ΠΡΟΣΕΓΓΙΣΕΙΣ ΑΚΡΙΒΕΙΑΣ

Γενικά

Ευρύτατο πεδίο

Στόχος:
α) χρήση ή όχι ενός φαρμάκου σε ένα ασθενή, ή
β) ακριβής χρήση της ελάχιστης η/και κατάλληλης αποτελεσματικής δόσης ενός θεραπευτικού σχήματος

Προσαρμογή σχήματος στα συγκεκριμένα χαρακτηριστικά ενός ατόμου ή πληθυσμού

Παραδείγματα:

Προσαρμογή δόσης ή σκευάσματος αμφοτερικίνης Β σε νεφροπαθείς

Προσαρμογή δόσης βαρφαρίνης σε άτομο που λαμβάνει ευρέος φάσματος αντιβακτηριδιακά

Επιλογή κατάλληλου αντινεοπλασματικού ανάλογα με την έκφραση ή/και μετάλλαξη στόχου

Αυξομοίωση δόσης ανάλογα με πολυμορφισμό ενζύμου μεταβολισμού

ΠΡΟΣΕΓΓΙΣΕΙΣ ΑΚΡΙΒΕΙΑΣ

Ορισμός «εξατομικευμένης θεραπείας» και «θεραπείας ακριβείας»

Γενωμική μόνο ένα μικρό μέρος της προσέγγισης

NIH U.S. NATIONAL LIBRARY OF MEDICINE

Genetics Home Reference | Your Guide to Understanding Genetic Conditions

What is the difference between precision medicine and personalized medicine? What about pharmacogenomics?

There is a lot of overlap between the terms "precision medicine" and "personalized medicine." According to the National Research Council, "personalized medicine" is an older term with a meaning similar to "precision medicine." However, there was concern that the word "personalized" could be misinterpreted to imply that treatments and preventions are being developed uniquely for each individual; in precision medicine, the focus is on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors. The Council therefore preferred the term "precision medicine" to "personalized medicine." However, some people still use the two terms interchangeably.

Pharmacogenomics is a part of precision medicine. Pharmacogenomics is the study of how genes affect a person's response to particular drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that are tailored to variations in a person's genes.

Read more about precision medicine, personalized medicine, and pharmacogenomics:

A 2011 report from the National Research Council (PDF) provides a detailed overview of precision medicine, including the reasoning behind the Council's preference for the term "precision medicine" over "personalized medicine."

Genetics Home Reference provides an introduction to pharmacogenomics. Additional information about pharmacogenomics is available from the National Human Genome Research Institute (NHGRI).

PRECISION MEDICINE

The evidence landscape in precision medicine

Spencer Phillips Hey[1,2]*, Cory V. Gerlach[3,4,5], Garrett Dunlap[3,6], Vinay Prasad[7], Aaron S. Kesselheim[1,2]

For example, one challenge arises from the fact that the unit of testing in precision medicine is a complex intervention ensemble that combines a therapeutic agent, a marker, and a diagnostic assay for detecting that marker (*1*). Rigorous testing of this complex intervention ensemble requires that each component—treatment, marker, and assay—has been optimized for a given condition.

Γενικά μίας νέας θεώρησης

A second challenge arises from the fact that diagnostic assays require their own multistep development and validation process, which involves assessment of the assay's preanalytical validity (proper specimen handling and processing), analytical validity (test accuracy, reliability, and reproducibility), clinical validity (strong association between test result and a clinical outcome of interest), and clinical utility (use of the test to direct patient care results in a more favorable risk-benefit balance than nonuse of the test) (*2*). Failure to

A third challenge arises from disagreement about the level of evidence necessary to demonstrate the effectiveness of the intervention ensemble. Simon *et al.*'s influential evidence hierarchy for precision medicine marker validation (*5*) stipulates that level 1A evidence requires randomized controlled trials (RCTs) that stratify patients according to their marker status and then randomize them to a therapy, thus providing a rigorous test of the interaction between a patient's marker test result and their clinical outcomes with a particular intervention. Level 1B evidence can be produced by retrospective analyses of RCTs that analyze the interaction between marker status and treatment response after the RCT has been carried out (*5*). However, a recent analysis of targeted drugs approved by the U.S. Food and Drug Administration (FDA) found that the majority were approved on the basis of evidence from enrichment trials only—that is, trials that restricted enrollment to patients who tested positive for the marker of interest (*6*). Whereas enrichment trials can provide evidence about how a therapy works in the marker-positive patient population, their exclusion of the marker-negative population means that they do not provide evidence about the clinical validity of the marker (*7*). Thus, for most approved targeted medicines, the complete intervention ensemble has not been fully tested, and it is not known whether the marker diagnostic is actually a necessary component of the therapeutic strategy.

Γενικά

Χημική σύσταση, δομή

Μεταβολίτες

ADME (Abs Dis Met Excr) και T (Tox)

Ενδοκυτταρική σηματοδότηση

Ιστική κατανομή και δραστικότητα

Ιδιοσυγκρασικοί παράγοντες

Γενετική προδιάθεση

Περιβάλλον

Αλλα φάρμακα

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

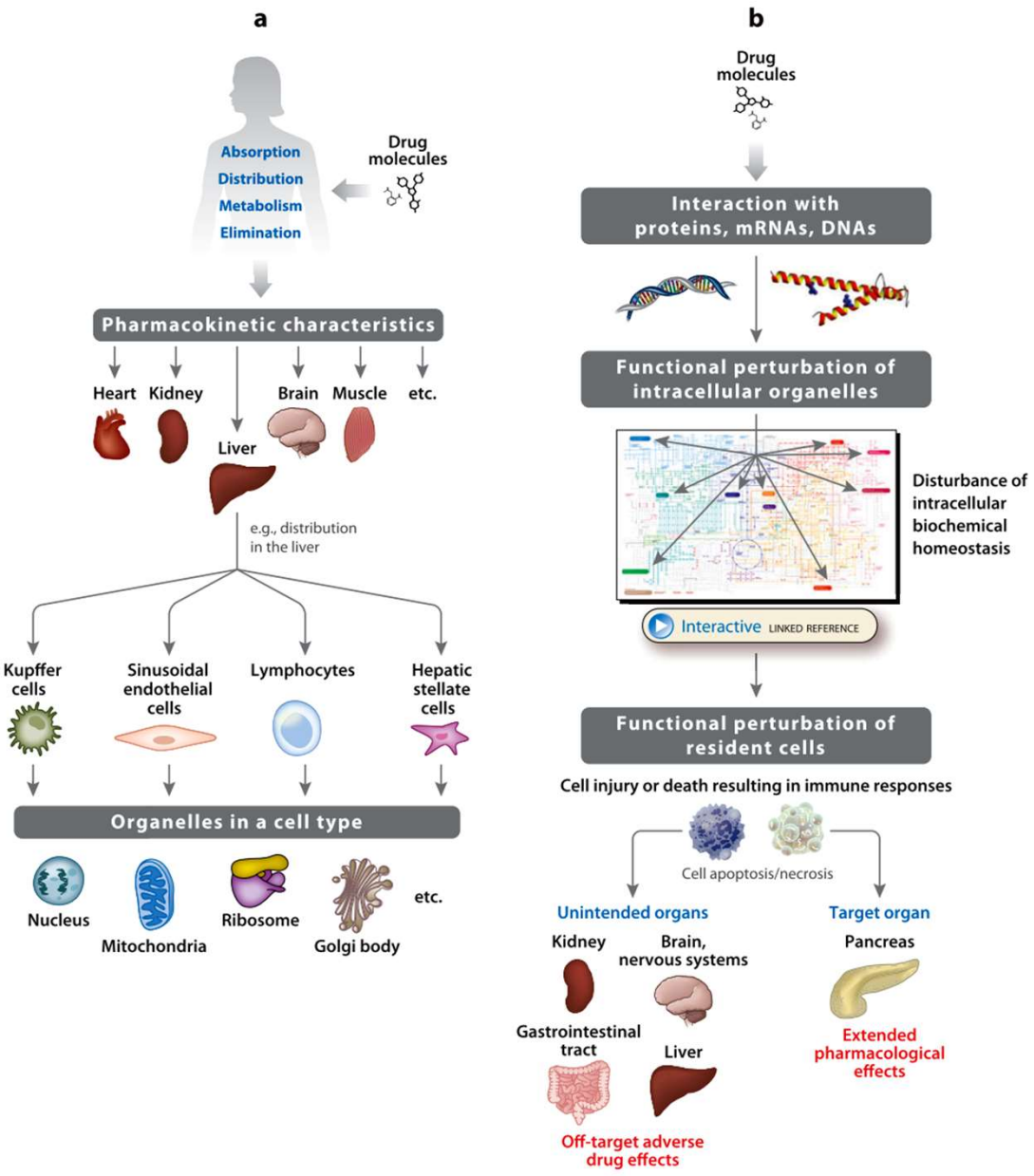

Figure 1

(*a*) Distribution hierarchy of drug molecules in the human body. (*b*) Propagation schematic of drug actions in the human body. The colored biochemical pathways map is taken from Reference 15 (**http://www.genome.jp/kegg**).

