.nmrfam.wisc.edu">http://mmcd.nmrfam.wisc.edu</a>
Golm Metabolome Database	Metabolite profiles for essential plant tissues	<a href="http://gmd.mpimp-golm.mpg.de/">http://gmd.mpimp-golm.mpg.de/</a>
MetabolomeExpress	Database for metabolomics with metabolite information	<a href="https://www.metabolome-express.org/">https://www.metabolome-express.org/</a>
Metabolism Enzymes	Drug metabolism enzymes	<a href="http://www.cypalleles.ki.se/">http://www.cypalleles.ki.se/</a>

The CYP enzymes maneuver an important function in metabolism and thus become an appreciable interest to carry out their sequence and structural analysis using Bioinformatics approaches (McDonnell & Dang, 2013). The CYP family of liver enzymes is accountable for the breakage of higher than 30 contrasting groups of drugs. DNA variants in genes that are coding concerning enzymes could alter their strength to metabolize some drugs. A drug will not be metabolized and removed from the body if related CYP is absent or poorly active. Any change in the expression of the above group of monooxygenases and CYP enzymes can adversely affect:

1. Inactivation of drugs: Drugs and their progressive metabolites are transformed into nonreactive or little active metabolites.
2. Synthesis of progressive metabolite through a progressive drug: Numerous drugs partially converted to some progressive metabolite; these changes are due to both the parent drug and its progressive metabolites.
3. Formation of prodrugs: Some drugs remain inactive in the body and it requires a transformation in the body to form other metabolites to become an active drug. These drugs are known as a prodrug. Several prodrugs are reactive by selection at the site of action.
4. Inhibition of drug metabolism: In case, two drugs are taken together, then one drug can competitively inhibit the metabolism of another drug if both drugs have to be metabolized by the same enzyme. Therefore the knowledge of CYP isoenzymes that carries out the metabolism of a particular drug is very helpful in understanding the drug–drug interaction.

Analysis of drug metabolism is an important part of drug designing. Lead optimization requires more information on pharmacokinetics, pharmacodynamics, or toxicological outcomes to incorporate suitable chemical changes in the lead (Mbah & Okorie, 2018) (Fig. 19.2). Factors governing dependable drug metabolism prediction consider:

1. interindividual constituents (stay unvarying for an organism) viz. animal species, genetic component, and gender;
2. intraindividual constituents (differ for an organism) viz. age, biological rhythms, disease, stress, pregnancy, nutrition, and the effect of stimulators and inhibitors; and
3. selectivity of metabolic procedures for instance selectivity at the receptor stage.

The pharmacodynamics effect of the drug varies from the molecular signals to clinical symptoms. Drug–drug interaction is also an important pharmacology parameter. Drug–drug interaction also describes a drug's pharmacokinetics or pharmacodynamics. Drug interaction because of pharmacodynamics is having a broad scope of rendering (Sayre, Wambaugh, & Grulke, 2020).

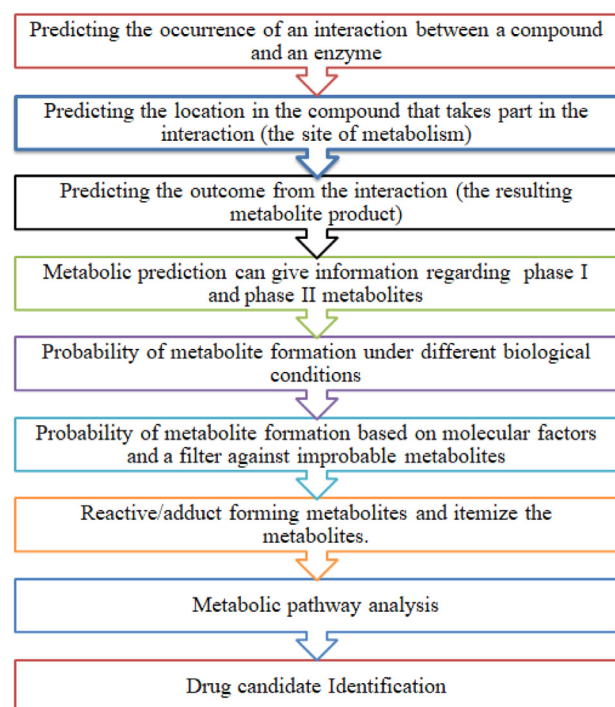


FIGURE 19.2 Bioinformatic-based prediction of metabolic pathways.

