Epithelial-mesenchymal transition (EMT) is known to play an important role in cancer progression, metastasis and drug resistance. Although there are controversies surrounding the causal relationship between EMT and cancer metastasis, the role of EMT in cancer drug resistance has been increasingly recognized. Numerous EMT-related signaling pathways are involved in drug resistance in cancer cells. Cells undergoing EMT show a feature similar to cancer stem cells (CSCs), such as an increase in drug efflux pumps and anti-apoptotic effects. Therefore, targeting EMT has been considered a novel opportunity to overcome cancer drug resistance. This review describes the mechanism by which EMT contributes to drug resistance in cancer cells and summarizes new advances in research in EMT-associated drug resistance.

Multiple drug hypersensitivity (MDH) is a syndrome that develops as a consequence of massive T-cell stimulations and is characterized by long-lasting drug hypersensitivity reactions (DHR) to different drugs. The initial symptoms are mostly severe exanthems or drug rash with eosinophilia and systemic symptoms (DRESS). Subsequent symptoms due to another drug often appear in the following weeks, overlapping with the first DHR, or months to years later after resolution of the initial presentation. The second DHR includes exanthema, erythroderma, DRESS, Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), hepatitis, and agranulocytosis. The eliciting drugs can be identified by positive skin or in vitro tests. The drugs involved in starting the MDH are the same as for DRESS, and they are usually given in rather high doses. Fixed drug combination therapies like sulfamethoxazole/trimethoprim or piperacillin/tazobactam are frequently involved in MDH, and 30-40% of patients with severe DHR to combination therapy show T-cell reactions to both components. The drug-induced T-cell stimulation appears to be due to the p-i mechanism. Importantly, a permanent T-cell activation characterized by PD-1+/CD38+ expression on CD4+/CD25low T cells can be found in the circulation of patients with MDH for many years. In conclusion, MDH is a drug-elicited syndrome characterized by a long-lasting hyperresponsiveness to multiple, structurally unrelated drugs with clinically diverse symptoms.

Life sciences provide reasonably sound prognosis for a number and nature of therapeutic targets on which drug design could be based, and search for new chemical entities--future new drugs, is now more than ever based on scientific principles. Nevertheless, current very long and incredibly costly drug discovery and development process is very inefficient, with attrition rate spanning from many thousands of new chemical structures, through a handful of validated drug leads, to single successful new drug launches, achieved in average after 13 years, with compounded cost estimates from hundreds of thousands to over one billion US dollars. Since radical pharmaceutical innovation is critically needed, number of new research projects concerning this area is steeply rising outside of big pharma industry--both in academic environment and in small private companies. Their prospective success will critically depend on project management, which requires combined knowledge of scientific, technical and legal matters, comprising regulations concerning admission of new drug candidates to be subjects of clinical studies. This paper attempts to explain basic rules and requirements of drug development within preclinical study period, in case of new chemical entities of natural or synthetic origin, which belong to low molecular weight category.

This article aims to provide an overview of drug discovery with a focus on application within dermatology. The term "drug" can be used to describe a wide variety of agents, including small molecules, cell therapies, and antibodies, which may be dosed intravenously, orally, topically, or by other routes of administration. We summarize the economics and risks involved in drug discovery. Understanding the needs of patients and clinicians through use of a target product profile before initiating drug discovery can reduce time and effort spent developing a poor or unneeded drug. For small molecule drug discovery, a chemical starting point is then required. We present four options for finding a chemical starting point for drug discovery projects: screening libraries of compounds or modifying, reformulating, or repositioning a known drug. Examples of each technique's use in dermatology are provided. We also describe the subsequent steps involved in discovery of a new drug.

To help interested readers, we provide information on how to engage with academic drug discovery centers or industrial partners.

Conventional drug delivery approaches are plagued by issues pertaining to systemic toxicity and repeated dosing. Hydrogels offer convenient drug delivery vehicles to ensure these disadvantages are minimized and the therapeutic benefits from the drug are optimized. With exquisitely tunable physical properties that confer them great controlled drug release features and the merits they offer for labile drug protection from degradation, hydrogels emerge as very efficient drug delivery systems. The versatility and diversity of the hydrogels extend their applications beyond targeted drug delivery also to wound dressings, contact lenses and tissue engineering to name but a few. They are 90% water, and highly porous to accommodate drugs for delivery and facilitate controlled release. Herein we discuss hydrogels and how they could be manipulated for targeted drug delivery applications. Suitable examples from the literature are provided that support the recent advancements of hydrogels in targeted drug delivery in diverse disease areas and how they could be suitably modified in very different ways for achieving significant impact in targeted drug delivery. With their enormous amenability to modification, hydrogels serve as promising delivery vehicles of therapeutic molecules in several disease conditions, including cancer and diabetes.

Increasing need for novel drugs and their application for treating diseases are the main reasons for the development of bioinformatics platforms for drug repositioning. The use of existing approved drugs for treating other diseases reduces cost and time needed for a drug to come to clinical use. Different strategies for drug repositioning have been reported. The use of several omics types is becoming increasingly important in drug repositioning. Although there are several public databases intended for drug repositioning, not many successful cases of novel use of drugs have been reported in the literature and transferred to clinical use. Additionally, the study approaches in published literature are very heterogeneous. A classification scheme - Drug Repositioning Evidence Level (DREL) - for drug repositioning projects, according to the level of scientific evidence has been proposed previously. In the present study, we have reviewed main databases and bioinformatics approaches enabling drug repositioning studies. We also reviewed six published studies and evaluated them according to the DREL classification. The evaluated cases used drug repositioning approach for therapy of rheumatoid arthritis, cancer, coronary artery disease, diabetes, and gulf war illness. The drug repositioning study field could benefit from clearer definition in published articles therefore including drug repositioning DREL classification scheme could be included in published original and review studies. Novel bioinformatics approaches to improve prediction of drug-target interactions, continuous updating of the databases, and development of novel validation techniques are needed to facilitate the development of the drug repositioning field. Although there are still many challenges in drug repositioning and personalized medicine, stratification of patients based on their molecular signatures and testing of signature-targeting drugs should improve drug efficacy in clinical trials.

The effect of drug on a person may be different than expected because that drug interacts with another drug the person is taking (drug-drug interaction), food, beverages, dietary supplements the person is consuming (drug-nutrient/food interaction) or another disease the person has (drug-disease interaction). A drug interaction is a situation in which a substance affects the activity of a drug, i.e. the effects are increased or decreased, or they produce a new effect that neither produces on its own. These interactions may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances. Regarding food-drug interactions physicians and pharmacists recognize that some foods and drugs, when taken simultaneously, can alter the body's ability to utilize a particular food or drug, or cause serious side effects. Clinically significant drug interactions, which pose potential harm to the patient, may result from changes in pharmaceutical, pharmacokinetic, or pharmacodynamic properties. Some may be taken advantage of, to the benefit of patients, but more commonly drug interactions result in adverse drug events. Therefore it is advisable for patients to follow the physician and doctors instructions to obtain maximum benefits with least food-drug interactions. The literature survey was conducted by extracting data from different review and original articles on general or

specific drug interactions with food. This review gives information about various interactions between different foods and drugs and will help physicians and pharmacists prescribe drugs cautiously with only suitable food supplement to get maximum benefit for the patient.

Model-based approaches have emerged as important tools for quantitatively understanding temporal relationships between drug dose, concentration, and effect over the course of treatment, and have now become central to optimal drug development and tailored drug treatment. In oncology, the therapeutic index of a chemotherapeutic drug is typically narrow and a full dose-response relationship is not available, often because of treatment failure. Noting the benefits of model-based approaches and the low therapeutic index of oncology drugs, in recent years, modeling approaches have been increasingly used to streamline oncologic drug development through early identification and quantification of dose-response relationships. With this background, this report reviews publications that used model-based approaches to evaluate drug treatment outcome variables in oncology therapeutics, ranging from tumor size dynamics to tumor/biomarker time courses and survival response.

In view of the role of pharmacotherapy in medicine, on the one hand, and the powerful technical possibilities that are now available on the other hand, therapeutic drug monitoring is a surprisingly neglected area of laboratory medicine. In this viewpoint article, an "omics approach" to pharmacovigilance and drug monitoring is proposed and discussed. A realistic goal for laboratory medicine in the 21st century should indeed be to enable clinicians to check whether the right drug is present in the right patient with an appropriate blood concentration for each compound.

A major concern when using two-drug anti-HIV regimens is the risk of viral resistance. However, no techniques to evaluate the barrier to resistance of two-drug combinations *in vitro* have been reported. We evaluated the emergence of drug-resistant mutants in a passage study with constant concentrations of two drugs simultaneously. The barrier to resistance of dolutegravir-containing two-drug combinations was higher than the other combinations evaluated in this study.

During 2019, the US Food and Drug Administration (FDA) approved 48 new drugs (38 New Chemical Entities and 10 Biologics). Although this figure is slightly lower than that registered in 2018 (59 divided between 42 New Chemical Entities and 17 Biologics), a year that broke a record with respect to new drugs approved by this agency, it builds on the trend initiated in 2017, when 46 drugs were approved. Of note, three antibody drug conjugates, three peptides, and two oligonucleotides were approved in 2019. This report analyzes the 48 new drugs of the class of 2019 from a strictly chemical perspective. The classification, which was carried out on the basis of chemical structure, includes the following: Biologics (antibody drug conjugates, antibodies, and proteins); TIDES (peptide and oligonucleotides); drug combinations; natural products; and small molecules.

Cancer drug development is proceeding at a rapid pace, with drug approvals in oncology outpacing the other disease indications. With high population growth and economic development of Asian countries, access to cancer drugs becomes a paramount necessity. Approval of these drugs is dependent on establishing their safety and efficacy in populations living in these countries. Ethnic and racial differences in drug pharmacokinetics, or drug receptor sensitivities may lead to differences in drug responses between populations. These differences may be due to intrinsic or extrinsic factors, and understanding of the magnitude of these differences and their etiologies is important. One key pharmacogenetic reason for ethnic variability of drug response arises from the different allelic frequencies of polymorphic drug-metabolising enzyme genes, resulting in altered drug disposition. Using race or ethnicity as a "biomarker" for pharmacotherapeutics is fraught with issues as they are difficult to define scientifically, and are considered more social constructs. Nonetheless, studying the genetics of ethno-geographical variability of drug response will allow genetic biomarkers to be uncovered, which would greatly facilitate precision medicine, and should justify broadening the involvement and accrual of patients from global diverse populations during the early phases of drug development for an oncology drug.

DrugBank is a richly annotated resource that combines detailed drug data with comprehensive drug target and drug action information. Since its first release in 2006, DrugBank has been widely used to facilitate in silico drug target discovery, drug design, drug docking or screening, drug metabolism prediction, drug interaction prediction and general pharmaceutical education. The latest version of DrugBank (release 2.0) has been expanded significantly over the previous release. With approximately 4900 drug entries, it now contains 60% more FDA-approved small molecule and biotech drugs including 10% more 'experimental' drugs. Significantly, more protein target data has also been added to the database, with the latest version of DrugBank containing three times as many non-redundant protein or drug target sequences as before (1565 versus 524). Each DrugCard entry now contains more than 100 data fields with half of the information being devoted to drug/chemical data and the other half devoted to pharmacological, pharmacogenomic and molecular biological data. A number of new data fields, including food-drug interactions, drug-drug interactions and experimental ADME data have been added in response to numerous user requests

Drug interactions are important causes of both unexpected toxic and therapeutic effects. Adverse reactions due to drug interaction are proportional to the number of drugs given and the duration of administration. Although drug interactions may be beneficial, they are most often recognized when they increase mortality or morbidity. The frequency of adverse drug interactions in clinical practice makes it mandatory for physicians to know the drugs and mechanisms involved.A drug may potentiate or antagonize the effects of another drug by direct chemical or physical combination, by altering gastrointestinal absorption, by influencing metabolism, transport, or renal clearance, by changing the activity of a drug at its receptor site, or by modifying the patient's response to the drug by a variety of means. This article stresses the importance of avoiding multible drug therapy. When such treatment is unavoidable, patients must be carefully observed for evidence of intensified or diminished drug effect. Only this permits the detection and prevention of untoward drug interactions.

This comprehensive health policy review of the prescription drug abuse epidemic is based on the written and oral testimony of witnesses at a July 26, 2006 Congressional Hearing, including that of Laxmaiah Manchikanti, MD, the chief executive officer of the American Society of Interventional Pain Physicians and additions from review of the literature. Honorable Mark E. Souder, chairman of the Subcommittee on Criminal Justice, Drug Policy, and Human Resources, introduced the issue as follows: "Prescription drug abuse today is second only to marijuana abuse. In the most recent household survey, initiates to drug abuse started with prescription drugs (especially pain medications) more often than with marijuana. The abuse of prescription drugs is facilitated by easy access (via physicians, the Internet, and the medicine cabinet) and a perception of safety (since the drugs are FDA approved). In addition to the personal toll of drug abuse using prescription drugs, indirect costs associated with prescription drug abuse and diversion include product theft, commission of other crimes to support addiction, law enforcement costs, and encouraging the practice of defensive medicine." The Administration witnesses, Bertha Madras, Nora D. Volkow, MD, Sandra Kweder, MD, and Joe Rannazzisi reviewed the problem of drug abuse and discussed what is being done at the present time as well as future strategies to combat drug abuse, including prescription drug monitoring programs, reducing malprescriptions, public education, eliminating Internet drug pharmacies, and the development of future drugs which are not only tamper-resistant but also non-addictive. The second panel, consisting of consumers and advocates, included Misty Fetco, Linda Surks, and Barbara van Rooyan, all of whom lost their children to drugs, presented their stories and strategies to prevent drug abuse, focusing on education at all levels, development of resistant drugs, and non-opioid treatment of chronic pain. Mathea Falco, JD, and Stephen E. Johnson presented issues related to drug abuse and measures to curb drug abuse by various means. Stephen J. Pasierb presented startling statistics on teen drug abuse and various educational programs to deter abuse. Laxmaiah Manchikanti, MD presented an overview of prescription drug abuse, strategies to prevent drug abuse, including immediate funding and rapid implementation of NASPER, education at all levels and improving relations with the DEA and the provider community.

Drug allergy is defined as an adverse drug reaction with an established immunological mechanism. The National Institute for Health and Care Excellence published clinical guidelines on drug allergy in 2014 and quality standards in 2015. The intention of this article is to highlight indications for referral to specialists for management of drug allergy. Accurate diagnosis of drug allergy is critical of course for patient safety, but also for better use of the drugs that we have available and to reduce unnecessary avoidance of drugs. However, there are significant limitations in terms of resource availability and also in terms of testing. There is a careful balance here in that drug allergy is very common and clearly there is neither indication nor sufficient resource in the NHS for all patients with drug allergy to be reviewed by a specialist. It is, therefore, important to highlight to general physicians and physicians of other specialties, those patients who do require referral for specialist review.

Despite the development of various new antiepileptic drugs (AEDs) since the early 1990s, the available evidence indicates that the efficacy and tolerability of drug treatment of epilepsy has not substantially improved. What are the reasons for this apparent failure of modern AED development to discover drugs with higher efficacy? One reason is certainly the fact that, with few exceptions, all AEDs have been discovered by the same conventional animal models, particularly the maximal electroshock seizure test (MES) in rodents, which served as a critical gatekeeper. These tests have led to useful new AEDs, but obviously did not help developing AEDs with higher efficacy in as yet AED-resistant patients. This concern is not new but, surprisingly, has largely been unappreciated for several decades. A second-admittedly speculative-reason is that progress in pharmacologic treatment of drug-resistant epilepsy will not be made unless and until we develop drugs that specifically target the underlying disease. Although better preclinical approaches will not be able to circumvent regulatory requirements, more efficacious drugs may allow us to abandon clinically questionable trials with intentionally less efficacious controls and noninferiority designs, and require evidence for comparative effectiveness. The failure of AED development has led to increasing disappointment among clinicians, basic scientists, and industry and may halt any further improvement in the treatment of epilepsy unless we find ways out of this dilemma. Therefore, we need new concepts and fresh thinking about how to radically change and improve AED discovery and development. In this respect, the authors of this critical review will discuss several new ideas that may hopefully lead to more efficacious drug treatment of epilepsy in the future.

Alternative to the conventional search for single-target, single-compound treatments, combination therapies can open entirely new opportunities to fight antibiotic resistance. However, combinatorial complexity prohibits experimental testing of drug combinations on a large scale, and methods to rationally design combination therapies are lagging behind. Here, we developed a combined experimental-computational approach to predict drug-drug interactions using high-throughput metabolomics. The approach was tested on 1,279 pharmacologically diverse drugs applied to the gram-negative bacterium Escherichia coli. Combining our metabolic profiling of drug response with previously generated metabolic and chemogenomic profiles of 3,807 single-gene deletion strains revealed an unexpectedly large space of inhibited gene functions and enabled rational design of drug combinations. This approach is applicable to other therapeutic areas and can unveil unprecedented insights into drug tolerance, side effects, and repurposing.

Over the years, drug products, including those indicated for diabetes, have been withdrawn from the marketplace because of quality concerns and/or severe adverse drug reactions. While the drug regulatory process is designed to detect, among other things, adverse drug reactions before a drug receives marketing authorization, for various reasons, premarket detection of all potential adverse reactions associated with a drug may not be possible. As such, regulatory authorities must also react to and manage adverse reactions identified at the postmarket stage. In this article, we provide a general overview of drug regulation in Canada and the United States and consider an example of a drug indicated for the treatment of diabetes and how newly identified potential safety concerns were managed in the postmarket environment.

Bioinformatic analysis can not only accelerate drug target identification and drug candidate screening and refinement, but also facilitate characterization of side effects and predict drug resistance. High-throughput data such as genomic, epigenetic, genome architecture, cistromic, transcriptomic, proteomic, and ribosome profiling data have all made significant contribution to mechanismbased drug discovery and drug repurposing. Accumulation of protein and RNA structures, as well as development of homology modeling and protein structure simulation, coupled with large structure databases of small molecules and metabolites, paved the way for more realistic protein-ligand docking experiments and more informative virtual screening. I present the conceptual framework that drives the collection of these high-throughput data, summarize the utility and potential of mining these data in drug discovery, outline a few inherent limitations in data and software mining these data, point out news ways to refine analysis of these diverse types of data, and highlight commonly used software and databases relevant to drug discovery.