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

Παρενέργεια
(Side effect)
≠
Ανεπιθύμητη ενέργεια
(Adverse drug reaction)

ΤΟΞΙΚΟΤΗΤΑ

The International Serious Adverse Events Consortium

Arthur L. Holden, Jorge L. Contreras, Sally John and Matthew R. Nelson

The International Serious Adverse Events Consortium is generating novel insights into the genetics and biology of drug-induced serious adverse events, and thereby improving pharmaceutical product development and decision-making.

FURTHER INFORMATION
iSAEC Data Access Site: https://dataportal.saeconsortium.org/
iSAEC Public Data Access Policy: http://www.saeconsortium.org/?q=node/27

SUPPLEMENTARY INFORMATION
See online article: S1 (table) | S2 (box)
ALL LINKS ARE ACTIVE IN THE ONLINE PDF

Scientific focus and organizational structure

The iSAEC is a pharmaceutical-industry-led and FDA-supported international research consortium, focused on identifying and validating DNA variants predictive of the risk of drug-induced SAEs. It was launched in 2007 with the scientific and financial support of six funding members (Abbott, GlaxoSmithKline, Johnson & Johnson, Pfizer, Roche and Sanofi-Aventis). Additional dues-paying members were added (Novartis, Takeda, Daiichi Sankyo, and The Wellcome Trust) as the consortium completed its Phase 1 research programme (focused on the genetics of drug-induced liver injury (DILI) and serious skin injury (DISI)). A separate call for funding and membership roster was developed for the Phase 2 research programme, which included ten dues-paying members (Abbott, GlaxoSmith-Kline, Pfizer, Takeda, Daiichi Sankyo, Novartis, Merck, Amgen, AstraZeneca and the Wellcome Trust), as well as three associate members that made in-kind, non-cash contributions to the research effort (Cerner, Clinical Data and Catholic Health Initiatives). The FDA has participated from the outset as an observer, advisor and research collaborator, but without formal membership status.

Since 2007, the iSAEC has collaborated with over 200 leading academic centres and scientists globally to:

- standardize and publish phenotype definitions for the major drug-induced SAEs (liver, skin, heart and renal injury);
- build diverse, well-phenotyped clinical cohorts and sample repositories for many of the major SAEs;
- apply optimal genomic and computational methods (including imputation) for effective genome-wide single nucleotide polymorphism (SNP) genotyping and exome sequencing;
- ensure timely public availability of scientific results/associated data (within 12 months after genotyping, regardless of publication timing) to the scientific community at no cost[2] (see Further information); and
- ensure the open use of all iSAEC data, unencumbered by intellectual property constraints[3].

Οργανα που συχνότερα παρουσιάζουν τοξικές επιδράσεις φαρμάκων;;

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

The International Serious Adverse Events Consortium

Arthur L. Holden, Jorge L. Contreras, Sally John and Matthew R. Nelson

The International Serious Adverse Events Consortium is generating novel insights into the genetics and biology of drug-induced serious adverse events, and thereby improving pharmaceutical product development and decision-making.

Box S2 | Publications from the International Serious Adverse Events Consortium to date (as of September 2014)

- Daly, A. K. *et al.* HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nature Genet.* **41**, 816-819 (2009).
- Lucena, M. I. *et al.* Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles. *Gastroenterology* **141**, 338-347 (2011).
- Shen, Y. *et al.* Genome-wide association study of serious blistering skin rash caused by drugs. *Pharmacogenomics J.* **12**, 96-104 (2012).
- McCormack, M. *et al.* HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N. Engl. J. Med.* **364**, 1134-1143 (2011).
- Pirmohamed, M. *et al.* The Phenotype Standardization Project: improving pharmacogenetic studies of serious adverse drug reactions. *Clin. Pharmacol. Ther.* **89**, 784-758 (2011).
- Pirmohamed, M. *et al.* Phenotype standardization for immune-mediated drug-induced skin injury. *Clin. Pharmacol. Ther.* **89**, 896-901 (2011).
- Aithal, G. P. *et al.* Case definition and phenotype standardization in drug-induced liver injury. *Clin. Pharmacol. Ther.* **89**, 806-815 (2011).
- Behr, E. R. *et al.* DiTdP à The International Serious Adverse Events Consortium (iSAEC) phenotype standardization for drug-induced torsades de pointes. *Eur. Heart J.* **34**, 1958-1963 (2013).
- Contreras, J. Information access. Prepublication data release, latency, and genome commons. *Science* **329**, 393-394 (2012).
- Behr, E. R. *et al.* Genome wide analysis of drug-induced torsades de pointes: lack of common variants with large effect sizes. *PLoS One* **8**, e78511 (2013).
- Sullivan, P. F. *et al.* Clozapine-induced agranulocytosis is associated with rare *HLA-B* and *HLA-DQB1* alleles". *Nature Comms.* 4 Sep 2014 (doi: 10.1038/ncomms 5757)
- Heap, G. A. *et al.* HLA DQA1-DRB1 variants confer susceptibility to pancreatitis induced by the thiopurine immunosuppressants. *Nature Genet.* 15 Sept 2014 (doi:10.1038/ng.3093)

What is the difference between adverse drug reaction and side effect??

They are sometimes used interchangeably but adverse drug reaction means an unintended and undesired reaction to a medicine given at the correct dose.
Any medicine can cause an adverse drug reaction.
An adverse drug reaction can start soon after you take the medicine,
or up to 2 weeks after you stop taking the medicine.
Drug reactions can affect your entire body (systemic),
or they can be limited to a specific organ. The skin is the most common area affected.
You may have an itchy rash, swelling, or blisters.
Systemic reactions can cause fevers, swelling of blood vessels,
or a life-threatening allergic reaction called anaphylaxis.
Παράδειγμα;
A side effect is a result of drug or other therapy in addition to or in extension of the desired therapeutic effect;
usually but not necessarily, connoting an undesirable effect.
Although technically the therapeutic effect carried beyond the desired limit
(a hemorrhage from an anticoagulant) is a side effect,
the term more often refers to pharmacologic results of therapy unrelated to the usual objective
(a development of signs of Cushing syndrome with steroid therapy).
Παράδειγμα;

Science Translational Medicine AAAS

Predicting Adverse Drug Events Using Pharmacological Network Models
Aurel Cami, *et al.*
Sci Transl Med **3**, 114ra127 (2011);
DOI: 10.1126/scitranslmed.3002774

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

και μερικά που δεν φανταζόμαστε, όπως;;