**TABLE 19.4** Resources related to knowledge from drug–protein interaction.

Resource	Description	URL
DIDB—Drug Interaction database	Information regarding pharmacokinetics, drug interactions, and drug safety	<a href="https://www.druginteractionsolutions.org/solutions/drug-interaction-database/">https://www.druginteractionsolutions.org/solutions/drug-interaction-database/</a>
Biological General Repository for Interaction (BioGRID)	Genetic, chemical interactions, and information of posttranslational modifications	<a href="http://thebiogrid.org/">http://thebiogrid.org/</a>
Database of Interacting Proteins (DIP)	Database of interactions between proteins having information from multiple sources	<a href="http://dip.doe-mbi.ucla.edu/dip/Main.cgi">http://dip.doe-mbi.ucla.edu/dip/Main.cgi</a>
STRING	Protein–protein interaction networks analysis. It requires protein name and organism name as input	<a href="http://string-db.org/">http://string-db.org/</a>
DTC	Analysis of drug–target interactions	<a href="http://www.drugtargetcommons.fimm.fi">http://www.drugtargetcommons.fimm.fi</a>

## 19.4 Pharmacodynamics

All drugs exert an effect after their interaction and binding with a specific target at the molecular level. Drugs induce a change in the dynamics of the target after binding to generate a therapeutic response that can be estimated by biochemical or clinical analysis. Some terms, such as  $E_{max}$  (maximal effect of a drug),  $EC_{50}$  (drug concentration to generate half of the maximum effect), and Hill coefficient (the relationship between drug concentration and its effect), are used to explain the pharmacodynamics of a drug (Marino, Jamal, & Zito, 2020). Pharmacodynamics also explain the extent and duration of action for a drug. In the case of off-target binding, a drug may interact with other biological targets of different pathways or receptors and may generate a toxic effect, adverse drug reaction, or unexpected outcome. Protein–drug interactions play important role in assessing the safety and efficacy of a drug after oral administration. Many resources have been developed to find information on the protein–drug interaction (Table 19.4).

### 19.4.1 Drug toxicity

Many drugs fail due to their toxic response to different organs of the human system. Several prediction tools, such as DSSTox (toxicity prediction), CPDB (carcinogenic potency database), Pre-ADMET (permeability across Caco-2 cell and BBB, skin, human oral/intestinal absorption), ChemTree (ADMET prediction), TOPKAT (toxicity prediction), QikProp (ADMET prediction), and MetaSite (metabolic site prediction), for ADMET-related analysis are available (Singh, 2020a, 2020b). A drug can have a toxic response due to any reason, such as poor bioavailability, binding to plasma proteins, off-target recognition, poor distribution and metabolism, production of toxic metabolite after drug metabolism, drug–drug or drug–herb interaction, and also due to the presence of toxic substructures in the drug molecules (Gupta, Bastikar, Bastikar, Chhajed, & Pathade, 2020). Data available from the previous studies and clinical trials indicate that many toxic substructures may cause toxicity if present in a drug. Therefore the toxic substructure must not be incorporated in a drug during lead optimization as well as if they are present in the drug they must be removed or replaced by similar bioisosteres or groups to maintain the activity and selectivity. Some known toxic substructures are alkyl nitrite, aliphatic halogens, quinones, epoxides, *S*-mustards, acyl halides, aromatic *N*-oxides, alkyl, aryl *N*-nitroso group, and propiolsultones (Singh, 2020a,b). Tools and databases related to the study of adverse drug reactions and toxicogenomic information have been developed for better knowledge about the fate of a drug candidate (Table 19.5).

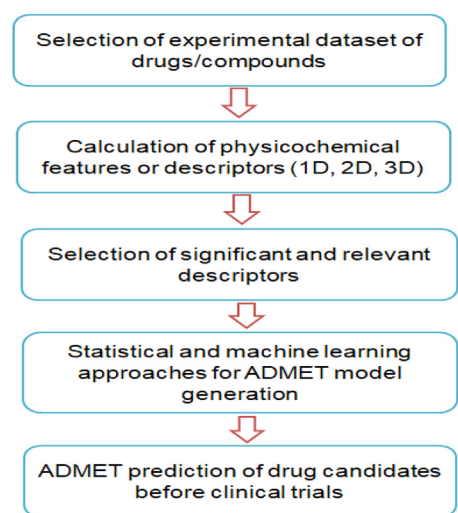
## 19.5 Computational approaches for ADMET prediction