The drug allergy "label" may have a lifetime of consequences for a child. Many children with alleged drug allergies are proven to be tolerant to the culprit medication when challenged. The field of drug hypersensitivity is a recently evolving field of research, but studies on its epidemiology and diagnostic tools are lacking in children. Clinical history is significant in the diagnosis and classification of drug hypersensitivity in children. Diagnostic tools have been evaluated in a limited number of children; therefore, the guidelines are mainly in line with those for adults. Here, we review the clinical characteristics, main drugs, risk factors, and diagnosis of drug hypersensitivity to aid in its accurate diagnosis in children.

This analysis presents a systematic evaluation of the extent of therapeutic opportunities that can be obtained from drug repurposing by connecting drug targets with disease genes. When using FDA-approved indications as a reference level we found that drug repurposing can offer an average of an 11-fold increase in disease coverage, with the maximum number of diseases covered per drug being increased from 134 to 167 after extending the drug targets with their high confidence first neighbors. Additionally, by network analysis to connect drugs to disease modules we found that drugs on average target 4 disease modules, yet the similarity between disease modules targeted by the same drug is generally low and the maximum number of disease modules targeted per drug increases from 158 to 229 when drug targets are neighbor-extended. Moreover, our results highlight that drug repurposing is more dependent on target proteins being shared between diseases than on polypharmacological properties of drugs. We apply our drug repurposing and network module analysis to COVID-19 and show that Fostamatinib is the drug with the highest module coverage.

Recently, drug-drug cocrystal attracts more and more attention. It offers a low risk, low-cost but high reward route to new and better medicines and could improve the physiochemical and biopharmaceutical properties of a medicine by addition of a suitable therapeutically effective component without any chemical modification. Having so many advantages, to date, the reported drug-drug cocrystals are rare. Here we review the drug-drug cocrystals that reported in last decade and shed light on the opportunities and challenges for the development of drug-drug cocrystals.

Effective design of combination therapies requires understanding the changes in cell physiology that result from drug interactions. Here, we show that the genome-wide transcriptional response to combinations of two drugs, measured at a rigorously controlled growth rate, can predict higher-order antagonism with a third drug in Saccharomyces cerevisiae. Using isogrowth profiling, over 90% of the variation in cellular response can be decomposed into three principal components (PCs) that have clear biological interpretations. We demonstrate that the third PC captures emergent transcriptional programs that are dependent on both drugs and can predict antagonism with a third drug targeting the emergent pathway. We further show that emergent gene expression patterns are most pronounced at a drug ratio where the drug interaction is strongest, providing a guideline for future measurements. Our results provide a readily applicable recipe for uncovering emergent responses in other systems and for higher-

order drug combinations. A record of this paper's transparent peer review process is included in the Supplemental Information.

The drug delivery system enables the release of the active pharmaceutical ingredient to achieve a desired therapeutic response. Conventional drug delivery systems (tablets, capsules, syrups, ointments, etc.) suffer from poor bioavailability and fluctuations in plasma drug level and are unable to achieve sustained release. Without an efficient delivery mechanism, the whole therapeutic process can be rendered useless. Moreover, the drug has to be delivered at a specified controlled rate and at the target site as precisely as possible to achieve maximum efficacy and safety. Controlled drug delivery systems are developed to combat the problems associated with conventional drug delivery. There has been a tremendous evolution in controlled drug delivery systems from the past two decades ranging from macro scale and nano scale to intelligent targeted delivery. The initial part of this review provides a basic understanding of drug delivery systems with an emphasis on the pharmacokinetics of the drug. It also discusses the conventional drug delivery systems and their limitations. Further, controlled drug delivery systems are discussed in detail with the design considerations, classifications and drawings. In addition, nano-drug delivery, targeted and smart drug delivery using stimuli-responsive and intelligent biomaterials is discussed with recent key findings. The paper concludes with the challenges faced and future directions in controlled drug delivery.

Clinically relevant antifungal drugs are scarce, and their effectiveness are hampered by the ability of fungal cells to develop drug resistance mechanisms. Drug effectiveness and drug resistance in human pathogens is very often affected by their "transportome". Many studies have covered a panoply of drug resistance mechanisms that depend on drug efflux pumps belonging to the ATP-Binding Cassette and Major Facilitator Superfamily. However, the study of drug uptake mechanisms has been, to some extent, overlooked in pathogenic fungi. This review focuses on discussing current knowledge on drug uptake systems in fungal pathogens, highlighting the need for further studies on this topic of great importance. The following subjects are covered: (i) drugs imported by known transporter(s) in pathogenic fungi; and (ii) drugs imported by known transporter(s) in the model yeast *Saccharomyces cerevisiae* or in human parasites, aimed at the identification of their homologs in pathogenic fungi. Besides its contribution to increase the understanding of drug-pathogen interactions, the practical implications of identifying drug importers in human pathogens are discussed, particularly focusing on drug development strategies.

While the world rushed to develop treatments for COVID-19, some turned hopefully to drug repurposing (drug repositioning). However, little study has addressed issues of drug repurposing in emergency situations from a broader perspective, taking into account the social and ethical ramifications. When drug repurposing is employed in emergency situations, the fairness of resource distribution becomes an issue that requires careful ethical consideration.This paper examines the drug repurposing in emergency situations focusing on the fairness using Japanese cases. Ethical issues under these circumstances addressed by the authors include: maintaining the evidence level, integrity of clinical research ethics, and voluntary consent by original indication patients. In order to address these issues, they argue that rapid accumulation of ethically and scientifically valid evidence is required, as is obtaining information on resource quantity

Recent pharmacological studies have been developed based on finding new disease-related genes, accompanied by the production of gene-manipulated disease model animals and high-affinity ligands for the target proteins. However, the emergence of this gene-based strategy in drug development has led to the rapid depletion of drug target molecules. To overcome this, we have attempted to utilize clinical big data to explore a novel and unexpected hypothesis of drug-drug interaction that would lead to drug repositioning. Here, we introduce our data-driven approach in which adverse event self-reports are statistically analyzed and compared in order to find and validate new drug targets. The hypotheses provided by such a data-driven approach will likely impact the style of future drug development and pharmaceutical study.

Discriminative stimulus and other drug effects are determined by the concentration of drug at its target receptor and by the pharmacodynamic consequences of drug-receptor interaction. For in vivo procedures such as drug discrimination, drug concentration at receptors in a given anatomical location (e.g., the brain) is determined both by the dose of drug administered and by pharmacokinetic processes of absorption, distribution, metabolism, and excretion that deliver drug to and from that anatomical location. Drug discrimination data are often analyzed by strategies of dose-effect analysis to determine parameters such as potency and efficacy. Pharmacokinetic-Pharmacodynamic (PKPD) analysis is an alternative to conventional dose-effect analysis, and it relates drug effects to a measure of drug concentration in a body compartment (e.g., venous blood) rather than to drug dose. PKPD analysis can yield insights on pharmacokinetic and pharmacodynamic determinants of drug action. PKPD analysis can also facilitate translational research by identifying species differences in pharmacokinetics and providing a basis for integrating these differences into interpretation of drug effects. Examples are discussed here to illustrate the application of PKPD analysis to the evaluation of drug effects in rhesus monkeys trained to discriminate cocaine from saline.

Phenotypic drug discovery (PDD) uses biological systems directly for new drug screening. While PDD has proved effective in the discovery of drugs with novel mechanisms, for broader adoption, key challenges need resolution: progression of poorly qualified leads and overloaded pipelines due to lack of effective tools to process and prioritize hits; and advancement of leads with undesirable mechanisms that fail at more expensive stages of discovery. Here I discuss how human-based phenotypic platforms are being applied throughout the discovery process for hit triage and prioritization, for elimination of hits with unsuitable mechanisms, and for supporting clinical strategies through pathway-based decision frameworks. Harnessing the data generated in these platforms can also fuel a deeper understanding of drug efficacy and toxicity mechanisms. As these approaches increase in use, they will gain in power for driving better decisions, generating better leads faster and in turn promoting greater adoption of PDD.

In the field of drug delivery, the most commonly used treatments have traditionally been systemically delivered using oral or intravenous administration. The problems associated with this type of delivery is that the drug concentration is controlled by first pass metabolism, and therefore may not always remain within the therapeutic window. Implantable drug delivery systems (IDDSs) are an excellent alternative to traditional delivery because they offer the ability to precisely control the drug release, deliver drugs locally to the target tissue, and avoid the toxic side effects often experienced with systemic administration. Since the creation of the first FDA-approved IDDS in 1990, there has been a surge in research devoted to fabricating and testing novel IDDS formulations. The versatility of these systems is evident when looking at the various biomedical applications that utilize IDDSs. This review provides an overview of the history of IDDSs, with examples of the different types of IDDS formulations, as well as looking at current and future biomedical applications for such systems. Though there are still obstacles that need to be overcome, ever-emerging new technologies are making the manufacturing of IDDSs a rewarding therapeutic endeavor with potential for further improvements.

Drugs are developed through basic studies and clinical trials. In basic studies, researchers seek drug candidates using in vitro evaluation systems and subsequently examine their effectiveness in animal experiments as in vivo evaluations. Drug candidates identified in basic studies are tested to determine whether they are effective against human diseases in clinical trials. However, most drug candidates identified in in vitro evaluation systems do not show therapeutic effects in animal experiments due to pharmacokinetics and toxicity problems in the in vivo evaluations. This review outlines drug discovery using insect disease models that allow us to perform in vivo screening. Since insects have various advantages as experimental animals such as low cost for rearing and few ethical concerns, researchers can perform large-scale in vivo screening to find drug candidates. Silkworms are insects frequently used for studies of drug efficacy, pharmacokinetics, and toxicity. Based on silkworm research, I describe the benefits of using insect disease models for drug discovery. The use of insect disease models for in vivo screening is expected to facilitate drug discovery.

Personalized medicine aims is to supply the proper drug to the proper patient within the right dose. Pharmacogenomics (PGx) is to recognize genetic variants that may influence drug efficacy and toxicity. All things considered, the fields cover a wide area, including basic drug discovery researches, the genetic origin of pharmacokinetics and pharmacodynamics, novel drug improvement, patient genetic assessment and clinical patient administration. At last, the objective of Pharmacogenomics is to anticipate a patient's genetic response to a particular drug as a way of presenting the best possible medical treatment. By predicting the drug response of an individual, it will be possible to increase the success of therapies and decrease the incidence of adverse side effect.

Targeted drug delivery to solid tumors is a very active research area, focusing mainly on improved drug formulation and associated best delivery methods/devices. Drug-targeting has the potential to greatly improve drug-delivery efficacy, reduce side effects, and lower the treatment costs. However, the vast majority of drug-targeting studies assume that the drug-particles are already at the target site or at least in its direct vicinity. In this review, drug-delivery methodologies, drug types and drug-delivery devices are discussed with examples in two major application areas: (1) inhaled drug-aerosol delivery into human lung-airways; and (2) intravascular drug-delivery for solid tumor targeting. The major problem addressed is how to deliver efficiently the drug-particles from the entry/infusion point to the target site. So far, most experimental results are based on animal studies. Concerning pulmonary drug delivery, the focus is on the pros and cons of three inhaler types, i.e., pressurized metered dose inhaler, dry powder inhaler and nebulizer, in addition to drug-aerosol formulations. Computational fluid-particle dynamics techniques and the underlying methodology for a smart inhaler system are discussed as well. Concerning intravascular drug-delivery for solid tumor targeting, passive and active targeting are reviewed as well as direct drug-targeting, using optimal delivery of radioactive microspheres to liver tumors as an example. The review concludes with suggestions for future work, considereing both pulmonary drug targeting and direct drug delivery to solid tumors in the vascular system.

Various aspects of the presented score were examined to determine its reliability and usefulness: the abundance of common domains for the predicted drug pairs, c.a. 80% coverage for known targets, successful identifications of unknown targets, and a meaningful correlation with another cutting-edge method for analyzing drug similarities. The most significant strength of our method is that the DRS can be used to describe phenotypic similarities, such as pharmacological effects.

The drug network is reinforced in terms of the coverage and connections of drugs: the drug coverage increases from 4738 to 5442, and the drug-drug associations as well from 808,752 to 982,361. Along with the network enhancement, drug recommendation becomes more reliable: AUC of 0.89 was achieved lifted from 0.79. For typical cases, 11 recommended drugs were shown for vascular dementia: amantadine, conotoxin GV, tenocyclidine, cycloeucine, etc.

Elderly patients often suffer from a variety of diseases and therefore may be prescribed several kinds of drugs. Interactions between these drugs may cause problems in some patients. Guidelines for drug interactions were released on July 8, 2014 "Drug Interaction Guideline for Drug Development and Labeling Recommendations (Final Draft)". These guidelines include the theoretical basis for evaluating the mechanisms of drug interaction, the possible extent of drug interactions, and take into consideration special populations (e.g., infants, children, elderly patients, patients with hepatic or renal dysfunction, and subjects with minor deficient alleles for drug metabolizing enzymes and drug transporters). In this symposium article, I discuss this last special population: altered drug metabolism and drug interactions in subjects with minor alleles of genes encoding deficient drug metabolizing enzymes. I further discuss a drug label for eliglustat (Cerdelga) with instructions for patients with ultra-rapid, extensive, intermediate, and poor metabolizer phenotypes that arise from different CYP2D6 gene alleles.

Concomitant administration of multiple drugs can lead to unanticipated drug interactions and resultant adverse drug events with their associated costs. A more thorough understanding of the different cytochrome P450 isoenzymes and drug transporters has led to new methods to try to predict and prevent

clinically relevant drug interactions. There is also an increased recognition of the need to identify the impact of pharmacogenetic polymorphisms on drug interactions. More stringent regulatory requirements have evolved for industry to classify cytochrome inhibitors and inducers, test the effect of drug interactions in the presence of polymorphic enzymes, and evaluate multiple potentially interacting drugs simultaneously. In clinical practice, drug alert software programs have been developed. This review discusses drug interaction mechanisms and strategies for screening and minimizing exposure to drug interactions. We also provide future perspectives for reducing the risk of clinically significant drug interactions.

Neuro psychiatric illnesses are commonly recognised these days in the intensive care especially with the increasing aging population and more intensive care admissions. However they are still inadequately diagnosed and treated disease entities as a majority of these patients do not seek the help of specialists psychiatrists Of course the number of drugs used in psychiatry has explosively increased in recent years. As a corollary to this, the phenomenon of drug- drug interaction between psychiatric drugs and other drugs has come to the forefront. Drug- drug interaction (DDI)) is the response (pharmacological or clinical) of altered drug effects or increase in adverse effects when two or more drugs are used simultaneously[1,2] This effect may be different from the usual action of the individual drugs when used alone. Potential drug- drug interaction (PDDI) are those where theoretically there may be an interaction between the drugs but have not clinically occurred

Black Americans are overrepresented among those incarcerated for drug-related offenses. Drug use, postincarceration, is associated with high risk of recidivism and overdose deaths. We explored factors influencing drug use among former Black drug offenders. Qualitative interviews with 30 Black Americans released from prison within the past year explored drug behavior as well as institutional, environmental, and social factors that influence drug use. Findings show participants reentered drug-enticing environments and social networks. Being on parole, drug programs, and social support influenced abating drug use. Drug interventions postincarceration should consider the environment and social networks as leverage points for behavior change.

Drug metabolism as a discipline plays an important role in drug discovery and development and the effects of drug metabolism on pharmacokinetics (PK), pharmacodynamics (PD), and safety should be carefully considered. This communication provides an overview of common strategies in the area of drug metabolism for improving PK/PD and safety profiles of drug candidates; these include, but are not limited to, collaboration with medicinal chemists on structure-activity relationships (SAR) to overcome high clearance, using deuterium replacement to further optimize a lead, prodrug approaches to circumvent formulation and delivery difficulties, and addressing issues such as species differences in metabolism, drug-drug interactions (DDI) and formation of reactive metabolites.

The development of drug-loading technology will bring new and rapid development to the treatment of diseases. At present, drug delivery by nanoparticles, erythrocyte, and platelet have been studied extensively. Compared with traditional anticancer drugs, nano-drugs have shown many obvious advantages, disease treatment based on nanotechnology will bring a revolution in cancer treatment. Due to its inherent biocompatibility, large drug load and long half-life in the blood circulation, erythrocyte-inspired antibiotics, and some anticancer drugs delivery systems have also entered the clinical trial stage. At present, there are relatively few studies on drug delivery by platelets as carriers. It is necessary to overcome the shortcomings of platelets, such as easy activation, deformation, thrombosis, and difficult preservation. There are many ways to combine drugs with these carriers, and each has its own advantages and disadvantages. It is necessary to seek the best combination scheme to increase drug loading and reduce the damage to therapeutic components to the carriers, so as to bring more mature and reliable methods for the clinical application of drug delivery technology. Several drug-loading technologies and their development were described according to various categories. The combination of drugs and carriers is summarized for better understanding of its practical application.

Drug molecules transformed into nanoparticles or endowed with nanostructures with or without the aid of carrier materials are referred to as "nanomedicines" and can overcome some inherent drawbacks of free drugs, such as poor water solubility, high drug dosage, and short drug half-life in vivo. However, most of the existing nanomedicines possess the drawback of low drug-loading (generally less than 10%) associated with more carrier materials. For intravenous administration, the extensive use of carrier materials might cause systemic toxicity and impose an extra burden of degradation, metabolism, and excretion of the materials for patients. Therefore, on the premise of guaranteeing therapeutic effect and function, reducing or avoiding the use of carrier materials is a promising alternative approach to solve these problems. Recently, high drug-loading nanomedicines, which have a drug-loading content higher than 10%, are attracting increasing interest. According to the fabrication strategies of nanomedicines, high drug-loading nanomedicines are divided into four main classes: nanomedicines with inert porous material as carrier, nanomedicines with drug as part of carrier, carrier-free nanomedicines, and nanomedicines following niche and complex strategies. To date, most of the existing high drug-loading nanomedicines belong to the first class, and few research studies have focused on other classes. In this review, we investigate the research status of high drug-loading nanomedicines and discuss the features of their fabrication strategies and optimum proposal in detail. We also point out deficiencies and developing direction of high drug-loading nanomedicines. We envision that high drug-loading nanomedicines will occupy an important position in the field of drug-delivery systems, and hope that novel perspectives will be proposed for the development of high drug-loading nanomedicines..