νάτριο, λακτόζη

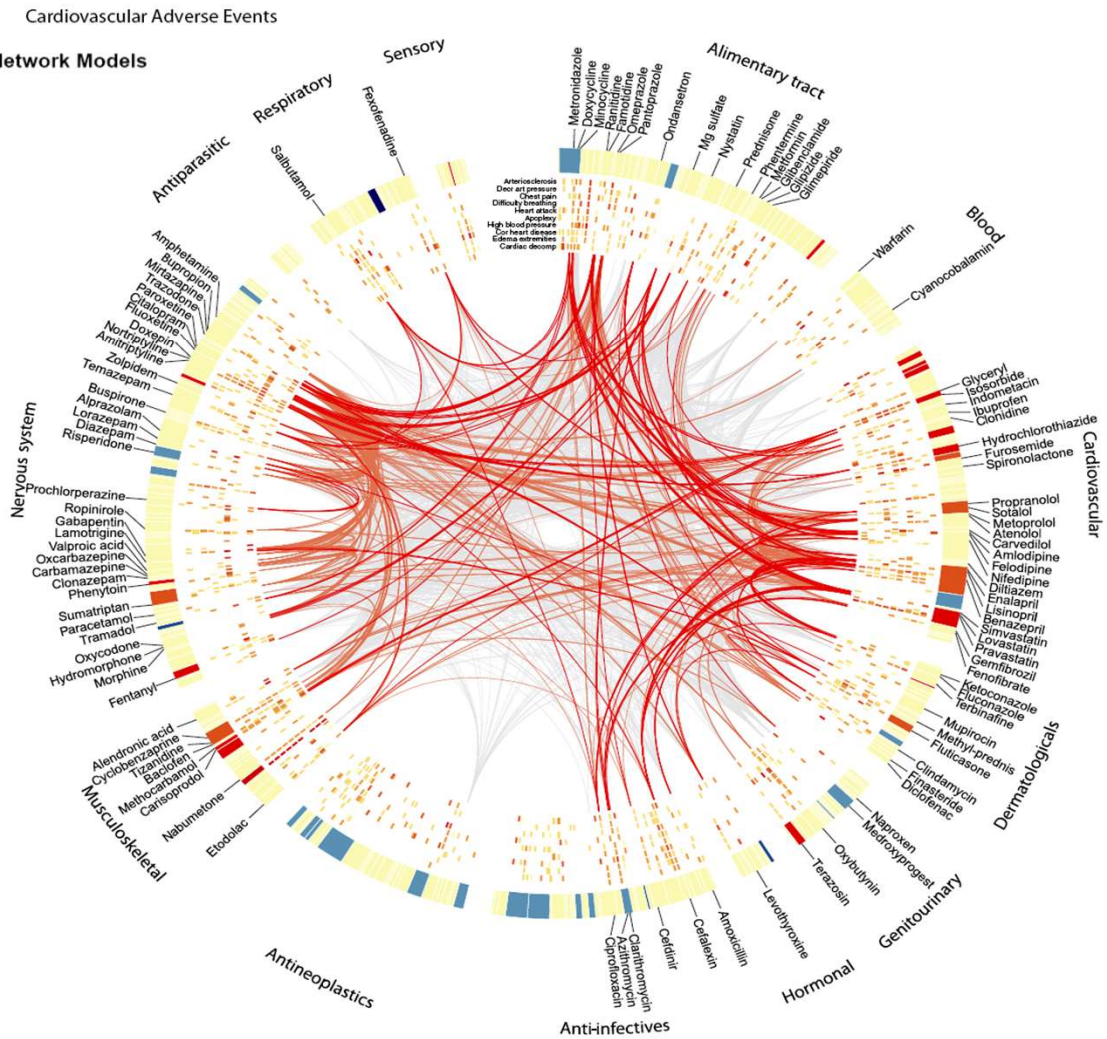

Fig. 6. Interaction diagram depicting single-drug effects, drug-class effects, DDIs, and class-class interactions for cardiovascular adverse events. Drugs are sorted clockwise around the ring by the physiological system they treat. Drugs labeled by name are members of data-mined DDIs. Within each physiological system, drugs are grouped into lower-order drug classes according to structural similarity or treatment indication. These lower-order classes are colored by their class-wide association with adverse cardiovascular effects (red for most severe to blue for least severe). Each arc across the center represents one DDI according to the data mining. The arc is colored red if the drug interaction is corroborated with evidence from the EMRs and brown if the drugs are members of class-class interactions. The heat map around the interior of the ring indicates the individual drug effects with the top 10 cardiovascular adverse events (arteriosclerosis, decreased arteriole pressure, chest pain, difficulty breathing, heart attack, apoplexy, high blood pressure, coronary heart disease, edema in extremities, cardiac decompression) (dark red for strong associations to white for weak or no association).

ΑΛΛΗΛΕΠΙΔΡΑΣΕΙΣ ΦΑΡΜΑΚΩΝ

Editor's Summary

Science Translational Medicine AAAS

Predicting Adverse Drug Events Using Pharmacological Network Models
Aurel Cami, *et al.*
Sci Transl Med **3**, 114ra127 (2011);
DOI: 10.1126/scitranslmed.3002774

The Power of Prediction

We've all done it: googled a combination of medical terms to describe how we feel after taking a new medication. The result is a seemingly infinite list of Web sites telling us that the nausea is normal, or that the headaches warrant another visit to the doctor. Oftentimes, important adverse effects of drugs are discovered and added to the drug label only years after a drug goes on the market. But what if scientists could know about certain adverse drug effects before they are clinically discovered? Cami and colleagues develop a mathematical approach to predicting such adverse events associated with the drugs we take, in hopes of reducing drug-related morbidity —and mortality.

After its release to the market, any given drug undergoes rigorous evaluation to determine associated ADEs (adverse drug effects). This post hoc analysis is usually unable to detect rare or delayed-onset ADEs until enough clinical evidence accumulates–a process that may take years. The method devised by Cami and coauthors does not need to wait for such evidence to accumulate. Instead, it can inform drug safety practitioners early on of likely ADEs that will be detected down the line.

The authors first collected a "snapshot" of 809 drugs and their 852 related adverse events that had been documented in 2005. These drug-safety associations were combined with taxonomic and biological data to construct a network that is reminiscent of a web. Cami *et al.* then used this drug-ADE network to train a logistic regression predictive model —basically creating a formula that would indicate the likelihood of unknown side effects of any drug in the network. The predictive capabilities of the model were prospectively validated using drug-ADE associations newly reported between 2006 and 2010. Such prospective evaluation preserves the chronological order of drug adverse event reporting, making it a realistic method for predicting future ADEs. With their network, the authors were able to predict with high specificity seven of eight drug ADEs identified by pharmacological experts as having emerged after 2005, including the relationship between the anti-diabetes drug rosiglitazone (Avandia) and heart attack.

The benefit for patients? With this powerful model in place, certain unknown adverse drug effects may be discovered earlier, helping to prevent drug-related morbidity and mortality through appropriate consumer label warnings.

Science Translational Medicine AAAS

Predicting Adverse Drug Events Using Pharmacological Network Models
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Sci Transl Med 3, 114ra127 (2011);
DOI: 10.1126/scitranslmed.3002774

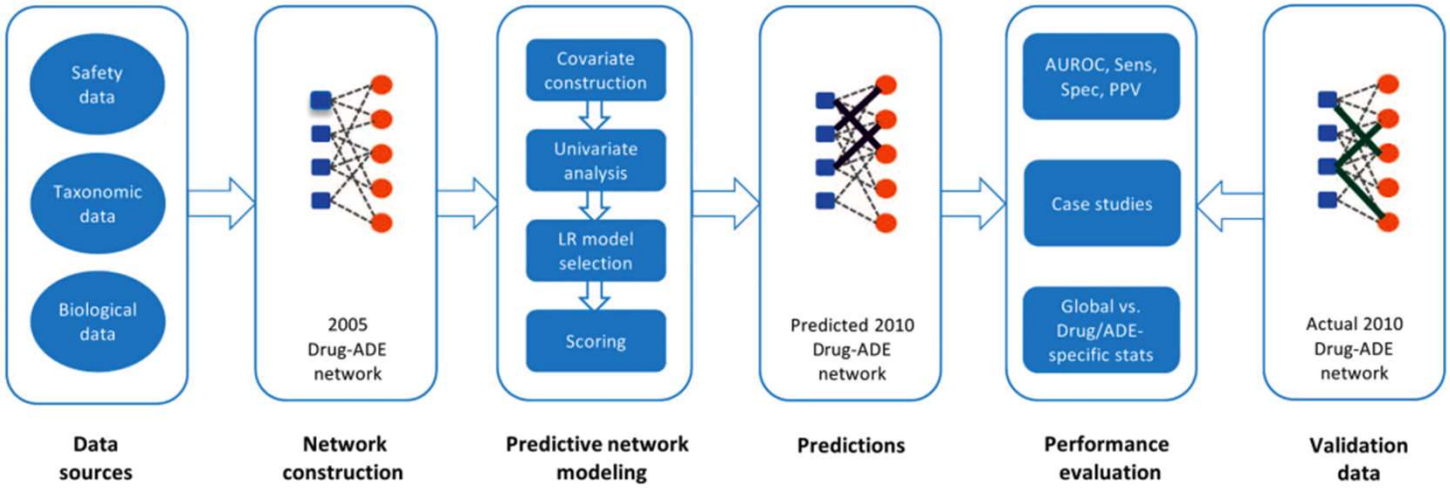

Fig. 1. Overview of the PPN approach. First, data were integrated from multiple sources, including safety data (drug-ADE associations contained in two chronologically separated snapshots of a drug safety database: one from 2005 and another from 2010), taxonomic data (ATC taxonomy of drugs and MedDRA taxonomy of ADEs), and biological data (intrinsic drug properties). Next, a network representation of the drug-ADE associations contained in the 2005 database snapshot was constructed. The drug-ADE network was used to derive a collection of network, taxonomic, and intrinsic covariates and to train a logistic regression (LR) predictive model. The trained LR model was used to generate scores for all the non-edges of the 2005 network. Next, the actual drug-ADE associations that were newly reported during the 5-year period from 2006 to 2010 were identified by comparing the 2005 snapshot with the 2010 snapshot. Finally, a systematic evaluation of the model's performance was performed by comparing the model-generated scores with the set of newly reported drug-ADE associations.