More than 60% of drugs fail in clinical trials due to poor pharmacokinetics and pharmacodynamics response. Computational prediction of these properties before a clinical trial can reduce the risk of drug failure. The drug with poor ADMET properties can undergo the process of lead optimization to improve the biological response. Data sets related to adverse drug reactions, clinical trials, and toxicogenomics can be used for building the accurate model for ADMET predictions. Oral bioavailability, BBB, CYP metabolism, hERG blockage, Pgp substrate and inhibitions,

**TABLE 19.5** Resources for adverse drug reaction and toxicogenomic information.

Resources	Description	URL
DrugMatrix	Comprehensive toxicogenomic reference resources database	<a href="https://norecopa.no/3r-guide/drugmatrix">https://norecopa.no/3r-guide/drugmatrix</a>
Open TG-GATE	Toxicogenomics database	<a href="https://toxico.nibiohn.go.jp/english/index.html">https://toxico.nibiohn.go.jp/english/index.html</a>
Adverse reaction database	Database with information for side effect and adverse reactions	<a href="http://www.fda.gov/Drugs/">http://www.fda.gov/Drugs/</a>
SIDER	Medicines available in the market and their observed cases of adverse drug reactions	<a href="http://sideeffects.embl.de/">http://sideeffects.embl.de/</a>
Clinicaltrial.gov	Clinical study-related database for better understanding of the drug-related side effects	<a href="http://clinicaltrials.gov">http://clinicaltrials.gov</a>
ADReCS-TargetMetabolExpert	A collection of ADRs caused by drug interaction with the protein, gene, and genetic variation	<a href="http://www.bioinf.xmu.edu.cn">http://www.bioinf.xmu.edu.cn</a>
OMOP	Healthcare databases for the analysis of effects of drugs	<a href="http://www.ohdsi.org">http://www.ohdsi.org</a>
MedDRA	Medical terminology database for adverse drug events	<a href="http://www.meddra.org">http://www.meddra.org</a>
GDSC	Resources on drug sensitivity in cancer cells and molecular markers of drug response	<a href="https://www.cancerxgene.org/">https://www.cancerxgene.org/</a>
Transporters	Drug transportation enzymes	<a href="http://www.tcdb.org">http://www.tcdb.org</a>

*OMOP*, observational medical outcomes partnership.

**FIGURE 19.3** Basic concept of the flow used for the development of ADMET prediction tools.

mutagenicity, and other related properties can be predicted to estimate the fate of a drug once taken orally (Singh & Dwivedi, 2019; Singh, Gupta, Kesharwani, & Misra, 2013).

The accuracy of an ADMET model depends on the selection of dataset, parameters used, and also the approaches used for generating the model. The basic steps involved in the process of ADMET prediction tools are shown in Fig. 19.3. There are many types of molecular descriptors, such as 1D, 2D, and 3D descriptors, that are calculated from the available experimental data of known drugs/compounds. The selection of relevant descriptors and their integration for building a mathematical model/equation is a very important step in the development of ADMET tools (Singh, 2020a,b). There are a large number of descriptors and are categorized under different groups, such as physicochemical, geometrical, topological, quantum chemical, and molecular fingerprints, based on their features. Some descriptor calculation tools are E-Dragon, MOLE db (molecular descriptors database), EPISUITE, Online Chemical Modeling Environment, and ChemDraw. Several statistical and machine learning approaches, such as recursive partitioning

regression, partial least square regression, random forests, decision trees, k-nearest neighbor, and support vector machine, are used for building ADMET prediction models (Kesharwani et al., 2020).

## 19.6 Translational bioinformatics

Translational bioinformatics deals with the improvements in the data storage system, analytical and interpretative methods used for the proteomics, transcriptomics, metabolomics, epigenomics, interatomics, pharmacogenomics, phenomics, and biomedical data for prediction and health. Improved standardization process will promote the development of pharmacology models through translational bioinformatics procedures (Li, 2015). The translational bioinformatics paradigm is extremely complementary to present pharmacological requirements for drug discovery. Information and knowledge representation is a basic measure to connect various resources of big data. Clinical pharmacology research-associated big data sources include observational records. Current pharmacokinetic and pharmacodynamic research begins with sharing information among different databases. This is further depending on the availability of standardized data annotation approaches, such as observational medical outcomes partnership (OMOP), which incorporate various observational databases using a common data model.

The OMOP has also generated an annotation strategy to characterize the time-oriented nature of medications, laboratory tests, diagnoses, and adverse drug events. Adverse drug event is standardized using MedDRA (a medical database for unfavorable drug consequence) [www.meddra.org](http://www.meddra.org). Advanced developments in text mining and data mining will assist clinical pharmacology by retrieving information from medical records, molecular data, and literature search.