During the last decade, nanomedicine has emerged as a new field of medicine that utilises nanoscale materials for delivery of drugs, genes and imaging agents. The efficiency of drug delivery may be enhanced by the application of directed energy, which provides for drug targeting and enhanced intracellular uptake. In this paper, we present a review of recent advances in the ultrasound-mediated drug delivery with the emphasis on polymeric micelles as tumour-targeted drug carriers. This new modality of drug targeting to tumours is based on the drug encapsulation in polymeric micelles followed by a localised release at the tumour site triggered by focused ultrasound. The rationale behind this approach is that drug encapsulation in micelles decreases systemic concentration of free drug and provides for a passive drug targeting to tumours via the enhanced permeability and retention (EPR) effect, therefore reducing unwanted drug interactions with healthy tissues. Ultrasound affects micellar drug delivery on various levels. Mild hyperthermia induced by ultrasound may enhance micelle extravasation into tumour tissue; mechanical action of ultrasound results in drug release from micelles and enhances the intracellular uptake of both released and encapsulated drug. In addition, polymeric micelles sensitise multidrug resistant (MDR) cells to the action of drugs.

The glyconanoparticle (GlycoNP) has multiple effects and has important applications in drug delivery and bioimaging. It not only has the advantages of nano drug delivery system but also utilizes the characteristics of multivalent interaction of sugar, which greatly improves the targeting of drug delivery. Herein, the application of GlycoNP in drug delivery was analyzed and discussed, the solution to its problem was proposed, and its prospects were forecasted.

In this review, 9 compounds with insufficient absorption characteristics, safety or efficacy were selected from among the compounds for which the author was in charge of development between 2000 and 2005, in order to evaluate the pharmacokinetic (PK) approaches used to develop these compounds. Optimization of the PK characteristics of a compound at the early stage of chemical design was found to be the most important factor for successful development. For example, (i) selecting class I or II drugs in the biopharmaceutical classification system, while avoiding efflux transporters, and introducing an appropriate dissociation moiety into a compound to make it soluble lead to sufficient drug absorption; (ii) designing compounds whose production of reactive metabolites, such as acyl glucuronide, does not largely affect total metabolism, yet helps to prevent abnormal PK caused by reactive metabolites. Other factors include (i) selection of a drug efficacy evaluation system based on the correct understanding of the relationship between PK and pharmacodynamics (PD) helps to solve species differences in PD; (ii) the establishment of a nonclinical study based on the identification of the involvement of specific

cytochrome P450 molecules in the total metabolic clearance of a drug ($f_{m,CYP}$s) helps to solve species differences in PK; and (iii) PK analysis using the tube model for hepatic extraction kinetics, and knowledge of the $f_{m,CYP}$s of the victim drug, lead to successful drug-drug interaction (DDI) prediction. I hope that this review aids in future drug discovery or development.

Dextran as a drug carrier for inhibiting cancer cells effectively reduces the toxic and side effects of the drug in the biological body. Targeting improves the concentration of active substance around the target tissue, which reduces damage to other heavy organs and other normal tissues. Dextran will be a potential carrier for the delivery of antitumor drugs in the future, which provides the possibility of slow-release chemotherapy and targeted drug delivery. Herein, the preparation and drug delivery of dextran-drug complex were summarized and discussed in detail.

It is increasingly difficult to keep track of information on drug-drug interactions in HIV therapeutics, and the clinical implications of much of the data reported are not immediately evident. Nevertheless, knowledge of drug-drug interactions is necessary to preserve antiretroviral efficacy and to avoid undue risk of toxicity. The following article reviews important drug-drug interactions and accumulating data on newer antiretroviral agents.

The proposed learning model on semi-bipartite graph model, can integrate drug-drug and protein-protein similarities which are semantically different than drug-protein information in a drug-target interaction network. We show our model can determine interaction likelihood for each drug-target pair and outperform other heuristics.

In patients with drug hypersensitivity reactions, confirmation of causality frequently facilitates decision on a continuation or withdrawal of a given treatment. Unfortunately, identification of the culprit drug often proves difficult. In vivo methods possess well-known disadvantages like low sensitivity of skin tests or the risk of relapse during drug provocation tests. Therefore, laboratory assays are of great interest as they may improve causal diagnosis without putting patients at risk. In this article, the mechanistic principles and methodological issues of the enzyme-linked immunospot (ELISpot) assay were recapped the context of drug hypersensitivity reactions. A review of ELISpot application in causal diagnosis of drug hypersensitivity was based on literature search. The main findings are: (i) ELISpot assay has a good performance in the detection of drug-specific response. (ii) ELISpot results seem to be not substantially impacted by the type of drug or phenotype of the reaction. (iii) Testing within 30 days since the episode of drug hypersensitivity reaction shows a better performance than in later recovery phase. (iv) Data from pediatric population are too scarce to draw any conclusions. (v) Differences in laboratory protocols and in criteria used in the assessment of ELISpot plates along with the issue of the technical feasibility and reproducibility may limit the use of this assay in the routine diagnostic of drug hypersensitivity reactions.

Different from traditional methods for judging drug synergy and antagonism, we propose the framework of how to enhance the efficiency by perturbing two sensitive targets in a combinatorial way, how to decrease the drug dose and therefore its side effect and cost by perturbing combinatorially a main sensitive target and an auxiliary insensitive target, and how to perturb two insensitive targets to realize the transition from a disease state to a healthy one which cannot be realized by perturbing each insensitive target alone. Although the idea is mainly applied to an AA metabolic network, the strategy holds for more general molecular networks such as combinatorial regulation in gene regulatory networks.

Quantitative measurement of clinical drug-drug similarity has many potential applications in assessing medication therapy similarity and patient similarity. Currently, most of the methods to measure drug-drug similarity were not directly obtained from clinical data and cannot cover clinical drugs. We sought to propose a computational approach to measure clinical drug-drug similarity based on the Electronic Medical Record (EMR) system.

Precision drug therapy requires accounting for pertinent factors in pharmacokinetic (PK) inter-individual variability (*i.e.*, pharmacogenetics, diseases, polypharmacy, and natural product use) that can cause sub-therapeutic or adverse effects. Although each of these individual factors can alter victim drug PK, multi-factorial interactions can cause additive, synergistic, or opposing effects. Determining the magnitude and direction of these complex multi-factorial effects requires understanding the rate-limiting redundant and/or sequential PK processes for each drug.

For more than 60years drug delivery systems have produced numerous controlled release formulations helping patients improve compliance and maximize the drug efficacy. Development of new controlled drug delivery systems was very productive during the period 1950-1980. The productivity, as measured by the number of clinically used formulations, dropped significantly during 1980-2010. This reduced productivity needs to be understood so that the future development of drug delivery systems can be accelerated and prolific again. This requires critical evaluation of the current drug delivery field, so that the factors inhibiting rapid progress can be identified and resolved. The current drug delivery field is faced with an invisible gorilla syndrome, i.e., seeing a gorilla when it is not present and missing a gorilla when it actually exists. Overcoming this syndrome requires a new way of thinking, questioning the status quo. Advances in drug delivery technologies occur by an evolutionary process, and thus, the more trials and errors lead to faster advances. The drug delivery area needs to nurture the environment where vastly different ideas can be tested, and all data, positive or negative, need to be exchanged freely as they have equal importance.

Death certificate data from the Multiple Cause of Death (MCOD) files were analyzed to better understand the drug categories most responsible for the increase in fatal overdoses occurring between 1999 and 2014. Statistical adjustment methods were used to account for the understatement in reported drug involvement occurring because death certificates frequently do not specify which drugs were involved in the deaths. The frequency of combination drug use introduced additional uncertainty and so a distinction was made between *any* versus *exclusive* drug involvement. Many results were sensitive to the starting and ending years chosen for examination. Opioid analgesics played a major role in the increased drug deaths for analysis windows starting in 1999 but other drugs, particularly heroin, became more significant for recent time periods. Combination drug use was important for all time periods and needs to be accounted for when designing policies to slow or reverse the increase in overdose deaths.

Adverse drug reactions (ADRs) can be dose dependent or idiosyncratic. Most idiosyncratic reactions are believed to be immune-mediated; such drug hypersensitivities and allergies are unpredictable. Cutaneous reactions are the most common presentation of drug allergies. In veterinary medicine it can be difficult to assess the true prevalence of adverse drug reactions, although reports available suggest that they occur quite commonly. There are multiple theories that attempt to explain how drug allergies occur, because the pathogenesis is not yet well understood. These include the (pro)-hapten hypothesis, the Danger Theory, the pi concept, and the viral reactivation theory. Cutaneous drug allergies in veterinary medicine can have a variety of clinical manifestations, ranging from pruritus to often fatal toxic epidermal necrolysis. Diagnosis can be challenging, as the reactions are highly pleomorphic and may be mistaken for other dermatologic diseases. One must rely heavily on history and physical examination to rule out other possibilities. Dechallenge of the drug, histopathology, and other diagnostic tests can help to confirm the diagnosis. New diagnostic tools are beginning to be used, such as antibody or cellular testing, and may be used more in the future. There is much yet to learn about drug allergies, which makes future research vitally important. Treatment of drug allergies involves supportive care, and additional treatments, such as immunosuppressive medications, depend on the manifestation of the disease. Of utmost importance is to avoid the use of the incriminating drug in future treatment of the patient, as subsequent reactions can be worse, and ultimately can prove fatal.

Since Human Genome Project (HGP) revealed the heterogeneity of individuals, precision medicine that proposes the customized healthcare has become an intractable and hot research. Meanwhile, as the Precision Medicine Initiative launched, precision drug design which aims at maximizing therapeutic

effects while minimizing undesired side effects for an individual patient has entered a new stage. One of the key strategies of precision drug design is target based drug design. Once a key pathogenic target is identified, rational drug design which constitutes the major part of precision drug design can be performed. Examples of rational drug design on novel druggable targets and protein-protein interaction surfaces are summarized in this review. Besides, various kinds of computational modeling and simulation approaches increasingly benefit for the drug discovery progress. Molecular dynamic simulation, drug target prediction and *in silico* clinical trials are discussed. Moreover, due to the powerful ability in handling high-dimensional data and complex system, deep learning has efficiently promoted the applications of artificial intelligence in drug discovery and design. In this review, deep learning methods that tailor to precision drug design are carefully discussed. When a drug molecule is discovered, the development of specific targeted drug delivery system becomes another key aspect of precision drug design. Therefore, state-of-the-art techniques of drug delivery system including antibody-drug conjugates (ADCs), and ligand-targeted conjugates are also included in this review.

Drug-drug interactions are frequent among hepatitis C-infected patients receiving treatment with direct-acting antivirals. However, the collaboration between physicians and clinical pharmacists makes it possible to detect, evaluate, avoid or clinically manage these drug-drug interactions, in order to maintain whole treatment therapeutic safety and the effectiveness of direct-acting antivirals.

Scope and completeness were high for drug-ethanol interactions, but low for drug-tobacco interactions. Consistency was highly variable across both interaction types.

Immunologically mediated drug reactions have been traditionally classified as unpredictable based on the fact that they cannot be predicted strictly on the pharmacological action of the drug. Such adverse drug reactions are associated with considerable morbidity and include severe cutaneous adverse reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis and the drug hypersensitivity syndromes (drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome). Over the last decade there have been many associations between these syndromes and Class I and II HLA alleles of the MHC, which have enriched and driven our knowledge of their immunopathogenesis. Significant translation has also occurred in the case of HLA-B*5701 screening being used to exclude at risk patients from abacavir and prevent abacavir hypersensitivity. The ultimate translation of the knowledge of how drugs interact with HLA would be applicable to preclinical drug screening programs to improve the safety and cost-effectiveness of drug design and development..

Drug repositioning (also referred to as drug repurposing), the process of finding new uses of existing drugs, has been gaining popularity in recent years. The availability of several established clinical drug libraries and rapid advances in disease biology, genomics and bioinformatics has accelerated the pace of both activity-based and in silico drug repositioning. Drug repositioning has attracted particular attention from the communities engaged in anticancer drug discovery due to the combination of great demand for new anticancer drugs and the availability of a wide variety of cell- and target-based screening assays. With the successful clinical introduction of a number of non-cancer drugs for cancer treatment, drug repositioning now became a powerful alternative strategy to discover and develop novel anticancer drug candidates from the existing drug space. In this review, recent successful examples of drug repositioning for anticancer drug discovery from non-cancer drugs will be discussed.

A drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe T cell mediated hypersensitivity reaction. Relapses of symptoms in the recovery phase are frequent and linked to the reduction of the corticosteroid treatment, to viral reactivations or to the exposure to new drugs. Here, we analyzed, how often the exposure to new drugs leads to new sensitization or drug-related relapses without detectable sensitization.

The drug classification system, as prescription or non-prescription drug category, has been utilized as a regulatory strategy to ensure patient safety. In Thailand, the same system has been used for decades, though the drug classification criteria were updated to accommodate drug re-classification in 2016.

These new criteria, however, have not been applied retroactively. Inconsistency in drug classification has been observed leading to concerns regarding the drug classification system. This has prompted the need for a review of the drug classification system in Thailand. This study aims to explore Thailand and other selected countries' regulatory management regarding the drug classification system, drug classification criteria, and drug classification itself.

The emergence of nanomaterials for drug delivery provides the opportunity to avoid the side effects of systemic drug administration and injury caused by the removal of tumors, delivering great promise for future cancer treatments. However, the efficacy of current nano drugs is not significantly better than that of the original drug treatments. The important reason is that nano drugs enter the tumor vasculature, remaining close to the blood vessels and unable to enter the tumor tissue or tumor cells to complete the drug delivery process. The low efficiency of drug penetration into tumors has become a bottleneck restricting the development of nano-drugs. Herein, we present a systematic overview of recent advances on the design of nano-drug carriers in drug delivery systems for enhancing drug penetration into tumors. The review is organized into four sections: The drug penetration process in tumor tissue includes paracellular and transcellular transport, which is summarized first. Strategies that promote tumor penetration are then introduced, including methods of remodeling the tumor microenvironment, charge inversion, dimensional change, and surface modification of ligands which promote tissue penetration. Conclusion and the prospects for the future development of drug penetration are finally briefly illustrated. The review is intended to provide thoughts for effective treatment of cancer by summarizing strategies for promoting the endocytosis of nano drugs into tumor cells.

Adverse drug reactions adverse drug reaction (ADR) occur in approximately 17% of patients. Avoiding ADR is thus mandatory from both an ethical and an economic point of view. Whereas, pharmacogenetics changes of the pharmacokinetics may contribute to the explanation of some type A reactions, strong relationships of genetic markers has also been shown for drug hypersensitivity belonging to type B reactions. We present the classifications of ADR, discuss genetic influences and focus on delayed-onset hypersensitivity reactions, i.e., drug-induced liver injury, drug-induced agranulocytosis, and severe cutaneous ADR. A guidance how to read and interpret the contingency table is provided as well as an algorithm whether and how a test for a pharmacogenetic biomarker should be conducted.

The accumulation of various types of drug informatics data and computational approaches for drug repositioning can accelerate pharmaceutical research and development. However, the integration of multi-dimensional drug data for precision repositioning remains a pressing challenge. Here, we propose a systematic framework named PIMD to predict drug therapeutic properties by integrating multi-dimensional data for drug repositioning. In PIMD, drug similarity networks (DSNs) based on chemical, pharmacological, and clinical data are fused into an integrated DSN (iDSN) composed of many clusters. Rather than simple fusion, PIMD offers a systematic way to annotate clusters. Unexpected drugs within clusters and drug pairs with a high iDSN similarity score are therefore identified to predict novel therapeutic uses. PIMD provides new insights into the universality, individuality, and complementarity of different drug properties by evaluating the contribution of each property data. To test the performance of PIMD, we use chemical, pharmacological, and clinical properties to generate an iDSN. Analyses of the contributions of each drug property indicate that this iDSN was driven by all data types and performs better than other DSNs. Within the top 20 recommended drug pairs, 7 drugs have been reported to be repurposed.

The descriptive cross-sectional study was planned to evaluate drug-related problems, including drug-drug interactions, dose error, use of nephrotoxic drugs and polypharmacy, with special emphasis on kidney disease patients. The study was conducted from January to June 2019 in the Nephrology Ward of Ayub Teaching Hospital, Abbottabad, Pakistan. Doses of medicine and drug-drug interactions were evaluated by comparing it with standard protocols in British National Formulary and Lexicomp. Prescriptions were also evaluated for polypharmacy and use of nephrotoxic drugs. Out of 131 patients,

72 (55%) were males. Drug-drug interactions were found in 69 (52.7%) patients among whom the highest percentage was of moderate drug-drug interaction 63 (48.1%), followed by major 39 (29.8%) and minor 29 (22%) drug-drug interactions. Incidence of polypharmacy 68 (51.9%) and use of nephrotoxic drug 101 (77%) was high, while dose error was low 14 (10.7%). All drug-related problems were present with a high percentage in patients with chronic kidney diseases 29 (78.4) out of 37 (28.2%) such patients. There was significant association of chronic kidney diseases stages with drug-drug interactions, polypharmacy, dose error and prescribing drugs ($p<0.05$). The higher incidence of drug-related problems reflected irrational prescribing trends and deficiency of professional staff dealing with kidney disease patients.

Low drug loading efficiency is one of the main obstacles hindering the application of contact lenses (CLs) as the carrier for extended ocular drug delivery. Here in this study, a simple and effective drug loading method based on salt induced modulation was proposed and demonstrated with mechanism elucidation. First of all, using poly (2-hydroxyethyl methacrylate) (p-HEMA) as the contact lens material, betaxolol hydrochloride, Diclofenac Sodium and Betaxolol Base as the model drugs with different solubility, influence of salt concentration, salt type (sodium salts of sulfate, chloride, and sulfocyanate) and drug properties in the loading solution on drug loading efficiency was investigated. Mechanism of enhanced drug loading in contact lens was further explored via studying the influence of salt on the absorption isotherm, drug solubility and water content of CLs. Applicability of this method to other CLs materials was also investigated. It was demonstrated that adjusting the ionic strength of loading solutions resulted in significant increase of drug loading in CLs. Type and concentration of the salts and solubility of the drug were the main factors influencing enhancement ratio of drug loading. The mechanism for improved drug loading was related to the reduced drug solubility in loading solutions and the reduced bound water content in contact lenses. Modulation of drug loading by adjusting ionic strength was also applicable to other CLs and the light transmittance was not affected. This method was more suitable for salt-form drugs with high solubility. In summary, adjusting ionic strength of loading solution is an economical and effective way to improve drug loading in CLs, and this simple method may also find application in other hydrogel based drug delivery systems.