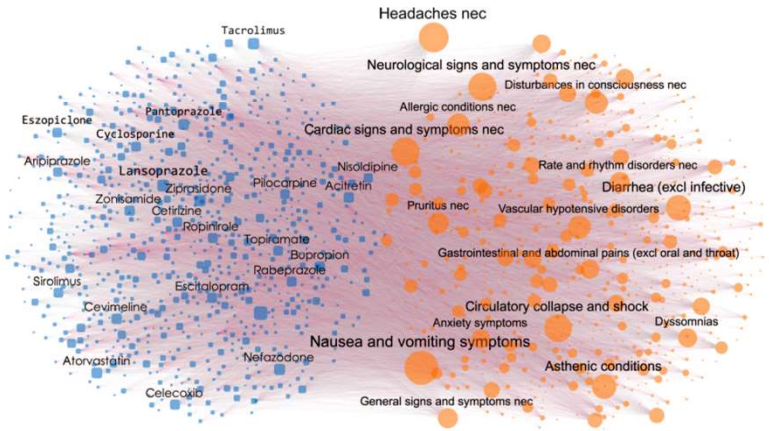

Fig. 2. A visualization of the drug-ADE network produced with the software package Cytoscape (http://www.cytoscape.org). The drug and ADE partitions are shown separated. The size of each node and node label is proportional to the node degree in the 2005 network. The edges of the 2005 network are shown in gray, whereas the edges newly introduced between 2006 and 2010 are shown in purple. A few drugs and ADEs have been labeled for illustrative purposes; the labeling of all nodes was not possible because of the commercial nature of the drug-ADE data used in this study. An expandable high-resolution version of this figure is available as the supplementary online file "Fig2-highres.tif."

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

Available online at www.sciencedirect.com
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Current Opinion in Pharmacology

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

In silico methods to predict drug toxicity

Alessandra Roncaglioni, Andrey A Toropov, Alla P Toropova and Emilio Benfenati

to predict toxicity. They include quantitative structure–activity relationship (QSAR) models, expert systems, 3D-QSAR and docking models. The QSAR methods seek a mathematical relationship between a group of molecular descriptors, used to describe each molecule present in a set of chemicals, and their toxicity values. It is funda-

SAR-QSAR

particular models and approaches dealing with ADME (adsorption, distribution, metabolism, and excretion)

when there is a set of known toxic fragments (often called 'structural alerts'), and the software recognizes their presence in the target chemical. An issue associated with this kind of approach is that the set of toxic fragments can be incomplete and thus may produce false negatives, that is, falsely predict chemicals as safe. 3D-QSAR is based on the concept of so-called 'molecular interaction fields'. With this technique the variation in the steric and electrostatic interaction energies calculated between each molecule and a probe is correlated with the variation in the investigated property. 3D-QSAR is usually focused on a set of structurally similar compounds with associated toxicity data, while docking mimics the binding to a biological macromolecule (usually a protein) [2]. In gen-

CYP isoforms, metabolic product

relative quantities of metabolite formation,

environment. Moreover, interactions with the biological system are also evaluated, such as intestinal permeability [6] (with models derived on the basis of *in vivo* [8•] or *in vitro* data [9••]). Interest is now growing also in the role of active transporters [10] together with passive diffusion.

Some studies addressed the blood–brain barrier (BBB) permeability of compounds [11•,12] that can be related to possible neurotoxic effects. Binding to plasma proteins is also often evaluated [13].

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

More efficient compound safety screening methods are much-neede to help reduce the persistently high attrition rates in clinical development. Now, writing in the *Journal of Proteome Research*, Nicholson and colleagues present the novel approach taken by the Consortium on Metabonomic Toxicology (COMET), which provides the largest validation so far of the potential of metabolic profiling to predict drug toxicity.

Their metabonomics-based method involved profiling compound-induced perturbations in urinary metabolites using ^{1}H nuclear magnetic resonance spectroscopy (NMR). Their study included 80 compounds that were selected to cover a diverse range of structures and toxicities, with an emphasis on liver and kidney toxins as these are the major organs involved in toxicity.

To assess the effect of compounds on urinary metabolites, the authors first built a multivariate model of normal urine based on pre-processed ^{1}H NMR spectra of the samples. Classification of samples from dosed animals as normal or abnormal using this model revealed a high correspondence between toxicity and abnormal metabolic profiles, with 67 out of the 80 treatments showing agreement as to the presence or absence of an effect. Compared with the normal model, 62 treatments exerted an effect and these were used for subsequent studies.

Next, Nicholson *et al.* set out to determine whether urinary metabolite analysis could be used to detect specific organ toxicity. To do this, they used a density estimation method — Classification of Unknowns by Density Superposition (CLOUDS). This combines NMR data obtained from all animals across all time points within the studies for a particular treatment, which can then be compared as a single unit with the signatures of other treatments.

Using the CLOUDS method in blind tests the authors could correctly identify the target organ of the liver toxin azathioprine and the kidney toxin maleic acid, even at sub-toxic levels. Assessment of the system across all 62 treatments showed that it had a sensitivity — the proportion of all treatments affecting a given organ that are classified to that organ — to liver and kidney toxins of 67% and 41%, respectively. The corresponding specificities — the proportion of all treatments predicted to affect a given organ that truly affect that organ — were 77% and 100%, respectively.

ORIGINAL RESEARCH PAPER Ebbels, T. *et al.* Prediction and classification of drug toxicity using probabilistic modeling of temporal metabolic data: the consortium on metabonomic toxicology screening approach. *J. Prot. Res.* **6**, 4407–4422 (2007)

FURTHER READING Lindon, J. *et al.* The Consortium for Metabonomic Toxicology (COMET): aims, activities and achievements. *Pharmacogenomics* **6**, 691–699 (2005)

Metabonomics

NATURE|Vol 455|23 October 2008

Jeremy K. Nicholson and John C. Lindon

Organisms often respond in complex and unpredictable ways to stimuli that cause disease or injury. By measuring and mathematically modelling changes in the levels of products of metabolism found in biological fluids and tissues, metabonomics offers fresh insight into the effects of diet, drugs and disease.

What are the origins of the field?

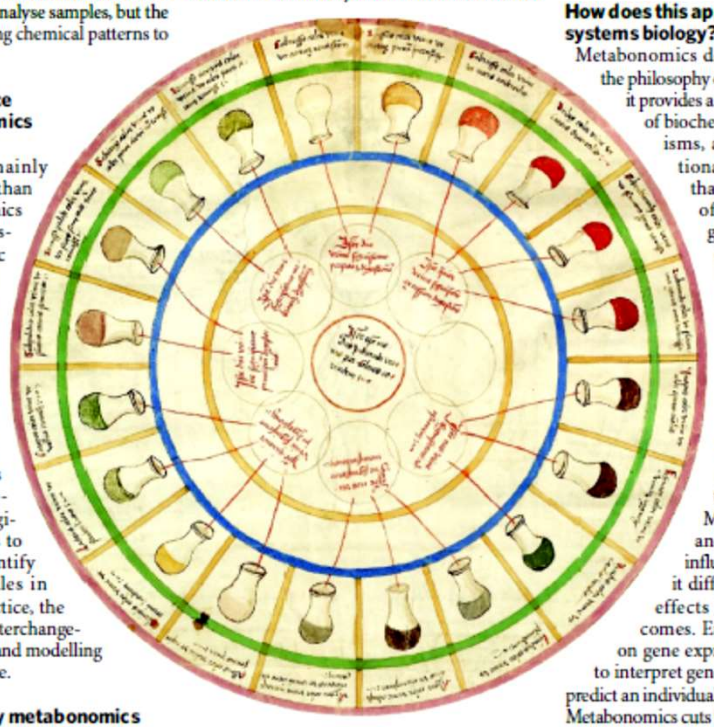
The idea that changes in tissues and biological fluids are indicative of disease goes back at least as far as ancient Greece. Diagnostic 'urine charts' were widely used from the Middle Ages onwards (Fig. 1). These charts linked the colours, smells and tastes of urine to various medical conditions. Such features are, of course, metabolic in origin. Metabonomics, and the related field of metabolomics, uses modern techniques to analyse samples, but the basic principle of relating chemical patterns to biology is the same.