Translational bioinformatics can explore big data generated in the postgenomic era to get insight into the pharmacological requirement of a particular disease. Therefore translational bioinformatics approaches will be more effective with the availability of a wide range of data sources. Traditional pharmacology research and translational bioinformatics approaches can now be used as complementary with each other, thus combining the advantages of both disciplines for the identification of suitable drug candidates (Wu, Karnik, & Subhadarshini, 2013).

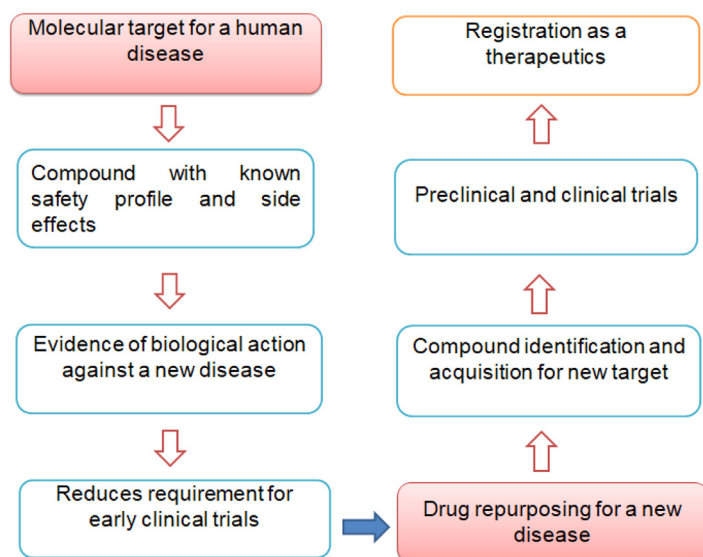
## 19.7 Drug repurposing

The approach of drug repurposing can be explored to reduce the time and cost of drug discovery by examining new applications for existing approved drugs (Pillaiyar, Meenakshisundaram, Manickam, & Sankaranarayanan, 2020). It is an emerging and impressive approach in identifying or developing drug molecules with new pharmacological or therapeutic signals. Drug repurposing (drug repositioning/drug reprofiling/drug redirection) is a procedure of determination of novel pharmacological signals from investigated, studied, failed, or approved drugs. It also deals with the usage of the recently formulated drugs for the treatment of diseases other than the drug's original/intentional therapeutic or pharmacological indication. Therefore drug repurposing regards to set up fresh therapeutic usage for better-known experimental drugs. There are many examples of processing novel drugs through the identification of new biological targets with the help of a drug repositioning strategy (Fig. 19.4).

### 19.7.1 Benefits of drug repurposing

Drug repositioning has various benefits as compared to conventional procedures to drug discovery. In comparison to conventional drug discovery systems, there is a very significant decrease in the time period exhausted in research and development. To develop a new drug by conventional procedure, there is no requirement of the initial 6–9 years for a repositioned drug; rather it gets in straightaway to testing and trials phase. Therefore it is decreasing the whole danger, time period, and expenditure of development. The *de novo* drug discovery is used for searching and designing novel molecular entities with better pharmacokinetics and pharmacodynamics response. This involves different stages, such as discovery design of drug candidates, preclinical and safety assessment, clinical trials, review and approval, and marketing and postapproval safety observation. But there are only four phases in the case of drug repurposing, it consists of compound determination, compound acquisition, development, and safety observation after released to the market.

In the case of drug repurposing, a lot of preclinical and clinical knowledge about the candidate drug exists as the drug has already passed through these stages. Drug repurposing suits well for the quickly nascent and reemerging infectious diseases for which no current therapeutics is available.



**FIGURE 19.4** Drug repositioning: processing novel drugs through the identification of new biological targets.

### 19.7.2 Computational drug repurposing

Computational biology, cheminformatics, structure-based drug design, proteomics, transcriptomics, metabolomics, and genomic-based approaches can be used for searching the unknown mechanisms of drug candidates. Drug repurposing uses activity-based experimental data and computational methodologies for the development and identification of novel drug molecules. Due to the availability of several biological and structural databases, drug repurposing is now an emerging approach for drug discovery in which already available tested medicines are redirected to treat some other diseases. Computationally designed drug candidates also go through the process of preclinical studies (in vitro and in vivo assays) and clinical studies for the safety and efficacy assessment. Computational approaches provide a strong analytical system for the searching and identification of new drug candidates with better pharmacokinetics and pharmacodynamics properties.