The study confirmed that the Spontaneous Reporting Database was a valuable resource for detecting actual drug-drug interactions. Also, it identified drugs leading to serious adverse drug reactions and deaths, thus indicating the areas which should be in the focus of health care education.

Drug switching is common in the Netherlands, and most of the drug switches we studied are between generic drugs. The observed annual peak of drug switches is most likely explained by a specific Dutch reimbursement policy. Not only are the data valuable as is, but they also serve as a first step towards elucidating the reasons for the occurrence of these drug switches. In addition, these data can be used to put into perspective the adverse drug reactions associated with drug switching.

Drug-drug interaction (DDI) prediction is one of the most important tasks in drug discovery. Prediction of potential DDIs helps to reduce unexpected side effects in the lifecycle of drugs, and is important for the drug safety surveillance. Here, we formulate the drug-drug interaction prediction as a matrix completion task, and project drugs in the interaction space into a low-dimensional space. We consider drug features, i.e., substructures, targets, enzymes, transporters, pathways, indications, side effects, and off side effects, to calculate drug-drug similarities, and assume them as manifolds in feature spaces. In this paper, we present a novel computational method named "Manifold Regularized Matrix Factorization" (MRMF) to predict potential drug-drug interactions, by introducing the drug feature-based manifold regularization into the matrix factorization. In the computational experiments, the MRMF models, which utilize known drug-drug interactions and the drug feature-based manifold, produce the area under precision-recall curves (AUPR) up to 0.7963. We test manifold regularizations based on different drug features, and the MRMF models can produce robust performances. Compared with other state-of-the-art methods, the MRMF models can produce better performances in the cross validation and case study. The manifold regularization is the critical factor for the high-accuracy

performances of our method. MRMF is promising and effective for the prediction of drug-drug interactions.

With the survey of reported information we concluded the development strategies of diagnosis and treatment against neurological diseases which leads to supportive progress in the drug discovery.

Drug-drug interactions can cause unanticipated patient morbidity and mortality. The consequences of drug-drug interactions can be especially severe when anticancer drugs are involved because of their narrow therapeutic index. Veterinary clinicians have traditionally been taught that drug-drug interactions result from alterations in drug metabolism, renal excretion or protein binding. More recently, drug-drug interactions resulting from inhibition of P-glycoprotein-mediated drug transport have been identified in both human and veterinary patients. Many drugs commonly used in veterinary patients are capable of inhibiting P-glycoprotein function and thereby causing an interaction that results in severe chemotherapeutic drug toxicity. The intent of this review is to describe the mechanism and clinical implications of drug-drug interactions involving P-glycoprotein and anticancer drugs. Equipped with this information, veterinarians can prevent serious drug-drug interactions by selecting alternate drugs or adjusting the dose of interacting drugs.

Drug interactions are a well-known cause of adverse drug events, and drug interaction databases can help the clinician to recognize and avoid such interactions and their adverse events. However, not every interaction leads to an adverse drug event. This is because the clinical relevance of drug-drug interactions also depends on the genetic profile of the patient. If inhibitors or inducers of drug metabolising enzymes (e.g., CYP and UGT) are added to the drug therapy, phenoconcversion can occur. This leads to a genetic phenotype that mismatches the observable phenotype. Drug-drug-gene and drug-gene-gene interactions influence the toxicity and/or ineffectivness of the drug therapy. To date, there have been limited published studies on the impact of genetic variations on drug-drug interactions. This review discusses the current evidence of drug-drug-gene interactions, as well as drug-gene-gene interactions. Phenoconversion is explained, the and methods to calculate the phenotypes are described. Clinical recommendations are given regarding the integratation of the PGx results in the assessment of the relevance of drug interactions in the future.

The novel coronavirus disease 2019 (COVID-19) pandemic has caused a massive health crisis worldwide and upended the global economy. However, vaccines and traditional drug discovery for COVID-19 cost too much in terms of time, manpower, and money. Drug repurposing becomes one of the promising treatment strategies amid the COVID-19 crisis. At present, there are no publicly existing databases for experimentally supported human drug-virus interactions, and most existing drug repurposing methods require the rich information, which is not always available, especially for a new virus. In this study, on the one hand, we put size-able efforts to collect drug-virus interaction entries from literature and build the Human Drug Virus Database (HDVD). On the other hand, we propose a new approach, called SCPMF (similarity constrained probabilistic matrix factorization), to identify new drug-virus interactions for drug repurposing. SCPMF is implemented on an adjacency matrix of a heterogeneous drug-virus network, which integrates the known drug-virus interactions, drug chemical structures, and virus genomic sequences. SCPMF projects the drug-virus interactions matrix into two latent feature matrices for the drugs and viruses, which reconstruct the drug-virus interactions matrix when multiplied together, and then introduces the weighted similarity interaction matrix as constraints for drugs and viruses. Benchmarking comparisons on two different datasets demonstrate that SCPMF has reliable prediction performance and outperforms several recent approaches. Moreover, SCPMF-predicted drug candidates of COVID-19 also confirm the accuracy and reliability of SCPMF.

Gelatin, a denatured form of collagen, is an attractive biomaterial for biotechnology. In particular, gelatin particles have been noted due to their attractive properties as drug carriers. The drug release from gelatin particles can be easily controlled by the crosslinking degree of gelatin molecule, responding to the purpose of the research. The gelatin particles capable of drug release are effective in

wound healing, drug screening models. For example, a sustained release of growth factors for tissue regeneration at the injured sites can heal a wound. In the case of the drug screening model, a tissue-like model composed of cells with high activity by the sustained release of drug or growth factor provides reliable results of drug effects. Gelatin particles are effective in drug delivery and the culture of spheroids or cell sheets because the particles prevent hypoxia-derived cell death. This review introduces recent research on gelatin microparticles-based strategies for regenerative therapy and drug screening models.

Gram-positive cocci, including enterococci and Staphylococcus aureus, have become the leading cause of hospital-acquired infections, and their resistance to antibiotics is increasing. Two important new drugs-quinupristin/dalfopristin (Synercid) and linezolid (Zyvox)-were designed specifically to treat infections due to drug-resistant gram-positive cocci. But their use must be tempered by their cost, toxicity, and concerns about further development of resistant strains.

Microfluidic platforms provide several unique advantages for drug development. In the production of drug carriers, physical properties such as size and shape, and chemical properties such as drug composition and pharmacokinetic parameters, can be modified simply and effectively by tuning the flow rate and geometries. Large numbers of carriers can then be fabricated with minimal effort and with little to no batch-to-batch variation. Additionally, cell or tissue culture models in microfluidic systems can be used as in vitro drug screening tools. Compared to in vivo animal models, microfluidic drug screening platforms allow for high-throughput and reproducible screening at a significantly lower cost, and when combined with current advances in tissue engineering, are also capable of mimicking native tissues. In this review, various microfluidic platforms for drug and gene carrier fabrication are reviewed to provide guidelines for designing appropriate carriers. In vitro microfluidic drug screening platforms designed for high-throughput analysis and replication of in vivo conditions are also reviewed to highlight future directions for drug research and development.

The dominant paradigm in understanding drug action focuses on the intended therapeutic effects and frequent adverse reactions. However, this approach may limit opportunities to grasp unintended drug actions, which can open up channels to repurpose existing drugs and identify rare adverse drug reactions. Advances in systems biology can be exploited to comprehensively understand pharmacodynamic actions, although proper frameworks to represent drug actions are still lacking.

Although safety of drug candidates is carefully monitored in preclinical and clinical studies using a variety of approaches, drug toxicity may still occur in clinical practice. Therefore, novel approaches are needed to complement the current drug safety evaluation system. Metabolomics comprehensively analyzes the metabolites altered by drug exposure, which can therefore be used to profile drug metabolism, endobiotic metabolism, and drug-microbiota interactions. The information from metabolomic analysis can be used to determine the off-targets of a drug candidate, and thus provide a mechanistic understanding of drug toxicity. We herein discuss the opportunities of metabolomics in drug safety evaluation.

Out-of-date or incomplete drug product labeling information may increase the risk of otherwise preventable adverse drug events. In recognition of these concerns, the United States Federal Drug Administration (FDA) requires drug product labels to include specific information. Unfortunately, several studies have found that drug product labeling fails to keep current with the scientific literature. We present a novel approach to addressing this issue. The primary goal of this novel approach is to better meet the information needs of persons who consult the drug product label for information on a drug's efficacy, effectiveness, and safety. Using FDA product label regulations as a guide, the approach links drug claims present in drug information sources available on the Semantic Web with specific product label sections. Here we report on pilot work that establishes the baseline performance characteristics of a proof-of-concept system implementing the novel approach. Claims from three drug information sources were linked to the Clinical Studies, Drug Interactions, and Clinical Pharmacology

sections of the labels for drug products that contain one of 29 psychotropic drugs. The resulting Linked Data set maps 409 efficacy/effectiveness study results, 784 drug-drug interactions, and 112 metabolic pathway assertions derived from three clinically-oriented drug information sources (ClinicalTrials.gov, the National Drug File - Reference Terminology, and the Drug Interaction Knowledge Base) to the sections of 1,102 product labels. Proof-of-concept web pages were created for all 1,102 drug product labels that demonstrate one possible approach to presenting information that dynamically enhances drug product labeling. We found that approximately one in five efficacy/effectiveness claims were relevant to the Clinical Studies section of a psychotropic drug product, with most relevant claims providing new information. We also identified several cases where all of the drug-drug interaction claims linked to the Drug Interactions section for a drug were potentially novel. The baseline performance characteristics of the proof-of-concept will enable further technical and user-centered research on robust methods for scaling the approach to the many thousands of product labels currently on the market.

Cells need to strictly control their internal milieu, a function which is performed by the plasma membrane. Selective passage of molecules across the plasma membrane is controlled by transport proteins. As the liver is the central organ for drug metabolism, hepatocytes are equipped with numerous drug transporters expressed at the plasma membrane. Drug disposition includes absorption, distribution, metabolism, and elimination of a drug and hence multiple passages of drugs and their metabolites across membranes. Consequently, understanding the exact mechanisms of drug transporters is essential both in drug development and in drug therapy. While many drug transporters are expressed in hepatocytes, and some of them are well characterized, several transporters have only recently been identified as new drug transporters. Novel powerful tools to deorphanize (drug) transporters are being applied and show promising results. Although a large set of tools are available for studying transport *in vitro* and in isolated cells, tools for studying transport in living organisms, including humans, are evolving now and rely predominantly on imaging techniques, e.g. positron emission tomography. Imaging is an area which, certainly in the near future, will provide important insights.

Tritryps diseases are devastating parasitic neglected infections caused by Leishmania spp., Trypanosoma cruzi and Trypanosoma brucei subspecies. Together, these parasites affect more than 30 million people worldwide and cause high mortality and morbidity. Leishmaniasis comprises a complex group of diseases with clinical manifestation ranging from cutaneous lesions to systemic visceral damage. Antimonials, the first-choice drugs used to treat leishmaniasis, lead to high toxicity and carry significant contraindications limiting its use. Drug-resistant parasite strains are also a matter for increasing concern, especially in areas with very limited resources. The current scenario calls for novel and/or improvement of existing therapeutics as key research priorities in the field. Although several studies have shown advances in drug discovery towards leishmaniasis in recent years, key knowledge gaps in drug discovery pipelines still need to be addressed. In this review we discuss not only scientific and non-scientific bottlenecks in drug development, but also the central role of public-private partnerships for a successful campaign for novel treatment options against this devastating disease.

A drug candidate suitable for clinical testing is expected to bind selectively to the receptor site on the target, to elicit the desired functional response of the target molecule, and to have adequate bioavailability and biodistribution to elicit the desired responses in animals and humans; it must also pass formal toxicity evaluation in animals. The path from lead to clinical drug candidate represents the most idiosyncratic segment of drug discovery and development. Each program is unique and setbacks are common, making it difficult to predict accurately the duration or costs of this segment. Because of incidents of unpredicted human toxicity seen in recent years, the regulatory agencies and public demands for safety of new drug candidates have become very strict, and safety issues are dominant when identifying a clinical drug candidate.

Adverse reactions to medication are common. Some are predictable side-effects of the drug, others involve individual sensitivity to the drug. Allergic reactions are an important subset of these, but other specific sensitivities are caused by variations in the metabolism or mode of action of the drug. Patients

who have experienced adverse reactions to medication will often refer to themselves as being allergic to the drug, regardless of the actual mechanism that caused the reaction. Consequently, anyone taking a history of 'drug allergy' needs to keep an open mind about the mechanism that may have been involved. Fortunately, most idiosyncratic reactions are minor, but some are severe, or even life-threatening. In most situations, there are satisfactory alternatives for the drug in question, but sometimes it is necessary to investigate and get an accurate diagnosis. The over-riding priority is to distinguish anaphylactic, potentially life-threatening reactions from other types of drug reaction, which are generally more protracted, less dangerous and usually managed by simple avoidance. While all doctors need to understand the underlying principles, drug challenges should only be undertaken by clinicians experienced in this area.

Clinically relevant drug-drug interactions are prevalent among elderly people with dementia living in Northern Sweden. Drug-drug interactions should be identified in order to manage and prevent adverse outcomes. This is particularly important among this group of people especially when multiple medications are being prescribed.

Drug repositioning aims to find new indications for existing drugs in order to reduce drug development cost and time. Currently,there are numerous stories of successful drug repositioning that have been reported and many repurposed drugs are already available on the market. Although drug repositioning is often a product of serendipity, repositioning opportunities can be uncovered systematically. There are three systematic approaches to drug repositioning: disease-centric approach, target-centric and drug-centric. Disease-centric approaches identify close relationships between an old and a new indication. A target-centric approach links a known target and its established drug to a new indication. Lastly, a drug-centric approach connects a known drug to a new target and its associated indication. These three approaches differ in their potential and their limitations, but above all else, in the required start information and computing power. This raises the question of which approach prevails in current drug discovery and what that implies for future developments. To address this question, we systematically evaluated over 100 drugs, 200 target structures and over 300 indications from the Drug Repositioning Database. Each analyzed case was classified as one of the three repositioning approaches. For the majority of cases (more than 60%) the disease-centric definition was assigned. Almost 30% of the cases were classified as target-centric and less than 10% as drug-centric approaches. We concluded that, despite the use of umbrella term "drug" repositioning, disease- and target-centric approaches have dominated the field until now. We propose the use of drug-centric approaches while discussing reasons, such as structure-based repositioning techniques, to exploit the full potential of drug-target-disease connections.

Reliable measurements of how drug affect disease-related proteins are critical to ongoing drug development in the genome medicine era. We demonstrated that DMAP can help drug development professionals assess drug-to-protein relationship data and improve chances of success for systematic drug repositioning efforts.

Acquired resistance is one of the major barriers to successful cancer therapy. The development of resistance is commonly attributed to genetic heterogeneity. However, heterogeneity of drug penetration of the tumor microenvironment both on the microscopic level within solid tumors as well as on the macroscopic level across metastases may also contribute to acquired drug resistance. Here we use mathematical models to investigate the effect of drug heterogeneity on the probability of escape from treatment and the time to resistance. Specifically we address scenarios with sufficiently potent therapies that suppress growth of all preexisting genetic variants in the compartment with the highest possible drug concentration. To study the joint effect of drug heterogeneity, growth rate, and evolution of resistance, we analyze a multi-type stochastic branching process describing growth of cancer cells in multiple compartments with different drug concentrations and limited migration between compartments. We show that resistance is likely to arise first in the sanctuary compartment with poor drug penetrations and from there populate non-sanctuary compartments with high drug concentrations.

Moreover, we show that only below a threshold rate of cell migration does spatial heterogeneity accelerate resistance evolution, otherwise deterring drug resistance with excessively high migration rates. Our results provide new insights into understanding why cancers tend to quickly become resistant, and that cell migration and the presence of sanctuary sites with little drug exposure are essential to this end.

Resistance of cancer cells to chemotherapeutics and emerging targeted drugs is a devastating problem in the treatment of cancer patients. Multiple mechanisms contribute to drug resistance such as increased drug efflux, altered drug metabolism, secondary mutations in drug targets, and activation of downstream or parallel signal transduction pathways. The rapid kinetics, the reversibility of acquired drug resistance and the absence of genetic mutations suggest an epigenetic basis for drug insensitivity. Similar to the cellular variance seen in the human body, epigenetic mechanisms, through reversible histone modifications and DNA methylation patterns, generate a variety of transcriptional states resulting in a dynamic heterogeneous tumor cell population. Consequently, epigenomes favoring survival in the presence of a drug by aberrant transcription of drug transporters, DNA-repair enzymes and pro-apoptotic factors render cytotoxic and targeted drugs ineffective and allow selection of rare drug-resistant tumor cells. Recent advances in charting cancer genomes indeed strongly indicate a role for epigenetic regulators in driving cancer, which may result in the acquisition of additional (epi)genetic modifications leading to drug resistance. These observations have important clinical consequences as they provide an opportunity for "epigenetic drugs" to change reversible drug-resistance-associated epigenomes to prevent or reverse non-responsiveness to anti-cancer drugs.

DDIs as well as their side-effects are challenging regarding their precise evaluation, especially due to the need for multidrug treatment in critically ill patients. Concentration-controlled therapy should be recommended, especially for treatment with vancomycin, digoxin and valproate. Pantoprazole should be a proton pump-inhibitor of choice. Drug dose modification is necessary in combined treatment with fluconazole and amiodarone or rifampicin. From a clinical point of view, the most important impact of drug-drug interactions is on antibiotic treatment effectiveness, especially with meropenem when valproate is also prescribed.