What's the difference between metabonomics and metabolomics?

The distinction is mainly philosophical, rather than technical. Metabonomics broadly aims to measure the global, dynamic metabolic response of living systems to biological stimuli or genetic manipulation. The focus is on understanding systemic change through time in complex multicellular systems. Metabolomics seeks an analytical description of complex biological samples, and aims to characterize and quantify all the small molecules in such a sample. In practice, the terms are often used interchangeably, and the analytical and modelling procedures are the same.

How did modern-day metabonomics begin?

There were two, largely independent, starting points. The first was metabolic-control analysis, a mathematical method developed in the 1960s for modelling metabolism in cells. This required metabolite concentrations to be quantified, and so methods were developed to do this — often using gas chromatography (GC) or GC coupled to mass spectrometry (MS). The second contributing factor was the development of nuclear magnetic resonance (NMR) spectroscopy. By the mid-1980s, NMR was sensitive enough to identify metabolites in unmodified biological fluids. This led to the discovery that altered metabolite profiles are caused by certain diseases or by adverse side effects to drugs. MS techniques were also developed for profiling biological fluids. But metabonomics really took off with the realization that pattern-recognition methods (also known as chemometrics or multivariate statistical analysis) could help to interpret the complex data sets that result from these studies.



THE ROYAL LIBRARY, COPENHAGEN

Figure 1 | Metabonomics of yore. This urine wheel was published in 1506 by Ullrich Pinder, in his book *Epiphanie Medicorum*. It describes the possible colours, smells and tastes of urine, and uses them to diagnose disease.

How does this approach fit in with systems biology?

Metabonomics dovetails beautifully with the philosophy of systems biology, because it provides a 'top-down', integrated view of biochemistry in complex organisms, as opposed to the traditional 'bottom-up' approach that investigates the network of interactions between genes, proteins and metabolites in individual cell types. A problem with systems biology is that each level of biological organization and control — genomics, gene expression, protein expression and metabolism — operates on a markedly different timescale from the others, making it difficult to find causal linkages. Moreover, environmental and lifestyle factors greatly influence metabolism, making it difficult to disentangle their effects from gene-related outcomes. Environmental influences on gene expression also make it hard to interpret genomic data, for example to predict an individual's susceptibility to diseases. Metabonomics cuts through these problems by monitoring the global outcome of all the influencing factors, without making assumptions about the effect of any single contribution to that outcome. Yet in so doing, the individual contributions can be teased out.

Metabolomics and Metabonomics - Just more omics?

Metabolomics and metabonomics have seen a surge in popularity in recent scientific research. They may seem like two interchangable terms, with some groups favouring one over the other, but there is some difference between the two terms. Metabolomics as defined by Oliver Fiehn involves "...a comprehensive analysis in which all the metabolites of a biological system are identified and quantified...“

whereas Metabonomics was defined by Jeremy Nicholson as "the quantitative measurement of the multiparametric time-related metabolic responses of a complex (multicellular) system to a pathophysiolocigal intervention or genetic modification.“

In other words, metabolomics is the process of measuring the whole metabolome, whereas metabonomics is the measurement of changes across the metabolome, with respect to time, due to an intervention, which is a smaller set of metabolites.

From
https://www.metabolomics.strath.ac.uk/Metabolomics.htm

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

OPEN ACCESS Freely available online

PLOS ONE

Predicting Chemical Toxicity Effects Based on Chemical-Chemical Interactions

Lei Chen[2☯], Jing Lu[3☯], Jian Zhang[4], Kai-Rui Feng[5], Ming-Yue Zheng[3*], Yu-Dong Cai[1*]

Accelrys Toxicity is a database of toxicity information compiled from the open scientific literature [3] and containing toxicological data for approximately 0.17 million chemicals. This database is of

Table 1. Distribution of compounds in each category of compound toxicity.

Tag	Toxicity	Total
T_1	Acute Toxicity	12,633
T_2	Mutagenicity	6,110
T_3	Tumorigenicity	2,293
T_4	Skin and Eye Irritation	2,353
T_5	Reproductive Effects	2,501
T_6	Multiple Dose Effects	4,198
T_7	Non-toxicity	646
Total	–	30,734

doi:10.1371/journal.pone.0056517.t001

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

Annu. Rev. Pharmacol. Toxicol. 2013. 53:451–73

Systems Pharmacology to Predict Drug Toxicity: Integration Across Levels of Biological Organization*

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To achieve sensitive and specific mechanism-based prediction of drug toxicity, the tools of systems pharmacology will be integrated using structured ontological approaches, analytics, mathematics, and statistics. Success of this effort is based on the assumption that a systems network that consists of drug-induced perturbations of physiological functions can be characterized. This network spans the hierarchy of biological organization, from gene to mRNA to protein to intracellular organelle to cell to organ to organism. It is populated with data from each of these levels of biological organization.

Table 1 Key knowledge bases and databases

Database or knowledge base	URL
SIDER (computer-readable side effect resource)	**http://sideeffects.embl.de**
DrugBank	**http://www.drugbank.ca**
Chemical Effects in Biological Systems (CEBS)	**http://cebs.niehs.nih.gov/**
NCBI Database of Genotypes and Phenotypes (dbGaP)	**http://www.ncbi.nlm.nih.gov/gap/**
Comparative Toxicogenomics Database	**http://ctd.mdibl.org/**
Genetic Association Database (archive of human genetic association studies of complex diseases and disorders)	**http://geneticassociationdb.nih.gov**
Kyoto Encyclopedia of Genes and Genomes (KEGG) (bioinformatics resource for linking genomics to life)	**http://www.genome.jp/kegg**
The Pharmacogenomics Knowledgebase (PharmGKB) (resource describing how variation in human genetics leads to variation in response to drugs)	**http://www.pharmgkb.org**
Gene Expression Omnibus (GEO) (database repository of high-throughput gene expression data and hybridization arrays, chips, and microarrays)	**http://www.ncbi.nlm.nih.gov/geo**
Connectivity Map (detailed map that links gene patterns associated with disease to corresponding patterns produced by drug candidates and a variety of genetic manipulations)	**http://www.broadinstitute.org/genome_bio/connectivitymap.html**
The Gene Ontology (GO) (standardized representation of gene and gene product attributes across species and databases)	**http://www.geneontology.org**
Tox21 (Computational Toxicology Research program)	**http://epa.gov/ncct/Tox21**
International HapMap Project (database of genes associated with human disease and response to pharmaceuticals)	**http://hapmap.ncbi.nlm.nih.gov**
Human Interactome Database (database of human binary protein-protein interaction networks)	**http://interactome.dfci.harvard.edu/H_sapiens**
European Bioinformatics Institute (EBI) ArrayExpress Archive	**http://www.ebi.ac.uk/microarray-as/ae/**
NCI-60 DTP Human Tumor Cell Line Screen	**http://dtp.nci.nih.gov/branches/btb/ivclsp.html**
Library of Integrated Network-Based Cellular Signatures (LINCS)	**http://commonfund.nih.gov/lincs/**
Reactome	**http://www.reactome.org/ReactomeGWT/entrypoint.html**
Online Mendelian Inheritance in Man®	**http://www.ncbi.nlm.nih.gov/omim**

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of organ, cellular, and subcellular drug distribution, in addition to systemic drug exposure that is derived from absorption, distribution, metabolism, and elimination (ADME) studies (**Figure 1*a***).

organelles [such as mitochondria (5, 6)], to cells (7), and to organs (8), with the final result being detectable or measurable drug action(s). One action may be the desired therapeutic effect, but other actions may result in parallel propagations that cause other (off-target) effects and systemic adverse reactions (8) (**Figure 1*b***). Both drug chemistry and individual patient phenotype form the basis for drug response, either therapeutic or toxic. Although individual drugs possess unique and diverse chemical structures, they are linked to one another by structural fingerprints and similarity (9), by overlapping transcriptomic patterns (10), by adverse reactions (11), by shared mechanisms of biotransformation such as cytochrome 450 enzyme-mediated metabolism (12), and by Anatomical Therapeutic Chemical (ATC) classification of pharmacological target (13) and pathway (14).