Based on the availability of qualitative and quantitative data, drug repurposing is three types, that is, pharmacological, toxicological, and biological. These may be primarily based on drug, drug target, and related disease. In the case of the drug-based approach, we mainly focus on the structure, its biological response, and side effects. This kind of drug repurposing is based on the basic rules of conventional pharmacology and drug discovery with the main aim to identify the biological efficiency of the drug molecules without having knowledge of their targets. Target-based drug repurposing approach comprises (bioinformatics based) high-throughput screening of drugs or drug-like compounds. Virtual high-throughput screening deals with a screening of ligands using molecular docking or other virtual approaches. The in vitro and in vivo high-throughput screening of a drug is done for a protein molecule or biomarker. Target-based drug repurposing is more successful in comparison to the drug-oriented method because, in the case of target-based repurposing, detailed information about drug target, metabolic pathway, and mechanism of action is already known. Network biology and systems biology can identify novel mechanisms of various activities with detailed knowledge of the drug–target interaction at the molecular and genetic levels. The disease/therapy-oriented drug repurposing is under consideration if large data on the disease model are accessible. It can be based on the disease and/or treatment.

## 19.8 Role of pharmacogenomics in precision medicine

Pharmacogenomics represents the response of genomics on the pharmacology of a drug. Pharmacogenomics can be defined as a branch of pharmacology, which is the study of genetic variations with the response to the drug in various kinds of patients. It correlates gene expression or single-nucleotide polymorphism to the efficaciousness or toxicity of a drug. Pharmacogenomics also provides a connection between a genotype of a respective person and the ability of that person to metabolize a drug. Nowadays, many disease biomarkers related to drugs are available, which guides the drug and dose that can be prescribed to a particular genotype. Pharmacogenomics knowledge is useful in the many stages of clinical drug development (Katara, 2013). Pharmacogenomics can be used to determine the genes or loci which are participating in determining the responsiveness to a given drug. It can further be explored for the genetic characterization

of individuals and related drug responses for a particular genotype. Pharmacogenetic variations can also modify the pharmacokinetics and pharmacodynamics response of the drug. Pharmacogenomics can suggest a more precise medication to an individual with better efficacy and fewer side effects (Singh, 2020a,b).

## 19.9 Chemical diversity of natural products: a source for computer-aided drug discovery

Natural products and metabolites are considered an important source for drug discovery as they provide a vast set of structurally diverse compounds. It is also believed that natural compounds can have fewer side effects as compared to the synthetic drug, and it suggests that natural chemical scaffolds can be a better source for designing the drugs, owing to the huge chemical structure diversities and their biodiversities. Virtual screening-based strategies can be a fast approach to assess the binding interaction and affinity of a vast set of compounds in a short period of time (Singh, Singh, & Singh, 2019). Natural compounds are produced by specific metabolic pathways recruited by gene clusters. Genome mining can identify the uncharacterized gene clusters related to the synthesis of natural products in a sequenced genome (Liu & Wang, 2017). Natural products are being used as a lead compound for the development of new drugs. A large number of the drugs have been designed from natural products either by taking basic pharmacophore or by considering the lead optimization in the existing one. All organisms, such as bacteria, plants, and animals, are capable of producing many secondary metabolites with some biological response/activities that can be used for the development of new therapeutics against a disease (Katiyar, Gupta, Kanjilal, & Katiyar, 2012). Chemoinformatics deals with the use of computational tools and methods for chemical compound designing, structure representation, structural comparison, and similarity searching, pharmacophore modeling, target–ligand docking, descriptor calculations, structure–property analysis, manipulation/modification in the compound, and ADMET prediction and in silico evaluation (Leach & Gillet, 2003).

## 19.10 Conclusion

The process of drug designing is very complex, costly, laborious, and full of failure during trials. Computational biology approaches have played a significant role in solving and overcoming the limitation of drug designing. Bioinformatics provides a vast number of drug-based databases, servers, and software that are being used for solving several issues of drug designing and evaluation procedures. More pharmacokinetics and pharmacodynamics parameters need to be analyzed and utilized in drug designing. The availability of experimental data on pharmacokinetics and pharmacodynamics of various drugs has significantly improved the prediction accuracy of ADMET prediction tools and servers that can be a useful resource to estimate the safety, efficacy, and toxicity issues related to the drugs.

## Conflict of interest

The authors declare that they have no conflict of interest.

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## Further reading

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