Firstly, the collected data may help other researchers to develop and verify similar techniques. Secondly, the proposed method is successful in identifying drug resistance determinants. Thirdly, the in-silico identified genetic mutations, which are putatively involved in drug resistance mechanisms, may increase our understanding of the drug resistance mechanisms

The impact of prescription drug promotion on health-care professionals (HCPs) is significant. Pharmaceutical industry spending on promotion to HCPs greatly outpaces spending on direct-to-consumer promotion. According to Syneos Health™ PromotionalAnswers, in 2017, the pharmaceutical industry spent more than $24 billion on drug promotion, with more than $18.5 billion allotted for marketing to HCPs. Although prescription drug promotion can provide valuable information about drug therapies, it is essential that it be truthful, balanced, and not misleading, because HCPs may consider this information when making treatment decisions for their patients.

The principles of inter-species dose extrapolation are poorly understood and applied. We provide an overview of the principles underlying dose scaling for size and dose adjustment for size-independent differences. Scaling of a dose is required in three main situations: the anticipation of first-in-human doses for clinical trials, dose extrapolation in veterinary practice and dose extrapolation for experimental purposes. Each of these situations is discussed. Allometric scaling of drug doses is commonly used for practical reasons, but can be more accurate when one takes into account species differences in pharmacokinetic parameters (clearance, volume of distribution). Simple scaling of drug doses can be misleading for some drugs; correction for protein binding, physicochemical properties of the drug or species differences in physiological time can improve scaling. However, differences in drug transport and metabolism, and in the dose-response relationship, can override the effect of size alone.

For this reason, a range of modelling approaches have been developed, which combine in silico simulations with data obtained in vitro and/or in vivo. Drugs that are unlikely to be amenable to simple allometric scaling of their clearance or dose include drugs that are highly protein-bound, drugs that undergo extensive metabolism and active transport, drugs that undergo significant biliary excretion (MW > 500, ampiphilic, conjugated), drugs whose targets are subject to inter-species differences in expression, affinity and distribution and drugs that undergo extensive renal secretion. In addition to inter-species dose extrapolation, we provide an overview of dose extrapolation within species, discussing drug dosing in paediatrics and in the elderly.

After comparing different software programs, the potential drug-drug interactions found by the programs proved to be different. Therefore, we recommend that pharmacists confirm with a different program before making a decision when they detect clinically significant potential drug-drug interactions.

Over the past few decades, liposome drug delivery systems (liposome DDS) have attracted much attention as the most advanced DDS. Efficacy and toxicity profiles of liposomes are based on their characteristic pharmacokinetics, drug release, and disposition after administration. Many attempts have been made to develop these systems especially as liposomal anti-cancer drugs. In the development of liposome DDS, identification of critical quality attributes and establishment of a control strategy to ensure consistent drug product quality are crucial. Among the quality attributes, particle size, drug encapsulation, and drug release from liposomes would affect their in vivo pharmacokinetic and pharmacodynamic properties. Thus these features need to be evaluated with appropriate analytical methods to confirm the quality and performance of the drug products. This article focuses on drug release from liposomes and reviews the effects of physicochemical properties of loaded drugs on release, simulation of drug release from liposomes, and design of a simulated body fluid for drug release assay of drug products.

The high degree of perception of controlling drug use in the GP, and partially in drug users being treated, and the specific control strategies reported suggests that moderate use and drug control strategies are a great value alternative to bear in mind compared to abstinence.

Combining antibiotics is a promising strategy for increasing treatment efficacy and for controlling resistance evolution. When drugs are combined, their effects on cells may be amplified or weakened, that is the drugs may show synergistic or antagonistic interactions. Recent work revealed the underlying mechanisms of such drug interactions by elucidating the drugs' joint effects on cell physiology. Moreover, new treatment strategies that use drug combinations to exploit evolutionary tradeoffs were shown to affect the rate of resistance evolution in predictable ways. High throughput studies have further identified drug candidates based on their interactions with established antibiotics and general principles that enable the prediction of drug interactions were suggested. Overall, the conceptual and technical foundation for the rational design of potent drug combinations is rapidly developing.

The use of nanoparticles (NPs) for enhanced drug delivery has been heavily explored during the last decade. Within the field, it is has become increasingly apparent that the physical properties of the particles themselves dictate their efficacy, and the relevant non-covalent chemistry at the NP interface also influences how drugs are immobilized and delivered. In this review, we reflect on the physical chemistry of NP mediated drug delivery (and more specifically, non-covalent drug delivery) at the three main experimental stages of drug loading, NP-drug conjugate transport, and the resulting cellular drug delivery. Through a critical evaluation of advances in drug delivery within the last decade, an outlook for biomedical applications of nanoscale transport vectors will be presented.

Background Potential drug-drug interactions are important factors resulting in adverse drug reactions or therapeutic failure. Therefore, potential drug-drug interactions need to be identified to prevent the related risk and improve drug safety. Objective This study was designed to determine the prevalence of potential drug-drug interactions and investigate the association of potential drug-drug interactions with

characteristics in outpatient prescriptions. Setting A large-scale general university hospital in Jinshan District of Shanghai, China. Method The retrospective study was conducted on data obtained from prescriptions containing two or more drugs, written for outpatients older than 18 years. They were screened for potential drug-drug interactions using Lexi-Interact in UpToDate, Stockley's Drug Interactions and Medicine Specification in the order of priority. Main outcome measure Drug-drug interactions with C, D, X risk rating and clinical parameters recorded at the prescriptions. Results 16,120 prescriptions were screened for the presence of potential drug-drug interactions and 4882 (30.29%) prescriptions containing 6667 potential drug-drug interactions were identified. Among 6667 potential drug-drug interactions, 90.81% (6054/6667), 8.49% (566/6667), 0.70% (47/6667) potential drug-drug interactions belonged to the risk category of C, D and X, respectively. Male, old age and polypharmacy increased the likelihood of potential drug-drug interactions. The most frequently prescribed drugs responsible for potential drug-drug interactions included pioglitazone, dihydrocodeine, thalidomide, sotalol, amiodarone and amlodipine. The predominant potential adverse outcome of potential drug-drug interactions was the increased central nervous system suppression function with the mechanism of reinforced pharmacological effects. Conclusion This study showed that potentially significant drug-drug interactions in outpatients were prevalent in real-world practice. Considering the risk of potential clinical consequences related to potential drug-drug interactions, it is necessary to implement the computerized surveillance and warning systems with drug-drug interactions databases as well as develop the clinical guidelines regarding the widespread potential drug-drug interactions.

Clinicians had suspected for years that drug eruptions were probably mediated by immune mechanisms because their timing suggested sensitization and specific immunologic memory rather than direct toxicity. An immune response to medications was also demonstrated by positive skin tests and by several types of in vitro tests that evidenced immediate or delayed hypersensitivity. In the last decade several teams of researchers obtained in vitro drug-specific human T-cell clones, in a variety of clinical types of drug eruptions. These clones were produced from blood or skin mononuclear cells of patients with a history of drug reaction by stimulation in vitro with drug. They were either of CD4 or CD8 phenotypes. Drug specific clones were stimulated by the parent drug much more often than by reactive metabolites. That challenged the classical "hapten hypothesis" that the immune response was initiated by reactive metabolites combined to self proteins. The medication usually stimulated specific T-cells after non-covalent binding to major histocompatibility (MHC) molecules on antigen presenting cells. In toxic epidermal necrolysis, T-lymphocytes present at the site of lesions, exhibited a drug specific cytotoxicity against autologous target cells, or allogeneic cells that shared the same HLA than autologous cells. This MHC class I restriction and mediation of death by perforin/granzyme release, is the classical behavior of cytotoxic T lymphocytes, like those operating in the reject of a transplanted organ. MHC restriction could explain the key role of HLA genes as predisposing factors to severe drug reactions. A strong association between HLA and hypersensitivity to abacavir, SJS or TEN to carbamazepine or allopurinol has been recently demonstrated. Resemblance to graft rejection points to the possible therapeution value of immuno suppressive agents. Most drug eruptions appear to result from T-cell mediated delayed hypersensitivity. The secondary activation of different cascades of cytokines, may contribute to the heterogeneity of clinical presentations.

Drug discovery is a high-risk, expensive and lengthy process taking at least 12 years and costing upwards of US$500 million per drug to reach the clinic. For neglected diseases, the drug discovery process is driven by medical need and guided by pre-defined target product profiles. Assessment and prioritisation of the most promising targets for entry into screening programmes is crucial for maximising the chances of success. Here, we describe criteria used in our drug discovery unit for target assessment and introduce the 'traffic-light' system as a prioritisation and management tool. We hope this brief review will stimulate basic scientists to acquire additional information necessary for drug discovery.

Ovarian cancer remains a disease entity that is responsible for considerable morbidity and mortality among women worldwide. Modern drug research pipelines and accelerated drug development timelines

applied to other disease entities have begun to make an impact on treatment options for patients with advanced ovarian cancer, as exemplified by the recent accelerated approval of 2 agents for this disease as the forerunners of a growing number of registrational trials. Regulatory flexibility for this serious and life-threatening condition spurs the consideration of intermediate endpoints for regulatory trial design, including potential applications in the development of newer therapeutic classes such as targeted therapies and immunotherapies for patients with advanced ovarian cancer. Cancer 2017;123:2604-8. © 2017 American Cancer Society.

Cancer is one of the most difficult diseases to treat owing to the drug resistance of tumour cells. Recent studies have revealed that drug responses are closely associated with genomic alterations in cancer cells. Numerous state-of-the-art machine learning models have been developed for prediction of drug responses using various genomic data and diverse drug molecular information, but those methods are ineffective to predict drug response to untrained drugs and gene expression patterns, which is known as the cold-start problem. In this study, we present a novel deep neural network model, termed RefDNN, for improved prediction of drug resistance and identification of biomarkers related to drug response. RefDNN exploits a collection of drugs, called reference drugs, to learn representations for a high-dimensional gene expression vector and a molecular structure vector of a drug and predicts drug response labels using the reference drug-based representations. These calculations come from the observation that similar chemicals have similar effects. The proposed model not only outperformed existing computational prediction models in most comparative experiments, but also showed more robust prediction for untrained drugs and cancer types than traditional machine learning models. RefDNN exploits the ElasticNet regularization to deal with high-dimensional gene expression data, which allows identification of gene markers associated with drug resistance. Lastly, we described an application of RefDNN in exploring a new candidate drug for liver cancer. As the proposed model can guarantee good prediction of drug responses to untrained drugs for given gene expression patterns, it may be of potential benefit in drug repositioning and personalized medicine.

For decades, the paradigm of drug discovery and development has relied on immortalized cell lines, animal models of human disease, and clinical trials. With the discovery of induced pluripotent stem cell (iPSC) technology in 2007, a new human in vitro drug testing platform has potentially augmented this set of tools by providing additional ways to screen compounds for safety and efficacy. The growing number of human disease models made with patient-specific iPSCs has made it possible to conduct research on a wide range of disorders, including rare diseases and those with multifactorial origin, as well as to simulate drug effects on difficult-to-obtain tissues such as brain and cardiac muscle. Toxicity and teratogenicity assays developed with iPSC-derived cells can also provide an additional layer of safety before advancing drugs to clinical trials. The incorporation of iPSC technology into drug therapy development holds promise as a more powerful and nuanced approach to personalized medicine.

In the regulatory setting, clinical pharmacology focuses on the impact of intrinsic and extrinsic factors on inter-patient and intra-subject variability in drug exposure and response. This translational science contributes to the understanding of the benefit-risk profile in individual patients and the development of relevant therapeutic monitoring and management strategies. Clinical pharmacology also plays a major role in the development and qualification of drug development tools. This article presented some recent examples to illustrate the important roles of clinical pharmacology in drug development and evaluation. In addition, emerging trends in clinical pharmacology regulatory sciences were also discussed, including the Model-Informed Drug Development (MIDD) pilot program, the use of real-world data to generate real-world evidence, and leveraging advances in basic, biomedical, and clinical science into useful tools for drug development and evaluation. Continued advances in clinical pharmacology can be the basis of more rational and efficient drug development and improved access to new drug treatments that are tailored to the patient to achieve better efficacy and safety.

Oral administration is a desirable alternative of parenteral administration due to the convenience and increased compliance to patients, especially for chronic diseases that require frequent administration.

The oral drug delivery is a dynamic research field despite the numerous challenges limiting their effective delivery, such as enzyme degradation, hydrolysis and low permeability of intestinal epithelium in the gastrointestinal (GI) tract. pH-Responsive carriers offer excellent potential as oral therapeutic systems due to enhancing the stability of drug delivery in stomach and achieving controlled release in intestines. This review provides a wide perspective on current status of pH-responsive oral drug delivery systems prepared mainly with organic polymers or inorganic materials, including the strategies used to overcome GI barriers, the challenges in their development and future prospects, with focus on technology trends to improve the bioavailability of orally delivered drugs, the mechanisms of drug release from pH-responsive oral formulations, and their application for drug delivery, such as protein and peptide therapeutics, vaccination, inflammatory bowel disease (IBD) and bacterial infections.

Liquid crystal (LC) dosage forms, particularly those using lipid-based lyotropic LCs (LLCs), have generated considerable interest as potential drug delivery systems. LCs have the physical properties of liquids but retain some of the structural characteristics of crystalline solids. They are compatible with hydrophobic and hydrophilic compounds of many different classes and can protect even biologicals and nucleic acids from degradation. This review, focused on research conducted over the past 5 years, discusses the structural evaluation of LCs and their effects in drug formulations. The structural classification of LLCs into lamellar, hexagonal and micellar cubic phases is described. The structures of these phases are influenced by the addition of surfactants, which include a variety of nontoxic, biodegradable lipids; these also enhance drug solubility. LLC structure influences drug localization, particle size and viscosity, which, in turn, determine drug delivery properties. Through several specific examples, we describe the applications of LLCs in oral and topical drug formulations, the latter including transdermal and ocular delivery. In oral LLC formulations, micelle compositions and the resulting LLC structures can determine drug solubilization and stability as well as intestinal transport and absorption. Similarly, in topical LLC formulations, composition can influence whether the drug is retained in the skin or delivered transdermally. Owing to their enhancement of drug stability and promotion of controlled drug delivery, LLCs are becoming increasingly popular in pharmaceutical formulations.

Nanoparticle deployment in drug delivery is contingent upon controlled drug loading and a desired release profile, with simultaneous biocompatibility and cellular targeting. Iron oxide nanoparticles (IONPs), being biocompatible, are used as drug carriers. However, to prevent aggregation of bare IONPs, they are coated with stabilizing agents. We hypothesize that, zwitterionic drugs like norfloxacin (NOR, a fluoroquinolone) can manifest dual functionality - nanoparticle stabilization and antibiotic activity, eliminating the need of a separate stabilizing agent. Since these drugs have different charges, depending on the surrounding pH, drug loading enhancement could be pH dependent. Hence, upon synthesizing IONPs, they were coated with NOR, either at pH 5 (predominantly as cationic, NOR^{+}) or at pH 10 (predominantly as anionic, NOR^{-}). We observed that, drug loading at pH 5 exceeded that at pH 10 by 4.7-5.7 times. Furthermore, only the former (pH 5 system) exhibited a desirable slower drug release profile, compared to the free drug. NOR-coated IONPs also enable a 22 times higher drug accumulation in macrophages, compared to identical extracellular concentrations of the free drug. Thus, lowering the drug coating pH to 5 imparts multiple benefits - improved IONP stability, enhanced drug coating, higher drug uptake in macrophages at reduced toxicity and slower drug release.

Drug susceptibility testing of Mycobacterium tuberculosis in the diagnostic laboratory classifies clinical isolates as either drug-'resistant' or drug-'susceptible', on the basis of their ability to grow in the presence of a 'critical concentration' of the test compound. From knowledge of the mechanisms that underlie drug resistance, it has become evident that drug resistance in M. tuberculosis is quite heterogeneous and involves low-level, moderate-level and high-level drug resistance phenotypes. Different mutations are associated with different levels of phenotypic resistance, and the acquisition of a genetic alteration leading to a decrease in drug susceptibility does not inevitably exclude the affected compound from treatment regimens. As a result, the simple categorization of clinical M. tuberculosis isolates as 'resistant' on the basis of susceptibility testing at 'critical concentrations' may need to be revised and

supplemented by quantitative measures of resistance testing to reflect the biological complexity of drug resistance, with the view of optimally exploiting the compounds available for treatment.

Adverse drug events are common in older patients, particularly in those taking at least five medications, but such events are predictable and often preventable. A rational approach to prescribing in older adults integrates physiologic changes of aging with knowledge of pharmacology. Focusing on specific outcomes, such as the prompt recognition of adverse drug events, allows the family physician to approach prescribing cautiously and confidently. Physicians need to find ways to streamline the medical regimen, such as periodically reviewing all medications in relation to the Beers criteria and avoiding new prescriptions to counteract adverse drug reactions. The incorporation of computerized alerts and a multidisciplinary approach can reduce adverse drug events.

Drug resistance in cancer is an overwhelming problem, because drug-resistant cancer cells are harder to kill with the same drug. The mechanism of drug resistance differs for various cancers based on the type of drug being used for its treatment. Most current drugs are shown to increase reactive oxygen species (ROS) in respective cancer cells that induces apoptosis, but continuous treatment with the same drug may reduce cellular ROS levels and may convert drug sensitive cancer cells into drug resistant cells. In addition, exogenous elevation of ROS in conjunction with drug resensitizes drug-resistant cancer cells. Thus, constant maintenance of higher ROS level in cancer cells may be a prerequisite for drug efficacy in certain type of cancer cells. Thus, modulation of ROS-mediated genetic pathway genes could be an efficient alternative to maintain higher ROS level in cancer cells for "combinational chemotherapy" with the drug. In this review, I discuss whether ROS reduction in drug-resistant cancer cells could be a general mechanism of drug resistance for most cancers with its specific drug, and whether elevation of ROS levels with the drug could be a valuable strategy for increasing drug efficacy in most cancers.

Drug eruptions affecting the skin or mucosas (toxicoderma) are the most common adverse effects of drugs and represent one of the more common diagnostic challenges for the dermatologist. A better understanding of the pathogenic mechanisms of drug reactions, pharmacogenetics, and pharmacoepidemiology will help us to resolve the main dilemmas and to anticipate and even prevent such reactions. Many drug eruptions are due to T cell-mediated hypersensitivity reactions that can involve activation of different proinflammatory mechanisms, which would explain the varied manifestations. Some aspects defy the classical understanding of antigen processing and presentation. New immunological hypotheses, such as the «p-i concept», have been introduced to complement the hapten theory and, at least in part, help to explain why drug reactions tend to affect the skin and why certain viral infections increase the risk of drug eruptions. In this paper we analyze these pathogenic concepts and the role of HLA genes in the susceptibility to certain severe adverse drug reactions, and also examine other advances in the diagnosis of drug eruptions. We briefly discuss a number of recently described reactions to new drugs.