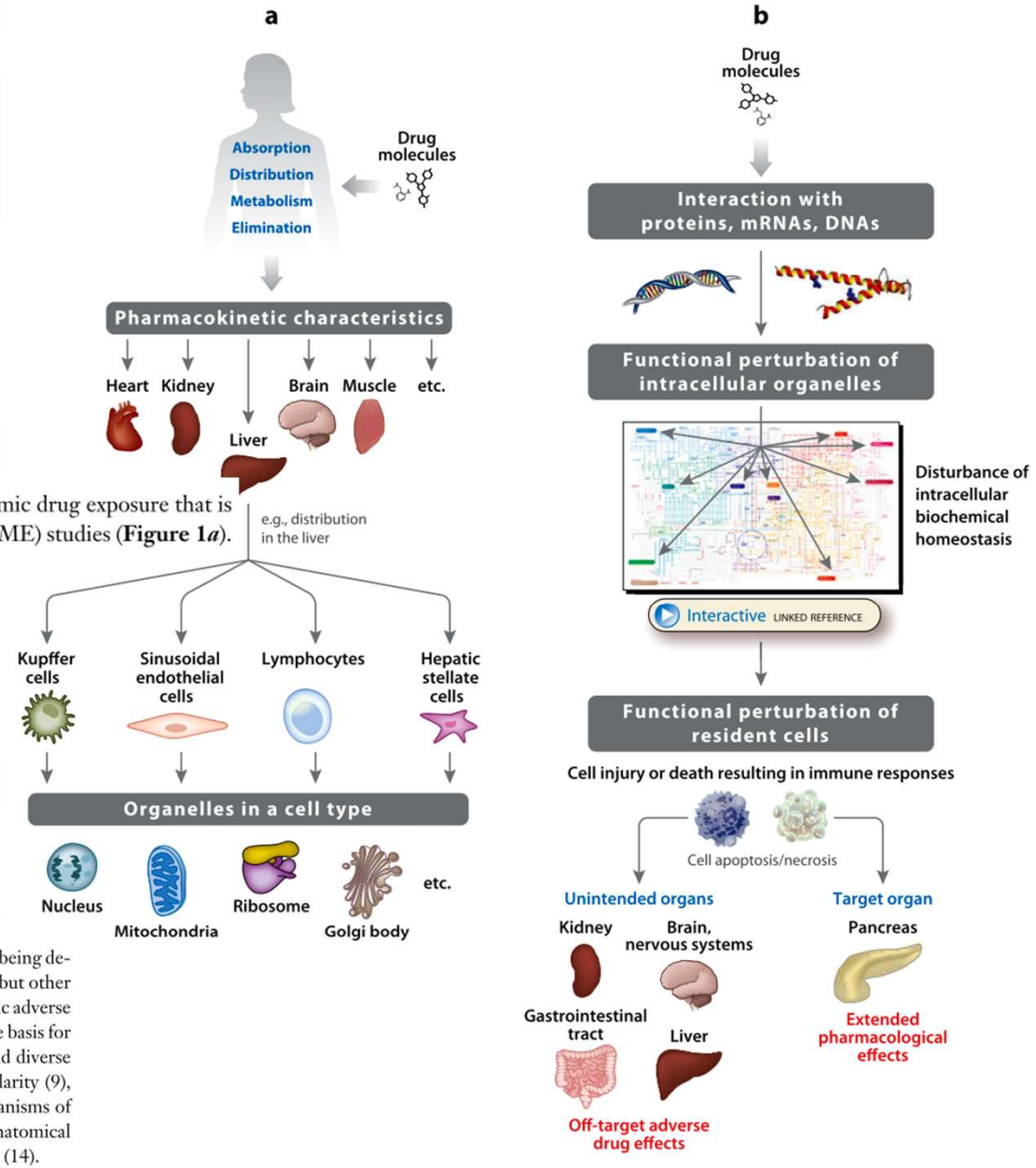

Figure 1

(*a*) Distribution hierarchy of drug molecules in the human body. (*b*) Propagation schematic of drug actions in the human body. The colored biochemical pathways map is taken from Reference 15 (**http://www.genome.jp/kegg**).

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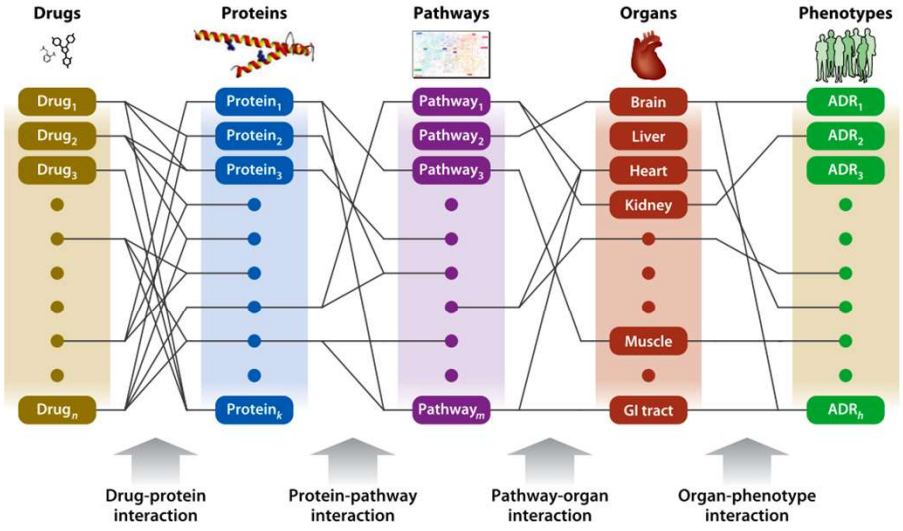

Figure 3

Interaction map showing *n* number of drugs, *k* number of proteins, *m* number of pathways, and *h* number of adverse drug reactions (ADRs). Abbreviation: GI, gastrointestinal.

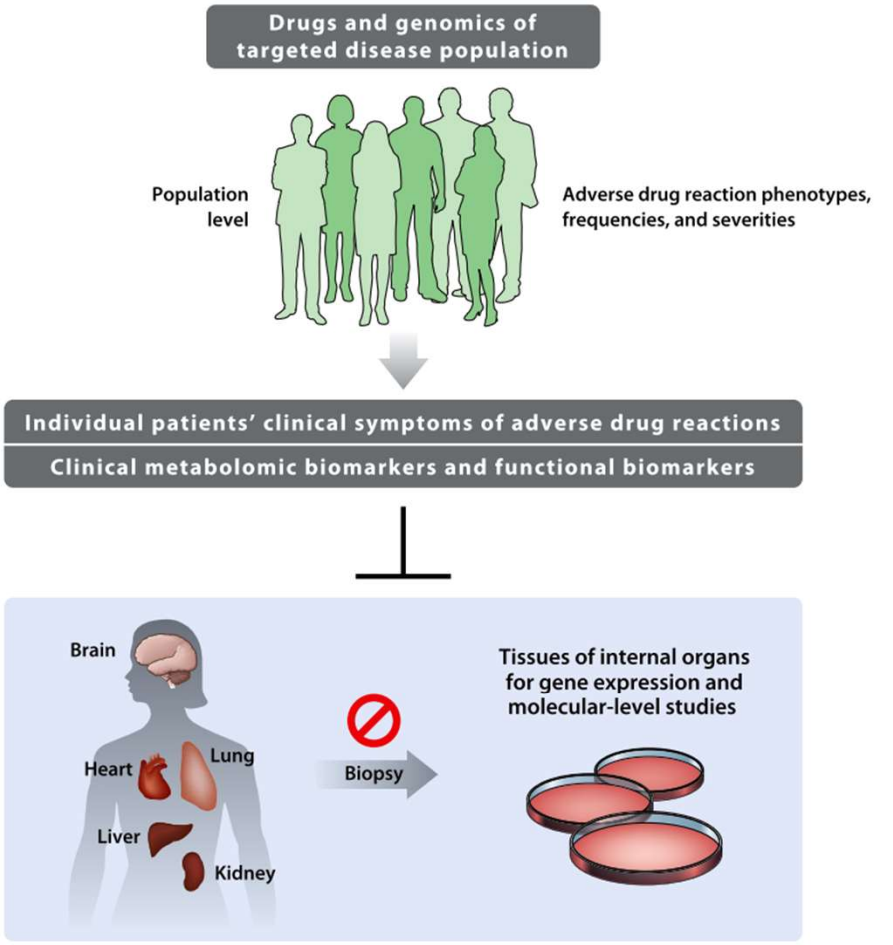

Figure 2

Current paradigm of drug safety needs translational bridging between clinical phenotype and molecular phenotype.

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Genetic signature and toxicogenomics

Genetic Signature as a Predictor of Connectivity

Single-nucleotide polymorphisms and haplotypes have been extensively used to explore as well as to describe the genetic basis of many human diseases and their response to treatment [see the Pharmacogenomics Knowledgebase (PharmGKB) at **http://www.pharmgkb.org/**]. Development of statistical connectivity between a genetic signature and a patient phenotype (47, 48) has been attempted for several diseases; for example, one study (49) links phenome to genome to describe and genetically define neuropsychiatric disorders.

Genome-wide association studies and candidate gene studies have been successfully used to identify causal genetic mutations associated with idiosyncratic ADRs. A recent review that highlighted research and accomplishments in this area (16) noted some successes, including association of HLA-B*5701 with abacavir hypersensitivity. Many strains of genetically manipulated (transgenic, knockout, and knockin) mice have been developed to investigate the relationship between a specific gene and animal phenotype (50, 51). Perhaps owing to the uncertainty about the interaction networks of a gene and its gene product, in some cases the observed phenotype is unlike that predicted from either the function of the protein encoded or the clinical phenotype in individuals carrying that genetic mutation. Protein expression assays may be conducted in transgenic animals to better understand the phenotype actually observed (52). One example: 36 inbred mouse strains were used to explore the high variability in acetaminophen drug-induced liver injury (DILI) in mice, and the genetic polymorphisms of these mice were selected to extensively cover human genetic variability (53). Humanized mouse models are increasingly used in drug toxicity research (54, 55), with most efforts centered on hepatotoxicity (55, 56). Most of the useful extrapolations of results from animals to humans have come from studies utilizing genes that are highly preserved across the species.

e.g. HLA / abacavir hypersensitivity

mouse to human humanized mice

Transcriptomic Signature as a Predictor of Connectivity

Advances in microarray and next-generation sequencing technologies have allowed affordable gene expression profiling and enabled integration of transcriptomic profiling into drug discovery and development (57). Tox21 is a National Institutes of Health (NIH) program that focuses on high-throughput toxicity testing (58), and the Gene Expression Omnibus (GEO) is a functional genomics data repository sponsored by the National Center for Bioinformatics for data mining (**http://www.ncbi.nlm.nih.gov/geo/**). The Japanese Toxicogenomics Project

Both whole-genome microarray (61) and differential expression of candidate genes (19) have been used to identify genes that are up- or downregulated, to allow generation of hypotheses and deduction of the biological pathways and networks that are perturbed (62) in relation to specific ADRs. Pinpointing the causative biological pathways perturbed by a drug that leads to an ADR, however, requires confirmation by changes at the translational level of corresponding proteins and requires availability of detection methods such as monoclonal antibodies (19). Furthermore, mass spectrometry methods are being developed for low-level protein identification and quantification (63). Clinical transcriptomics analysis to delineate the mechanisms of drug toxicity in humans is limited by inaccessibility of the target organ's tissue (**Figure 2**). Human peripheral blood mononuclear cells are therefore often used as a surrogate for inaccessible organs (64, 65).

confirmation of gene expression levels by protein expression

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organelle-focused toxicity

Organelle-Based Approaches as Predictors of Connectivity

Drug-induced mitochondrial toxicity is responsible, at the organelle level, for several clinical ADRs. The key role of mitochondria in the production of cellular energy via ATP formation due to aerobic respiration is consistent with the adverse cellular consequences of drug-induced mitochondrial dysfunction. Toxicity can be measured by the change in mitochondria permeability and the production of reactive oxygen species (oxidative stress). Such changes are the hallmarks of mitochondrial dysfunction in acetaminophen hepatotoxicity, presumably caused by its reactive metabolite NAPQI (*N*-acetyl *p*-benzoquinone imine) (5, 6). In addition, inhibition of mitochondrial fatty acid oxidation has also been implicated in DILI (91, 92). Amiodarone and tetracycline differ greatly from each other, but both cause treatment-related hepatic steatosis (25). Exposure to either drug can result in the formation of intracytoplasmic lipid droplets and significant elevations of intracellular triglycerides. These histological features result from altered expression profiles of the genes involved in fatty acid transport and lipid metabolism (25). The mitochondrial basis of drug toxicity prediction is usually assessed using a composite score, such as the one that includes the mitochondrial DNA (mtDNA) expression profile, mitochondrial membrane potential, ATP level, electron transport chain, cell viability, and cellular reactive oxygen species level (93). The human mtDNA has been completely sequenced (94). Future understanding of mtDNA mutations and mtDNA transcriptomics in relation to ADRs may help shed light on the incidence of rare ADRs. The data supporting drug-induced mitochondrial dysfunction will constitute the information base that will support organelle-level connectivity in a systems pharmacology predictive network. The database for drug-induced toxicity for other cellular organelles is more limited and will require further development.

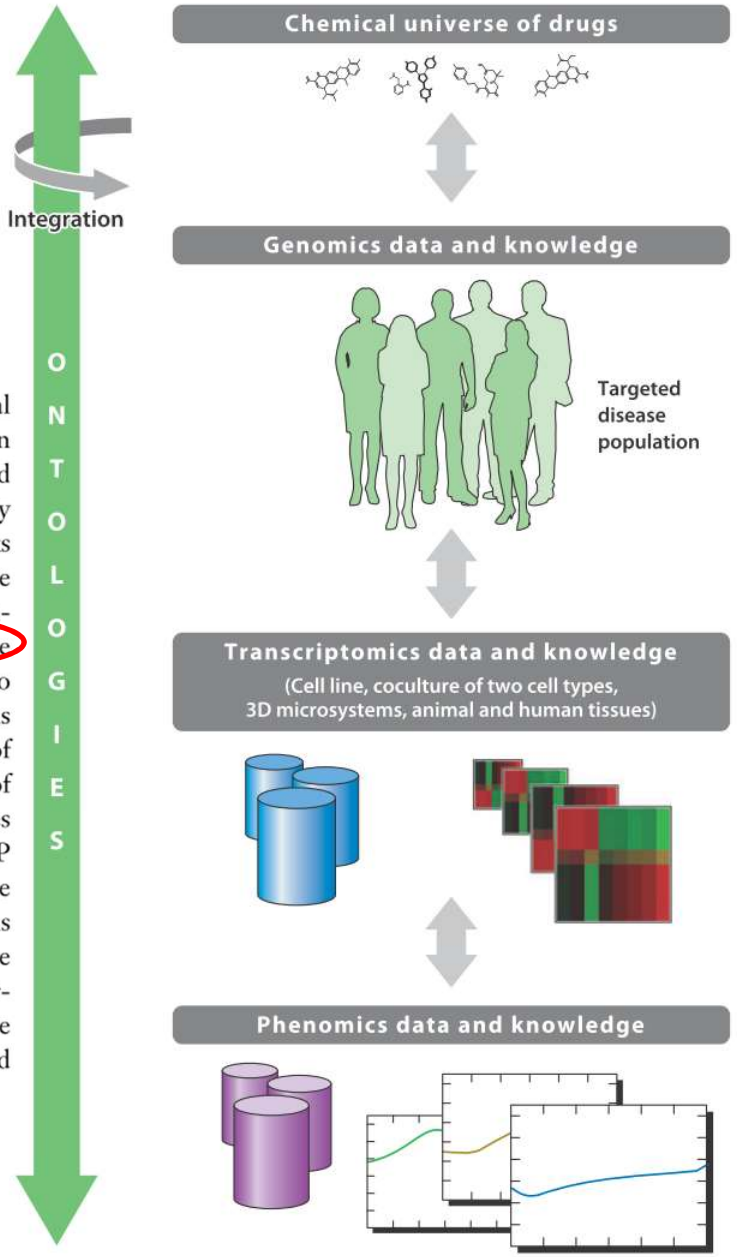

Figure 4

Schematic framework of analytic integration of genomics, transcriptomics, and phenomics.