Multiple factors make conducting drug studies in the pediatric population difficult, resulting in a historic lack of information surrounding safe and efficacious drug dosing in children. The paradigm in pediatric drug development has shifted from normal science being that children are therapeutic orphans in the drug development system, to a model drift caused by pediatric legislation, to a model crisis caused by failed pediatric drug development trials, to finally a model revolution that includes pediatric patients routinely in drug development. Major regulatory actions and the accumulation of scientific evidence has created an environment where clinicians can expect properly labeled drug usage information for the pediatric population.

Evidence-based treatment of drug-susceptible TB is the best means of preventing the development of drug-resistant disease. Suspecting the possibility of drug-resistant TB, and prompt detection of all forms of drug-resistant TB, not only multidrug-resistant and extensively drug-resistant TB, should be part of the algorithm for diagnosis and management of all patients with active TB.

Clinical Pharmacology Drug Interaction Report, Lexicomp Interactions, and Micromedex Drug Interactions scored highest in scope. Micromedex Drug Interactions and Lexicomp Interactions scored highest in completeness. Consistency scores were overall low, but Micromedex Drug Interactions was the highest.

Agonist therapy for opioid use disorder (OUD) is often inaccessible in the US at a time of high overdose mortality.OUD therapy could be offered by drug treatment courts as an alternative to criminal prosecution for some drug offenses.Many drug courts, however, reject gold-standard agonist therapies, seeing them as "another form of addiction".Drug courts often prefer to offer extended-release naltrexone, but it is costly and requires pre-treatment abstinence.Drug courts have had limited success in improving access to OUD treatment at a time of high overdose mortality

Drug related cue-induced reactivity plays a significant role in maintaining drug use and relapse in addicted individuals. The activation of Dorsolateral striatum-Sensorimotor system (DLS-SM) has been suggested as an important route through which drug cues may induce automatic drug using behavior. The current study used fMRI to investigate the reactivity of heroin abstinent individuals to different types of cues, to clarify the characteristics of the cues that induce the activation of the sensorimotor area. Forty heroin-dependent abstinent individuals and 29 healthy subjects were recruited to perform the heroin cue-reactivity task during fMRI. The participants' subjective craving and physical signs were evaluated before and after scanning. Whole-brain analysis showed that compared to drug use tool and drug cues, cues related to drug use action were more likely to activate posterior central gyrus, para-hippocampus, supra marginal gyrus, superior parietal lobule (SPL) and inferior parietal lobule (IPL). These areas are involved in motor preparation and output, indicating that the sensorimotor area is also an important neural basis of craving and automatic drug using behavior, and may mediate craving and drug seeking behavior. Our findings thus suggest that cues related to drug using action may induce automatic drug seeking behavior more than cues related only to the drug itself.

Drug interaction studies on new drug applications (NDAs) for new molecular entities (NMEs) approved in Japan between 1997 and 2008 are examined in the Pharmaceuticals and Medical Devices Agency (PMDA). The situations of drug interaction studies in NDAs have changed over the past 12 years, especially in metabolizing enzyme and transporter-based drug interactions. Materials and approaches to study drug-metabolizing enzyme-based drug interactions have improved, and become more rational based on mechanistic theory and new technologies. On the basis of incremental evidence of transporter roles in human pharmacokinetics, transporter-based drug interactions have been increasingly studied during drug development and submitted in recent NDAs. Some recently approved NMEs include transporter-based drug interaction information in their package inserts (PIs). The regulatory document "Methods of Drug Interaction Studies," in addition to recent advances in science and technology, has also contributed to plan and evaluation of drug interaction studies in recent new drug development. This review summarizes current situations and further discussion points on drug interaction studies in NDAs in Japan.

Recycling old drugs, rescuing shelved drugs and extending patents' lives make drug repositioning an attractive form of drug discovery. Drug repositioning accounts for approximately 30% of the newly US Food and Drug Administration (FDA)-approved drugs and vaccines in recent years. The prevalence of drug-repositioning studies has resulted in a variety of innovative computational methods for the identification of new opportunities for the use of old drugs. Questions often arise from customizing or optimizing these methods into efficient drug-repositioning pipelines for alternative applications. It requires a comprehensive understanding of the available methods gained by evaluating both biological and pharmaceutical knowledge and the elucidated mechanism-of-action of drugs. Here, we provide guidance for prioritizing and integrating drug-repositioning methods for specific drug-repositioning pipelines.

The ability to predict how far a drug will penetrate into the tumour microenvironment within its pharmacokinetic (PK) lifespan would provide valuable information about therapeutic response. As the PK profile is directly related to the route and schedule of drug administration, an in silico tool that can predict the drug administration schedule that results in optimal drug delivery to tumours would streamline clinical trial design. This paper investigates the application of mathematical and computational modelling techniques to help improve our understanding of the fundamental mechanisms underlying drug delivery, and compares the performance of a simple model with more complex approaches. Three models of drug transport are developed, all based on the same drug binding model and parametrized by bespoke in vitro experiments. Their predictions, compared for a 'tumour cord' geometry, are qualitatively and quantitatively similar. We assess the effect of varying the PK profile of the supplied drug, and the binding affinity of the drug to tumour cells, on the concentration of drug reaching cells and the accumulated exposure of cells to drug at arbitrary distances from a supplying blood vessel. This is a contribution towards developing a useful drug transport modelling tool for informing strategies for the treatment of tumour cells which are 'pharmacokinetically resistant' to chemotherapeutic strategies.

The review focuses on the application of supercritical fluids as antisolvents in the pharmaceutical field and demonstrates the supercritical antisolvent method in the use of drug encapsulation. The main factors for choosing the solvent and biodegradable polymer to produce fine particles to ensure effective drug delivery are emphasized and the effect of polymer structure on drug encapsulation is illustrated. The review also demonstrates the drug release mechanism and polymeric controlled release system, and discusses the effects of the various conditions in the process, such as pressure, temperature, concentration, chemical compositions (organic solvents, drug, and biodegradable polymer), nozzle geometry, CO(2) flow rate, and the liquid phase flow rate on particle size and its distribution.

The emergence of drug resistance to traditional chemotherapy and newer targeted therapies in cancer patients is a major clinical challenge. Reactivation of the same or compensatory signaling pathways is a common class of drug resistance mechanisms. Employing drug combinations that inhibit multiple modules of reactivated signaling pathways is a promising strategy to overcome and prevent the onset of drug resistance. However, with thousands of available FDA-approved and investigational compounds, it is infeasible to experimentally screen millions of possible drug combinations with limited resources. Therefore, computational approaches are needed to constrain the search space and prioritize synergistic drug combinations for preclinical studies. In this study, we propose a novel approach for predicting drug combinations through investigating potential effects of drug targets on disease signaling network. We first construct a disease signaling network by integrating gene expression data with disease-associated driver genes. Individual drugs that can partially perturb the disease signaling network are then selected based on a drug-disease network "impact matrix", which is calculated using network diffusion distance from drug targets to signaling network elements. The selected drugs are subsequently clustered into communities (subgroups), which are proposed to share similar mechanisms of action. Finally, drug combinations are ranked according to maximal impact on signaling sub-networks from distinct mechanism-based communities. Our method is advantageous compared to other approaches in that it does not require large amounts drug dose response data, drug-induced "omics" profiles or clinical efficacy data, which are not often readily available. We validate our approach using a BRAF-mutant melanoma signaling network and combinatorial in vitro drug screening data, and report drug combinations with diverse mechanisms of action and opportunities for drug repositioning.

Future drug checking programming should consider ways to engage drug dealers to test their supplies and develop communication strategies to more accurately inform PWUD of drug contents and avert risks associated with using them. Additionally, drug policies that address the effects of criminalization should be considered to lessen potential barriers to DCT use by drug dealers

The Food and Drug Administration (FDA) is issuing final regulations amending the 1992 Orphan Drug Regulations issued to implement the Orphan Drug Act. These amendments are intended to clarify

regulatory provisions and make minor improvements to address issues that have arisen since those regulations were issued.

The "INTERACTIONS" section of package inserts aims to provide alert-type warnings in clinical practice; however, these also include many drug-drug interactions that occur rarely. Moreover, considering that drug-drug interaction alert systems were created based on package inserts, repeated alerts can lead to alert fatigue. Although investigations have been conducted to determine prescriptions that induce drug-drug interactions, no studies have focused explicitly on the adverse events induced by drug-drug interactions. We, therefore, sought to investigate the true occurrence of adverse events caused by drug pair contraindications for coadministration in routine clinical practice. Toward this, we created a list of drug combinations that were designated as "contraindications for coadministration" and extracted the cases of adverse drug events from the Japanese Adverse Drug Event Report database that occurred due to combined drug usage. We then calculated the reporters' recognition rate of the drug-drug interactions. Out of the 2121 investigated drug pairs, drug-drug interactions were reported in 43 pairs, 23 of which included an injected drug and many included catecholamines. Warfarin potassium and miconazole (19 reports), azathioprine and febuxostat (11 reports), and warfarin potassium and iguratimod (six reports) were among the 20 most-commonly reported oral medication pairs that were contraindicated for coadministration, for which recognition rates of drug-drug interactions were high. Although these results indicate that only a few drug pair contraindications for coadministration were associated with adverse drug events (43 pairs out of 2121 pairs), it remains necessary to translate these findings into clinical practice.

The Orphan Drug Act is an important piece of legislation that uses financial incentives to encourage the development of drugs that treat rare diseases. This analysis studies the effects of a portion of the Orphan Drug Act, the orphan drug designation. Specifically, it studies the value that investors place on the orphan drug designation, by investigating how investors react to companies' announcing that their product has received the designation.

Malaria is an infectious disease caused by a protozoan parasite which is transmitted by female *Anopheles* mosquitoes around tropical and sub-tropical regions. Half of the world's population is at risk of being infected by malaria. This mainly includes children, pregnant women and people living with chronic diseases. The main factor that has contributed to the spread of this disease is the increase in the number of drug-resistant parasites. To overcome drug resistance, researchers have developed drug delivery systems from biodegradable polymers for the loading of antimalarials. The drug delivery systems were characterized by distinct features such as good biocompatibility, high percentage drug encapsulation, reduced drug toxicity and targeted drug delivery. In this review article, we highlight the various types of drug delivery systems developed from polymeric nanocarriers used for the delivery of antimalarials.

This review describes and summarizes current preclinical research revealing important differences between drug and non-drug reinforcers in terms of their effects on behavior. Despite research showing that drugs are not especially strong reinforcers in animals, a number of other behavioral differences potentially relevant to addiction have been reported in studies that have compared drug and non-drug reinforcers. Several of these effects appear only after long-term access to drugs. These include an escalation of drug intake, an increased persistence in responding for the drug, and a decreased sensitivity to the effects of punishers or other suppressors of drug seeking. Further differences between drug and non-drug reinforcers include the effects that reinforcer-paired stimuli have on behavior. Drug cues, as compared to food cues, have been shown to exert greater control over reinforcer-seeking behavior after periods of abstinence. Similarly, behavior previously reinforced by drugs, but not food, has been shown to be susceptible to stress-induced reinstatement after extinction. The behavioral differences between drug and non-drug reinforcers reviewed here may identify special features of drugs that lead to addiction.

An important step to promote fragment-based drug design (FBDD) is to find high-quality fragment molecules. Therefore the design of the fragment library is the most crucial stage. In our fragment library, the main considerations are ligand efficiency (LE), diversity, and solubility with drug-like properties. We especially considered LE to raise hit probability in screening. We estimated LE of the fragment molecule based on known LE values of the active compounds. We also developed a docking program suitable for screening fragments rather than drug compounds. Furthermore, we explored fragment-linking program, which links together fragments that bind to adjacent sites on a target protein so as to promote FBDD in silico.

De novo drug discovery is a time-consuming and expensive process. Nowadays, drug repositioning is utilized as a common strategy to discover a new drug indication for existing drugs. This strategy is mostly used in cases with a limited number of candidate pairs of drugs and diseases. In other words, they are not scalable to a large number of drugs and diseases. Most of the in-silico methods mainly focus on linear approaches while non-linear models are still scarce for new indication predictions. Therefore, applying non-linear computational approaches can offer an opportunity to predict possible drug repositioning candidates.

A drug interaction is a process by which a drug or any other substance interacts with another drug and affects its activity by increasing or decreasing its effect, causing a side effect or producing a new effect unrelated to the effect of either. Interactions may be of various types-drug-drug interactions, drug-food interactions, drug-medical condition interactions, or drug-herb interactions. Interactions may occur by single or multiple mechanisms. They may occur in vivo or in vitro (pharmaceutical reactions). In vivo interactions may be further subdivided into pharmacodynamic or pharmacokinetic reactions. Topical drug interactions which may be agonistic or antagonistic may occur between two drugs applied topically or between a topical and a systemic drug. Topical drug-food interaction (for example, grape fruit juice and cyclosporine) and drug-disease interactions (for example, topical corticosteroid and aloe vera) may also occur. It is important for the dermatologist to be aware of such interactions to avoid complications of therapy in day-to-day practice.

Obtaining a uniform definition for drug shortages is important as well as identifying which conditions are preferable to report drug shortages in order to facilitate international benchmarking. This paper can be used as a guidance to point out all the different elements which should be considered to formulate a uniform definition to be applied in the EU.

A drug dataset containing international proprietary names is essential for researchers investigating different drugs from different countries worldwide. However, many websites on the internet offer free access for a single drug searching service to identify international drug trade names, but not for a list of drugs to be searched and identified. Therefore, it will be problematic if the researcher has a list of hundreds or thousands of drug trade names to be identified. In this project, we have created an International Drug Dictionary (IDD) by curating collected drug lists from open access websites belonging to official drug regulatory agencies, official healthcare systems, or recognized scientific bodies from 44 countries around the world in addition to the European public assessment reports (EPAR) and the DRUGBANK vocabulary published in the public domain. Researchers interested in pharmacovigilance, pharmacoepidemiology, or pharmacoeconomics can benefit from this dataset, especially when identifying lists of proprietary drug names, particularly of multi-national origin. To enhance its adaptability, we also mapped the IDD to the standardized drug vocabulary RxNorm. The IDD can also be used as a tool for mapping international drug trade names to RxNorm. Each drug entity in the IDD mapped to a unique identification number for each entity called Atom Unique Identifier (RXAUI) from RxNorm.

Illegal drug dealers no longer compete for customers only through the quality of their products, but also in convenience and speed of delivery. This article investigates "ring and bring" drug dealing, and argues

that a focus on dealers' use of mobile phones is useful for exploring current changes within retail level drug markets.

A morbilliform drug eruption is the most common condition leading to a dermatology consultation for a patient in the hospital. Timing is an important diagnostic tool since the onset of a skin rash usually takes place within days-to-weeks of the start of the implicated drug. A comprehensive, thorough, and reliable drug history by the clinician is essential. Therefore, to assist in the task of determining the causative medication of a new skin rash in a hospitalized patient, the creation of a drug calendar is recommended. The development of an electronic version of the drug calendar offers several benefits over the manual version. As the use of electronic medical records continues to become the standard in medicine, the electronic drug calendar will serve as an invaluable tool for the diagnosis of drug hypersensitivity.

Drug interactions in oncology are common place and largely ignored as we tolerate high thresholds of 'toxic' drug responses in these patients. However, in the era of 'targeted' or seemingly 'less toxic' therapy, these interactions are more commonly flagged and contribute significantly towards poor 'quality of life' and medical fatalities.

Electrospun nanofibers have the potential to achieve high drug loading and the ability to sustain drug release. Mechanical properties of the drug-incorporated fibers suggest the importance of drug-polymer interactions. In this study, we investigated the mechanical properties of electrospun polycaprolactone (PCL) and poly (D,L-lactic-co-glycolic) acid (PLGA) fibers at various blend ratios in the presence and absence of a small molecule hydrophilic drug, tenofovir (TFV). Young′s modulus of the blend fibers showed dependence on PLGA content and the addition of the drug. At a PCL/PLGA (20/80) composition, Young′s modulus and tensile strength were independent of drug loading up to 40wt% due to offsetting effects from drug-polymer interactions. In vitro drug release studies suggested that release of TFV significantly decreased fiber mechanical properties. In addition, mechanically stretched fibers displayed a faster release rate as compared to the non-stretched fibers. Finally, drug partition in the blend fibers was estimated using a mechanical model and then experimentally confirmed with a composite of individually stacked fiber meshes. This work provides scientific understanding on the dependence of drug release and drug loading on the mechanical properties of drug-eluting fibers.

Irrational use of drugs remains a major challenge especially in developing countries, which contributed to a heavy pharmaceutical expenditure burden. Price regulation has been taken to curb the growth of pharmaceutical expenditures in many countries. This study aimed to investigate the impact of different mark-up drug policies on drug-related expenditures in tertiary public hospitals in Shanghai, China. Data were drawn from the audited financial statement in 24 tertiary public hospitals in Shanghai from January 2015 to December 2018. Drug-related revenue data and per capita cost data pre- and post-intervention were included. Interrupted time series design was applied to assess the actual effects of Fixed Percent Mark-up Drug (FPM) policy and Zero Mark-up Drug (ZMD) policy respectively. Results showed that ZMD policy achieved better intervention effects on declining drug-related expenditures than FPM policy. Apart from a declining trend in drug proportion (coefficient = -0.0017, $p = 0.031$), no other significant changes were found during FPM implementation. However, ZMD policy was associated with a level decline in per capita outpatient drug cost (coefficient = -12.21, $p = 0.025$) and a trend decline in per capita inpatient drug cost (coefficient = -25.12, $p < 0.001$), as well as a level decrease (coefficient = -0.0256, $p = 0.001$) and a downward tendency (coefficient = -0.0018, $p < 0.001$) in drug proportion. ZMD policy was effective in regulating drug-related expenditures, while FPM policy was difficult to achieve expected results due to the existence of profit space. Further regulation should be strengthened in the future, especially on drug revenue and per capita drug cost.

Potential drug-drug interactions as well as drug-xenobiotic interactions are a major source of clinical problems, sometimes with dramatic consequences. Investigation of drug-drug interactions during drug development is a major concern for the drug companies while developing new drugs. Our knowledge

of the drug-metabolising enzymes, their mechanism of action, and their regulation has made considerable progress during the last decades. Various efficient in vitro approaches have been developed during recent years and powerful computer-based data handling is becoming widely available. All these tools allow us to initiate, early in the development of new chemical entities, large-scale studies on the interactions of drugs with selective cytochrome P-450 (CYP) isozymes, drug receptors, and other cellular entities. Standardisation and validation of these methodological approaches significantly improve the quality of the data generated and the reliability of their interpretation. The simplicity and the low costs associated with the use of in vitro techniques have made them a method of choice to investigate drug-drug interactions. Promising successes have been achieved in the extrapolation of in vitro data to the in vivo situation and in the prediction of drug-drug interaction. Nevertheless, linking in vitro and in vivo studies still remains fraught with difficulties and should be made with great caution.

he experiments demonstrate that different data sources provide diverse information, and the DDI network based on known DDIs is one of most important information for DDI prediction. The ensemble methods can produce better performances than individual methods, and outperform existing state-of-the-art methods

Drug eruptions are frequently encountered and they represent "diseases of medical progress". They are expected in about 2% of treated patients. Their putative diagnosis is based on a set of imputability factors. Several distinct drug-induced skin disorders are identified. They are initially recognized from personal experience, but the implication to a specific drug derives from the collective experience of published evidence. Their histopathological aspect is often evocative or demonstrative for the nature of the dermatosis. Some drug eruptions follow an indolent course, while others are life-threatening.

Among the challenges facing translational medicine today is the need for greater productivity and safety during the drug development process. To meet this need, practitioners of translational medicine are developing new technologies that can facilitate decision making during the early stages of drug discovery and clinical development. Ex Vivo Metrics is an emerging technology that addresses this need by using intact human organs ethically donated for research. After hypothermic storage, the organs are reanimated by blood perfusion, providing physiologically and biochemically stable preparations. In terms of emulating human exposure to drugs, Ex Vivo Metrics is the closest biological system available for clinical trials. Early application of this tool for evaluating drug targeting, efficacy, and toxicity could result in better selection among promising drug candidates, greater drug productivity, and increased safety.

According to the Organization for Economic Co-operation and Development (OECD), drug expenditures account for about 20 % of all health expenditures in high-income countries. The increase of these drug expenditures which has been observed in all these countries over a long period is due to the combination of aging populations, changes in medical practices and the dynamics of the pharmaceutical market, in particular the hospital market. France is no exception. Its consumption of drugs (which accounted for 17.5 % of health expenditures in 2014), historically among the highest in volume, has grown slower in the last decade than in other OECD countries. However, the particularly rapid and wide adoption of pharmaceutical innovations, which has always characterized France, has had in recent years a very significant effect on the soaring drug expenditures covered by the social protection system (plus 1.1 billion in 2014, a year marked by the introduction of new therapies against hepatitis C). This significant effect should continue with the introduction of new and very expensive therapies, particularly in oncology.

The cryptomarket may function in part as a virtual broker, linking wholesalers with offline retail-level distributors. For drugs like ecstasy, these marketplaces may link vendors in producer countries directly with retail level suppliers. Wholesale activity on cryptomarkets may serve to increase the diffusion of new drugs - and wider range of drugs - in offline drug markets, thereby indirectly serving drug users

who are not cryptomarket customers themselves. Cryptomarkets provide researchers and policy makers with a rich source of drug monitoring information. Further research should ascertain whether their virtual location may reduce the violence associated with middle market drug activity. We caution that conflict may instead manifest in other ways, including threats, fraud, and blackmail.

The DID is a database of structured drug-indication relations intended to facilitate building practical, comprehensive, integrated drug ontologies. The DID itself is not an ontology, but could be converted to one more easily than the contributing raw data. Our methodology could be adapted to the creation of other structured drug-disease databases such as for contraindications, precautions, warnings, and side effects.

Drug combinations are increasingly important in disease treatments, for combating drug resistance, and for elucidating fundamental relationships in cell physiology. When drugs are combined, their individual effects on cells may be amplified or weakened. Such drug interactions are crucial for treatment efficacy, but their underlying mechanisms remain largely unknown. To uncover the causes of drug interactions, we developed a systematic approach based on precise quantification of the individual and joint effects of antibiotics on growth of genome-wide Escherichia coli gene deletion strains. We found that drug interactions between antibiotics representing the main modes of action are highly robust to genetic perturbation. This robustness is encapsulated in a general principle of bacterial growth, which enables the quantitative prediction of mutant growth rates under drug combinations. Rare violations of this principle exposed recurring cellular functions controlling drug interactions. In particular, we found that polysaccharide and ATP synthesis control multiple drug interactions with previously unexplained mechanisms, and small molecule adjuvants targeting these functions synthetically reshape drug interactions in predictable ways. These results provide a new conceptual framework for the design of multidrug combinations and suggest that there are universal mechanisms at the heart of most drug interactions.

Identification of the biopharmaceutical risks of excipients and excipient variability on oral drug performance can be beneficial for the development of robust oral drug formulations. The current study investigated the impact of Hypromellose (HPMC) presence and varying viscosity type, when used as a binder in immediate release formulations, on the apparent solubility of drugs with wide range of physicochemical properties (drug ionization, drug lipophilicity, drug aqueous solubility). The role of physiological conditions on the impact of excipients on drug apparent solubility was assessed with the use of pharmacopoeia (compendial) and biorelevant media. Presence of HPMC affected drug solubility according to the physicochemical properties of studied compounds. The possible combined effects of polymer adsorption (drug shielding effect) or the formation of a polymeric viscous layer around drug particles may have retarded drug dissolution leading to reduced apparent solubility of highly soluble and/or highly ionized compounds and were pronounced mainly at early time points. Increase in the apparent solubility of poorly soluble low ionized drugs containing a neutral amine group was observed which may relate to enhanced drug solubilization or reduced drug precipitation. The use of multivariate data analysis confirmed the importance of drug physicochemical properties on the impact of excipients on drug apparent solubility and revealed that changes in HPMC material properties or amount may not be critical for oral drug performance when HPMC is used as a binder. The construction of a roadmap combining drug, excipient, and medium characteristics allowed the identification of the cases where HPMC presence may present risks in oral drug performance and bioavailability.

A relationship between viral infections and the simultaneous or subsequent development of allergic inflammation has often been observed in various clinical situations. Recent studies suggest an intimate relationship between reactivations of herpesviruses including human herpesvirus 6 (HHV-6) and the development of a severe systemic hypersensitivity reaction referred to as drug-induced hypersensitivity syndrome (DIHS). This syndrome has several important clinical features that cannot be solely explained by drug antigen-driven oligoclonal expansion of T cells: they include paradoxical worsening of clinical symptoms after discontinuation of the causative drug. In view of the similarity to GVHD or immune

reconstitution syndrome (IRS) in clinical manifestations and emergence of viral infections, the clinical symptoms observed during the course of DIHS and GVHD are likely to be mediated by antiviral T cells that can cross-react with the drug and alloantigens, respectively. In considering common intrinsic properties of the causative drugs to potentially induce immunosuppression, reconstitution of a valid immune response to these viruses, which is typically observed in IRS, may be the most crucial process that takes place after withdrawal of the causative drug in patients with DIHS. Thus, this syndrome should be regarded as a reaction induced by a complex interplay among several herpesviruses (EB virus, HHV-6, HHV-7, and cytomegalovirus), antiviral immune responses, and drug-specific immune responses. This review includes discussion of the pathomechanism, the clinical symptoms, laboratory findings, pathological findings and therapy.

The Food and Drug Administration (FDA) is amending its new drug and biological product regulations to allow appropriate studies in animals in certain cases to provide substantial evidence of the effectiveness of new drug and biological products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances. This rule will apply when adequate and well-controlled clinical studies in humans cannot be ethically conducted and field efficacy studies are not feasible. In these situations, certain new drug and biological products that are intended to reduce or prevent serious or life-threatening conditions may be approved for marketing based on evidence of effectiveness derived from appropriate studies in animals and any additional supporting data.

Our understanding of drug tissue distribution impacts a number of areas in drug development, including: pharmacology, pharmacokinetics, safety, drug-drug interactions, transport and metabolism. Despite their extensive use, autoradiography and tissue homogenate LC-MS analysis have limitations in providing a comprehensive assessment of tissue distributions. In the case of autoradiography, it is the inability to distinguish between parent drug and drug metabolites. In LC-MS analysis of tissue homogenate, all tissue localization information is lost. The emerging technique of MALDI imaging mass spectrometry has the capability to distinguish between parent and metabolites while maintaining spatial distribution in tissues. In this article, we will review the MALDI imaging MS methodology as applied to drug development and provide examples highlighting the impact of this important technique in drug development.

The lung is an attractive target for drug delivery due to noninvasive administration via inhalation aerosols, avoidance of first-pass metabolism, direct delivery to the site of action for the treatment of respiratory diseases, and the availability of a huge surface area for local drug action and systemic absorption of drug. Colloidal carriers (ie, nanocarrier systems) in pulmonary drug delivery offer many advantages such as the potential to achieve relatively uniform distribution of drug dose among the alveoli, achievement of improved solubility of the drug from its own aqueous solubility, a sustained drug release which consequently reduces dosing frequency, improves patient compliance, decreases incidence of side effects, and the potential of drug internalization by cells. This review focuses on the current status and explores the potential of colloidal carriers (ie, nanocarrier systems) in pulmonary drug delivery with special attention to their pharmaceutical aspects. Manufacturing processes, in vitro/in vivo evaluation methods, and regulatory/toxicity issues of nanomedicines in pulmonary delivery are also discussed.

Drug-eluting stents have revolutionised the treatment of coronary artery disease. These small medical devices have attracted much interest over the past decade from biologists, clinicians, engineers and mathematicians alike. This article provides a comprehensive review of the modelling of drug release from arterial stents and the subsequent drug transport through arterial tissue, and acts as a useful reference equally for those who are already involved in drug-eluting stents research and for those who are starting out in the field. Assembled in this review are the main models of drug release and arterial drug transport that have been published in the literature to date. Many of the models presented in this paper have evolved from drug transport models in other applications. Furthermore, the ideas presented

in this review may also be extended to other drug-delivery applications, such as drug coated balloons, transdermal patches and therapeutic contact lenses.

High throughput screening (HTS) facilitates screening large numbers of compounds against a biochemical target of interest using validated biological or biophysical assays. In recent years, a significant number of drugs in clinical trails originated from HTS campaigns, validating HTS as a bona fide mechanism for hit finding. In the current drug discovery landscape, the pharmaceutical industry is embracing open innovation strategies with academia to maximize their research capabilities and to feed their drug discovery pipeline. The goals of academic research have therefore expanded from target identification and validation to probe discovery, chemical genomics, and compound library screening. This trend is reflected in the emergence of HTS centers in the public domain over the past decade, ranging in size from modestly equipped academic screening centers to well endowed Molecular Libraries Probe Centers Network (MLPCN) centers funded by the NIH Roadmap initiative. These centers facilitate a comprehensive approach to probe discovery in academia and utilize both classical and cutting-edge assay technologies for executing primary and secondary screening campaigns. The various facets of academic HTS centers as well as their implications on technology transfer and drug discovery are discussed, and a roadmap for successful drug discovery in the public domain is presented. New lead discovery against therapeutic targets, especially those involving the rare and neglected diseases, is indeed a Mount Everestonian size task, and requires diligent implementation of pharmaceutical industry's best practices for a successful outcome.

The value of quantitative thinking in drug development and regulatory review is increasingly being appreciated. Modeling and simulation of data pertaining to pharmacokinetic, pharmacodynamic, and disease progression is often referred to as the pharmacometrics analyses. The objective of the current report is to assess the role of pharmacometrics at the US Food and Drug Administration (FDA) in making drug approval and labeling decisions. The New Drug Applications (NDAs) submitted between 2000 and 2004 to the Cardio-renal, Oncology, and Neuropharmacology drug products divisions were surveyed. For those NDA reviews that included a pharmacometrics consultation, the clinical pharmacology scientists ranked the impact on the regulatory decision(s). Of about a total of 244 NDAs, 42 included a pharmacometrics component. Review of NDAs involved independent, quantitative evaluation by FDA pharmacometricians, even when such analysis was not conducted by the sponsor. Pharmacometric analyses were pivotal in regulatory decision making in more than half of the 42 NDAs. Of the 14 reviews that were pivotal to approval related decisions, 5 identified the need for additional trials, whereas 6 reduced the burden of conducting additional trials. Collaboration among the FDA clinical pharmacology, medical, and statistical reviewers and effective communication with the sponsors was critical for the impact to occur. The survey and the case studies emphasize the need for early interaction between the FDA and sponsors to plan the development more efficiently by appreciating the regulatory expectations better.

Monitoring adherence with chronic opioid therapies is a critical yet often difficult task. Because chronic opioid therapy is often fraught with complex pharmacological, psychological, social, and legal issues, its application is often controversial or altogether avoided. Improved drug monitoring and surveillance may help reduce some of the reluctance to use chronic opioid therapy in patients with chronic pain states. We review the literature on patient adherence/compliance with chronic administration of opioids as well as novel methods by which adherence with opioid therapy can be measured.

Experienced drug-handling problems and inadequately considered expectations for drug therapy have an unfavorable influence on therapy. We performed a questionnaire survey in (i) parents of 0-5-year-old children and (ii) 6-17-year olds and their parents. We assessed (A) experienced drug-handling problems and (B) expectations for drug therapy. (i) Forty-six parents and (ii) 103 children and their parents participated in the study. Experienced drug-handling problems were described by (i) 100% of parents and (ii) 62% of children and 70% of parents. Problems concerned with the preparation of the drug, dosing, compliance with the time interval, and acceptance. (i) Sixty-five percent of parents

preferred a peroral route of drug administration, while (ii) 74% of children and 86% of parents did so. Preferred characteristics of peroral drug formulations, e.g., liquid versus solid drug formulations or flavor, were highly heterogeneous. Preferences of 6-17-year-old children and their parents matched in 43 to 66%. Conclusion: Most children and their parents had already experienced drug-handling problems. Preferences concerning the ideal pediatric drug were highly heterogeneous and in about half of cases, preferences of children and their parents differed. Thus, the children should be approached directly. If information is solely gained from parents, the children's needs might remain unmet. What is Known: • Pediatric drug administration is complex and therefore error-prone. • Experiences and expectations of children and their parents should be considered. What is New: •Most pediatric patients and their parents have already experienced drug-handling problems. • Expectations concerning the ideal pediatric drug are highly heterogeneous. Parents are often insufficiently aware of those expectations in their children.

he approach used in this study allowed for the detection of adverse drug events related to 9% of the potential drug-drug interactions that were identified; these adverse drug events affected 26% of the study population. With the monitoring of adverse drug events based on prescriptions, a combination of the evaluation of potential drug-drug interactions by clinical pharmacy services and the monitoring of critically ill patients is an effective strategy that can be used as a complementary tool for safety assessments and the prevention of adverse drug events.

Background Drug abuse has been on the increase over the last few years, contributing to the healthcare cost. An understanding of the overall impact of drug abuse hospitalizations is essential in combatting the drug abuse epidemic. Objective To evaluate inpatient outcomes of total charges and length of stay for patients with drug abuse comorbidity compared to non-drug abuse admissions. Method The Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample data was utilized. Drug abuse comorbidity was used as defined by HCUP. Various descriptive and inferential analyses were performed on the filtered data sets for the years 2010 to 2014. Results The average hospitalization length of stay was 4.5 days for non-drug abuse and 5.5 days for drug abuse comorbidity ($P < 0.001$). Mean charges for drug abuse comorbidity were significant for claims to private insurance and Medicaid. Conclusion Total charges and length of stay are higher for drug abuse than non-drug abuse cases. The results will aid as a reference for resource allocation and policy changes. Further research is needed for alternative and innovative interventions for conditions that are identified to be co-existing with drug abuse comorbidity.

A common view within the pharmaceutical industry is that there is a problem with drug discovery and we should do something about it. There is much sympathy for this from academics, regulators and politicians. In this article I propose that lessons learnt from evolution help identify those factors that favour successful drug discovery. This personal view is influenced by a decade spent reviewing drug development programmes submitted for European regulatory approval. During the prolonged gestation of a new medicine few candidate molecules survive. This process of elimination of many variants and the survival of so few has much in common with evolution, an analogy that encourages discussion of the forces that favour, and those that hinder, successful drug discovery. Imagining a world without vaccines, anaesthetics, contraception and anti-infectives reveals how medicines revolutionized humanity. How to manipulate conditions that favour such discoveries is worth consideration.

Drug-drug interactions lead to altered clinical effects, including adverse reactions. Therapeutic drug monitoring of digoxin is necessary due to its narrow therapeutic range. Linezolid can cause variable exposures in patients hospitalized in the intensive care unit owing to its possibility of drug-drug interactions. We present a patient with pneumonia and heart failure who experienced a possible drug interaction between linezolid and digoxin, resulting in high serum concentrations of both drugs. Also, the patient developed thrombocytopenia likely related to linezolid. The linezolid dose required to maintain sufficient levels had to reduce to 50% of the usual linezolid dose. A quarter dose of the standard digoxin dose was needed. Although the underlying mechanism of the drug interaction is

unclear, we recommend conducting therapeutic drug monitoring when linezolid and digoxin are administered concurrently.

Our results suggest that CPG-recommended pharmacologic therapies and SPL indications do not overlap frequently when identifying drug-disease associations using named entity recognition, although incorporating taxonomic relationships between drug names and drug classes into the approach improves the overlap. This has important implications in practice because conflicting or inconsistent evidence may complicate clinical decision making and implementation or measurement of best practices.

Drug courts are effective in resolving the criminal and drug-using behaviors in drug-only, nonviolent offenders. Family physicians can become involved in the drug court process by providing treatment for patients with both drug addiction and mental health diagnoses. In addition, as patients withdraw from drugs, it is important to treat withdrawal symptoms to prevent recidivism and encourage participation in the program.

Drug-loaded calcium pectinate gel (CaPG) beads were prepared by either mixing, absorption, or swelling method. The effects of drug loading method as well as the drug loading factors (i.e., drug concentration, soaking time in drug solution, type of solvent) on drug content and drug release were investigated. The amount of drug uptake (i.e., drug content) into CaPG beads increased as the initial drug concentration increased and varied depending on the loading method. The in vitro release studies in 0.1 N hydrochloric acid (HCl) and pH 6.8 buffer indicated that the drug loading method affected drug release and release parameter, time for 50% of drug release (T(50)). The mixing method provided a faster drug release and lower T(50) than the absorption method and swelling method, respectively. This is probably due to higher drug content in CaPG beads. The increased concentration of drug in soaking solution and soaking time resulted in higher drug content and thus faster drug release (lower in T(50) values). When using 0.1 N HCl as solvent for soaking instead of water, the drug release was slower owing to the increase in molecular tortuosity of CaPG beads. The drug release was also affected by pH of the release medium in which drug release in 0.1 N HCl was faster than in pH 6.8 buffer.

We conclude that the regressive nature of the GDUFA fee structure penalizes small, new, and foreign firms while benefiting the large established firms. A progressive fee structure in line with other human drug user fees is needed to ensure a healthy generic drug industry.

As demonstrated with the antipsychotic drug clozapine, the DTome tool was effective and promising for the investigation of relationships among drugs, adverse interaction drugs, drug primary targets, drug-associated genes, and proteins directly interacting with targets or genes. The resultant DTome network provides researchers with direct insights into their interest drug(s), such as the molecular mechanisms of drug actions. We believe such a tool can facilitate identification of drug targets and drug adverse interactions.

The increased viability of MTB drug-resistant strains compared with drug-sensitive strains is likely to be related to differential MazEF mRNA and protein expression. *mazEF*3,6,9 TASs contribute to MTB viability under stress conditions.

Drug transporters expressed in various tissues play a significant role in drug disposition. By regulating the function of such transporters, it may be possible to eventually develop drugs with ideal pharmacokinetic profiles. In this article, we summarize the significant role played by drug transporters in drug disposition, focusing particularly on their potential use during the drug development process. The ability to manipulate transporter function offers the opportunity of being able to deliver a drug to the target organ, avoiding distribution to other organs (thereby reducing the chance of toxic side-effects), controlling the elimination process, and/or improving oral bioavailability. During drug development, it would be very useful to be able to select a lead compound that may or may not interact with transporters, depending on whether such an interaction is desirable. The use of specific inhibitors of transporters is also an attractive approach to controlling drug disposition, leading to improved

efficacy. Currently, optimizing the pharmacokinetic properties of a drug during the early stages of its development is widely accepted as being of great importance. High-throughput screening systems using transporter gene transfected cells or computational (in silico) approaches are efficient tools for assessing transport activity during the early stage of drug development. In addition, drug-drug interactions involving drug transporters and functional genetic polymorphisms of drug transporters are also described. It would also be extremely valuable to be able to quantitatively predict inter-individual pharmacokinetic differences caused by transporter polymorphisms or pharmacokinetic changes caused by drug-drug interactions involving transporters during drug development.

We have developed a drug target prediction method based solely on protein sequence information without the knowledge of family/domain annotation, or the protein 3D structure. This method can be applied in novel drug target identification and validation, as well as genome scale drug target predictions.

The majority of adult people in western societies regularly consume psychoactive drugs. While this consumption is integrated in everyday life activities and controlled in most consumers, it may escalate and result in drug addiction. Non-addicted drug use requires the systematic establishment of highly organized behaviors, such as drug-seeking and -taking. While a significant role for classical and instrumental learning processes is well established in drug use and abuse, declarative drug memories have largely been neglected in research. Episodic memories are an important part of the declarative memories. Here a role of episodic drug memories in the establishment of non-addicted drug use and its transition to addiction is suggested. In relation to psychoactive drug consumption, episodic drug memories are formed when a person prepares for consumption, when the drug is consumed and, most important, when acute effects, withdrawal, craving, and relapse are experienced. Episodic drug memories are one-trial memories with emotional components that can be much stronger than "normal" episodic memories. Their establishment coincides with drug-induced neuronal activation and plasticity. These memories may be highly extinction resistant and influence psychoactive drug consumption, in particular during initial establishment and at the transition to "drug instrumentalization." In that, understanding how addictive drugs interact with episodic memory circuits in the brain may provide crucial information for how drug use and addiction are established.

Magnetism has wide applications in various fields, such as diagnostics, drug targeting, molecular biology, cell isolation, cell purification, hyperthermia, and radioimmunoassay. In this study, we synthesized niosomes doped with iron oxide nanoparticles and a fluorophore for potential applications in magnetically targeted drug delivery. Release kinetics of the fluorophore and cytotoxicity were assessed. The results demonstrate that niosomes doped with iron oxide nanoparticles can serve as proficient and effective drug carriers in magnetically targeted drug delivery

Understanding drugs and their modes of action is a fundamental challenge in systems medicine. Key to addressing this challenge is the elucidation of drug targets, an important step in the search for new drugs or novel targets for existing drugs. Incorporating multiple biological information sources is of essence for improving the accuracy of drug target prediction. In this article, we introduce a novel framework--Similarity-based Inference of drug-TARgets (SITAR)--for incorporating multiple drug-drug and gene-gene similarity measures for drug target prediction. The framework consists of a new scoring scheme for drug-gene associations based on a given pair of drug-drug and gene-gene similarity measures, combined with a logistic regression component that integrates the scores of multiple measures to yield the final association score. We apply our framework to predict targets for hundreds of drugs using both commonly used and novel drug-drug and gene-gene similarity measures and compare our results to existing state of the art methods, markedly outperforming them. We then employ our framework to make novel target predictions for hundreds of drugs; we validate these predictions via curated databases that were not used in the learning stage. Our framework provides an extensible platform for incorporating additional emerging similarity measures among drugs and genes.

Harmful effects associated with use of drugs are caused as a result of their side effects and combined use of different drugs. These drug interactions result in increased or decreased drug effects, or produce other new unwanted effects and are serious problems for medical institutions and pharmaceutical companies. In this study, we created a drug-drug interaction network from drug package inserts and characterized drug interactions. The known information about the potential risk of drug interactions is described in drug package inserts. Japanese drug package inserts are stored in the JAPIC (Japan Pharmaceutical Information Center) database and GenomeNet provides the GenomeNet pharmaceutical products database, which integrate the JAPIC and KEGG databases. We extracted drug interaction data from GenomeNet, where interactions are classified according to risks, contraindications or cautions for coadministration, and some entries include information about enzymes metabolizing the drugs. We defined drug target and drug-metabolizing enzymes as interaction factors using information on them in KEGG DRUG, and classified drugs into pharmacological/chemical subgroups. In the resulting drug-drug interaction network, the drugs that are associated with the same interaction factors are closely interconnected. Mechanisms of these interactions were then identified by each interaction factor.

Millions of patients worldwide have received drug-eluting stents to reduce their risk for in-stent restenosis. The efficacy and toxicity of these local therapeutics depend upon arterial drug deposition, distribution, and retention. To examine how administered dose and drug release kinetics control arterial drug uptake, a model was created using principles of computational fluid dynamics and transient drug diffusion-convection. The modeling predictions for drug elution were validated using empiric data from stented porcine coronary arteries. Inefficient, minimal arterial drug deposition was predicted when a bolus of drug was released and depleted within seconds. Month-long stent-based drug release efficiently delivered nearly continuous drug levels, but the slow rate of drug presentation limited arterial drug uptake. Uptake was only maximized when the rates of drug release and absorption matched, which occurred for hour-long drug release. Of the two possible means for increasing the amount of drug on the stent, modulation of drug concentration potently impacts the magnitude of arterial drug deposition, while changes in coating drug mass affect duration of release. We demonstrate the importance of drug release kinetics and administered drug dose in governing arterial drug uptake and suggest novel drug delivery strategies for controlling spatio-temporal arterial drug distribution.

The challenges of managing personal consumption while selling drugs exacerbates the hazards associated with drug dealing. Efforts to address drug dealing among IDUs should consider both drug dependency and the material conditions that propel drug users towards dealing activities. Interventions should explore the potential of combining enhanced drug treatment programs with low threshold employment and alternative income generation opportunities.

In-stent restenosis occurs in coronary arteries after implantation of drug-eluting stents with non-uniform restenosis thickness distribution in the artery cross section. Knowledge of the spatio-temporal drug uptake in the arterial wall is useful for investigating restenosis growth but may often be very expensive/difficult to acquire experimentally. In this study, local delivery of a hydrophobic drug from a drug-eluting stent implanted in a coronary artery is mathematically modelled to investigate the drug release and spatio-temporal drug distribution in the arterial wall. The model integrates drug diffusion in the coating and drug diffusion with reversible binding in the arterial wall. The model is solved by the finite volume method for both high and low drug loadings relative to its solubility in the stent coating with varied isotropic-anisotropic vascular drug diffusivities. Drug release profiles in the coating are observed to depend not only on the coating drug diffusivity but also on the properties of the surrounding arterial wall. Time dependencies of the spatially averaged free- and bound-drug levels in the arterial wall on the coating and vascular drug diffusivities are discussed. Anisotropic vascular drug diffusivities result in slightly different average drug levels in the arterial wall but with very different spatial distributions. Higher circumferential vascular diffusivity results in more uniform drug loading in the upper layers and is potentially beneficial in reducing in-stent restenosis. An analytical expression is derived which can be used to determine regions in the arterial with higher free-drug concentration than bound-drug concentration.

Drug repurposing has become an important branch of drug discovery. Several computational approaches that help to uncover new repurposing opportunities and aid the discovery process have been put forward, or adapted from previous applications. A number of successful examples are now available. Overall, future developments will greatly benefit from integration of different methods, approaches and disciplines. Steps forward in this direction are expected to help to clarify, and therefore to rationally predict, new drug-target, target-disease, and ultimately drug-disease associations.

Multiple resistance to cytotoxic cancer drugs dramatically reduces the effectiveness of these drugs on many occasions. ABC (ATP-binding cassette) transporters pump out cytotoxic cancer drugs from cells, preventing them from reaching therapeutic levels. However, co-administration ABC transporter inhibitors with cytotoxic cancer drugs did not effectively improve the treatment outcome. The mechanisms and remedies are discussed.

We present a novel study on label-free recognition and distinction of drug resistant breast cancer cells (MCF-7 DOX) from their parental cells (MCF-7 WT) via impedimetric measurements. Drug resistant cells exhibited significant differences in their dielectric properties compared to wild-type cells, exerting much higher extracellular resistance (Rextra). Immunostaining revealed that MCF-7 DOX cells gained a much denser F-actin network upon acquiring drug resistance indicating that remodeling of actin cytoskeleton is probably the reason behind higher Rextra , providing stronger cell architecture. Moreover, having exposed both cell types to doxorubicin, we were able to distinguish these two phenotypes based on their substantially different drug response. Interestingly, impedimetric measurements identified a concentration-dependent and reversible increase in cell stiffness in the presence of low non-lethal drug doses. Combined with a profound frequency analysis, these findings enabled distinguishing distinct cellular responses during drug exposure within four concentration ranges without using any labeling. Overall, this study highlights the possibility to differentiate drug resistant phenotypes from their parental cells and to assess their drug response by using microelectrodes, offering direct, real-time and noninvasive measurements of cell dependent parameters under drug exposure, hence providing a promising step for personalized medicine applications such as evaluation of the disease progress and optimization of the drug treatment of a patient during chemotherapy.

The hazards of prescribing many drugs, including side-effects, drug-drug interactions and difficulties of compliance have long been recognized as particular problems when prescribing. This study estimates the rate and factors associated with potential drug-drug interactions in prescriptions from wards of An Iranian General Hospital. Data were retrieved from the pharmacy of a general hospital (200 beds) during one year period 2010. Potential drug-drug interaction were identified using a computerized drug-drug interaction database system (Prescription Analyzer 2000, Sara Rayane Co., Iran). Patients of both genders and 15 years-old or more were included in this study. Prescriptions with two or more drugs prescribed were selected during one year period 2010. Gender number of drugs and therapeutic drug classes on prescriptions were explored as associated factors to drug-drug interaction. The overall prevalence of potential drug-drug interaction was 20.3%. The risks of severe potential drug interactions were relatively high and the rate of potential drug-drug interaction was significantly higher in women (60.6%) and the patients aged over 60 years old (57.1%). The frequency of the potentially severe drug-drug interaction was 10.8% with digoxin-furosemide as the most common interacting pair (5.91%). A positive correlation was found between drug-drug interaction, patient's age, number of drugs and drugs acting on cardiovascular system. So cardiology women inpatients, age more then 60 years old, and patients prescribed digoxin and angiotensin-converting enzyme inhibitors should be closely monitored for adverse outcomes from drug-drug interaction.

The article throws light on the process of importing a novel preclinical drug into India based on the real-life experience from one of our studies. A novel drug "X" acting through a new mechanism of action was hypothesized by us to function as a neuroprotectant. It was decided to import this novel drug from a university located in Brazil. An official collaboration pact was exchanged between both the sides. In accordance with the Indian Drug and Cosmetics Act 1940, unauthorized import of drug into

India is not permitted. Hence, we decided to apply for the import license from Government of India. During the process of registration, we realized that the CDSCO SUGAM portal did not have facilities for the application from academic institute. We further faced challenges in different steps of import such as registration of the institute, individual drug application, fee transaction through the bank for Form 12, and customs duty clearance in the New Delhi airport. The process of import of drug for the purpose of testing by academic institutes has not been regularized by the CDSCO, and we suggest the apex organization to make separate provision for the academic institutes. This will encourage more academic institutes in India to opt for global collaborative works. This narration will further help them in following the same footsteps without facing significant hurdles. If more research on novel chemical entities is carried out in various academic institutes of India, it would not be far that we discover a blockbuster drug making the whole world turn toward us.

New techniques are urgently needed to replace conventional long and costly pre-clinical testing in the new drug administration process. In this study, a laminated microfluidic device was fabricated to mimic the drug ADME response test in vivo. This proposed device was loaded and cultured with functional cells for drug response investigation and organ tissues that are involved in ADME testing. The drug was introduced from the top of the device and first absorbed by the Caco-2 cell layer, and then metabolized by the primary hepatocyte layer. It subsequently interacted with the MCF-7 cell layer, distributed in the lung, heart and fat tissues, and was finally eliminated through the dialysis membrane. Throughout this on-chip ADME process, the proposed device can be used as a reliable tool to simultaneously evaluate the drug anti-tumor activity, hepatotoxicity and pharmacokinetics. Furthermore, this device was proven to be able to reflect the hepatic metabolism of a drug, drug distribution in the target tissues, and the administration method of a drug. Furthermore, this microdevice is expected to reduce the number of drug candidates and accelerate the pre-clinical testing process subject to animal testing upon adaptation in new drug discovery.

Inconsistent information about drug-drug interactions can cause variations in prescribing, and possibly increase the incidence of morbidity and mortality. The aim of this study was to assess whether there is an inconsistency in drug-drug interaction listing and ranking in three authoritative, freely accessible online drug information sources: The British National Formulary; The Compendium about Drugs Licensed for Use in the United Kingdom (the Electronic Medicines Compendium) and the Compendium about Drugs Licensed for Use in the United States (the DailyMed). Information on drug-drug interactions for thirty drugs which have a high or medium potential for interactions have been selected for analysis. In total, 1971 drug-drug interactions were listed in all three drug information sources, of these 992 were ranked as the interactions with the potential of clinical significance. Comparative analysis identified that 63.98% of interactions were listed in only one drug information source, and 66.63% of interactions were ranked in only one drug information source. Only 15.12% listed and 11.19% ranked interactions were identified in all three information sources. Intraclass correlation coefficient indicated a weak correlation among the three drug information sources in listing (0.366), as well as in ranking drug interactions (0.467). This study showed inconsistency of information on drug-drug interaction for the selected drugs in three authoritative, freely accessible online drug information sources. The application of a uniform methodology in assessment of information, and then the presentation of information in a standardized format is required to prevent and adequately manage drug-drug interactions.

The primary aim of this study is to identify and analyze the importance of adverse drug reaction due to drug-drug interaction as a contributing factor towards drug safety. Patients more than 18 years of age admitted in multidisciplinary intensive care unit of a tertiary care hospital were included in this study. Patients who stayed less than 48 h and patients in whom all treatment modalities have been withdrawn and were on comfort measures only (no drugs were prescribed), were excluded. All the drugs that were given during intensive care unit stay were checked for presence of potential interactions which led to adverse drug reaction. Drug-drug interactions that were detected clinically or through investigations were recorded and also any therapeutic actions taken for drug-drug interactions were noted. From June

2006 to April 2007, 400 patients-prescriptions were analyzed. Adverse drug reactions due to drug-drug interactions were identified in 64% patients. Among those patients 38.67% had a single drug-drug interaction. Potential drug-drug interactions were 602. Clinically significant drug-drug interactions among the potential were 208 (34.55%). Clinically relevant drug-drug interactions were 103 (49.52% of 208 episodes). The adverse drug reactions due to drug-drug interactions in our sample were managed either by substituting another drug (50.48% of 103 episodes) or by adjusting the dose (1% of 103 episodes) or by omitting the drug (48.54% of 103 episodes). Among the 208 observed drug-drug interactions induced adverse drug reactions 21.63% was severe drug-drug interactions induced adverse drug reactions, 23.08% was moderate drug-drug interactions induced adverse drug reactions and 55.29% was minor drug-drug interactions induced adverse drug reactions. The interactions which were life threatening and/ or require medical intervention to minimize or prevent serious adverse effects were considered as severe drug-drug interactions and those interaction which resulted in an exacerbation of the patient's condition and/ or require an alteration in therapy were considered as moderate drug-drug interactions. The interactions which were limited clinical effects and manifestations may include an increase in the frequency or severity of side effects but generally would not require a major alteration in therapy were classified as minor drug-drug interactions. The correlation coefficient was 0.86 between the number of drugs given to the patient & number of average potential adverse drug reactions found among the patients. Increase in number of prescribed drug significantly (one way) increases number of potential adverse drug reaction due to drug-drug interaction ($p<0.0001$). Critically ill patients are more susceptible to drug-drug interactions due to the administration of multiple drugs and complex drug combinations. Several drug-drug interactions were clinically irrelevant.