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

Systems Pharmacology: Network Analysis to Identify Multiscale Mechanisms of Drug Action

Shan Zhao and Ravi Iyengar

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Annu. Rev. Pharmacol. Toxicol. 2012. 52:505–21

Abstract

Systems approaches have long been used in pharmacology to understand drug action at the organ and organismal levels. The application of computational and experimental systems biology approaches to pharmacology allows us to expand the definition of systems pharmacology to include network analyses at multiple scales of biological organization and to explain both therapeutic and adverse effects of drugs. Systems pharmacology analyses rely on experimental "omics" technologies that are capable of measuring changes in large numbers of variables, often at a genome-wide level, to build networks for analyzing drug action. A major use of omics technologies is to relate the genomic status of an individual to the therapeutic efficacy of a drug of interest. Combining pathway and network analyses, pharmacokinetic and pharmacodynamic models, and a knowledge of polymorphisms in the genome will enable the development of predictive models of therapeutic efficacy. Network analyses based on publicly available databases such as the U.S. Food and Drug Administration's Adverse Event Reporting System allow us to develop an initial understanding of the context within which molecular-level drug-target interactions can lead to distal effectors in a process that results in adverse phenotypes at the organ and organismal levels. The current state of systems pharmacology allows us to formulate a set of questions that could drive future research in the field. The long-term goal of such research is to develop polypharmacology for complex diseases and predict therapeutic efficacy and adverse event risk for individuals prior to commencement of therapy.

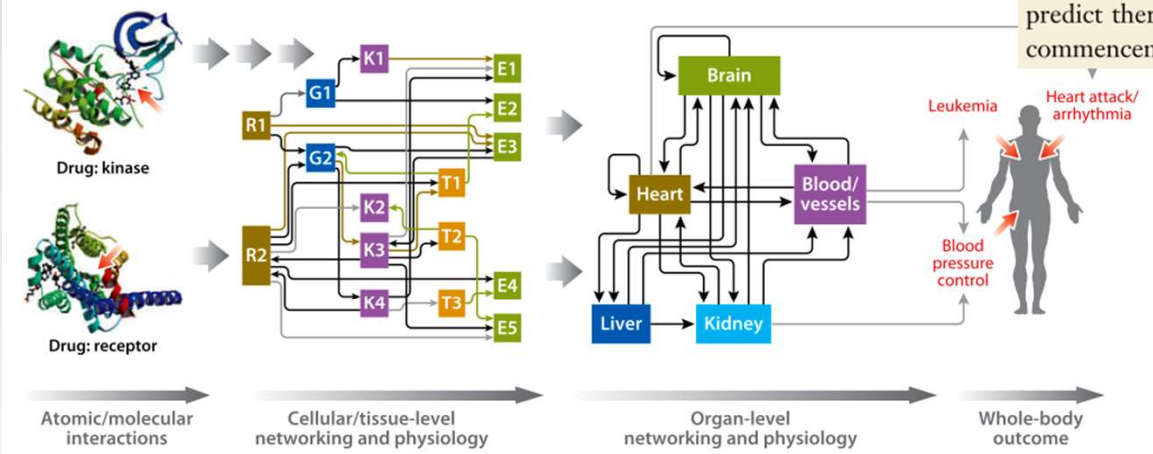

Figure 1

A schematic representation of the multiscale networks needed to understand and predict drug action. Atomic interactions between drug and target lead to alterations in the function of cellular regulatory networks, which lead to changes in cellular- and tissue-level physiology, which, in turn, lead to alterations in organ-level networking, which lead to changes in whole-body functions. Networks at both the cellular/tissue level and organ level are needed to understand the mechanism of drug action and to predict therapeutic efficacy and adverse event probability. The drug-protein structures are taken from structures deposited in the Protein Data Bank (**http://www.pdb.org**) with PDB IDs of 3QC4 and 2Y03 (88, 89), with the authors' permission.

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

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Proteomics Analyses

Proteomics involves the study of changes in the levels or states of large numbers of proteins in a sample of interest such as a cell extract, the plasma, or a tissue sample. Typically, the measurement of proteins is by mass spectrometry, although sometimes protein arrays are also used. In contrast to genomics approaches, the use of proteomics in drug discovery and study of drug action has been limited. A major issue is the difficulty in obtaining tissue biopsies sufficient for proteomics analyses to correlate changes in target tissues and organs with drug action in humans. Most proteomics studies have focused on human cancer cell lines and can be used for target profiling (25) and mechanism-based classification of potential drugs (26).

Genomics Analyses

Genomics analyses involve the sequencing or characterization of many genes, typically the whole genome simultaneously. At the DNA level, genomics involves sequencing of the genome to identify variations and to determine transcriptional binding sites and epigenetic status. At the mRNA level, genome-wide profiling is largely focused on characterizing gene expression patterns in a disease state or before and after drug treatment. This type of profiling was accomplished mostly through the use of microarrays, but in the past few years, direct sequencing, termed mRNA seq, has become more widely used.

Metabolomics Analyses

Metabolomics focuses on measuring changes in a large number of metabolites simultaneously (27). The method of choice for identification of metabolites is mass spectrometry, generally preceded by chromatographic resolution. The most readily available source for metabolic profiling in humans is plasma. Several studies have shown identifiable metabolic signatures associated with drug treatment. A study on 50 patients with schizophrenia being treated with antidepressants showed identifiable changes in lipid patterns after treatment (28). These observations raise the possibility that metabolic signatures of drug treatment could be an additional tool in assessing drug therapy in patients. A recent study (29) on patients with major depressive disorders has shown an interesting relationship between genomics and metabolomics in predicting drug action. Metabolomics was used to characterize levels of amino acids in plasma. Patients who were nonresponsive to therapy with the serotonin reuptake inhibitor citalopram showed higher baseline levels of glycine, which remained unaltered after treatment. Genomics analyses indicated that in nonresponders, the SNP rs10975641 in the glycine dehydrogenase gene was associated with treatment outcome.

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

Pharmacogenomic effects on:

- kinetics
- dynamics
- responsiveness
- unknown mech

Systems Pharmacology: Network Analysis to Identify Multiscale Mechanisms of Drug Action

Shan Zhao and Ravi Iyengar

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Table 1 Various types of pharmacogenomic effects in drug action

Drug	Gene	Effect
Pharmacokinetics		
Codeine	*CYP2D6* (34)	Increase in the amount of active drug by variants
Clopidogrel	*CYP2C19* (80)	Increase in the amount of active drug by variants
Warfarin	*CYP2C9* (81)	Changes in drug levels in blood by variants
Pharmacodynamics		
Warfarin	*VKORC1* (21)	Increase or decrease of effectiveness of drug
Capecitabine	*DPD* (82)	Decrease in breakdown of 5-FU metabolite
Responsiveness		
Panitumumab	*k-RAS* (83)	Requirement of wild-type *k-RAS* for drug efficacy
Imatinib	*c-KIT* (84)	Requirement of wild-type *c-KIT* for drug efficacy
Tretinoin	*PML/RARα* translocation (85)	Increased drug responsiveness
Unknown mechanisms		
Carbamazepine	*HLA-B*1502* (86)	Increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis
Abacavir	*HLA-B*5701* (87)	Multiorgan systemic hypersensitivity, which may lead to death

Abbreviations: 5-FU, fluorouracil; CYP, cytochrome P450; DPD, dihydropyrimidine dehydrogenase; HLA, human leukocyte antigen; PML, promyelocytic leukemia; RAR, retinoic acid receptor; VKOR, vitamin K epoxide reductase.

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

reactive metabolite can predict toxicity

A55CH12-Kalgutkar ARI 19 September 2014 12:49

REVIEWS IN ADVANCE

Review in Advance first posted online on October 6, 2014. (Changes may still occur before final publication online and in print.)

Predicting Toxicities of Reactive Metabolite–Positive Drug Candidates

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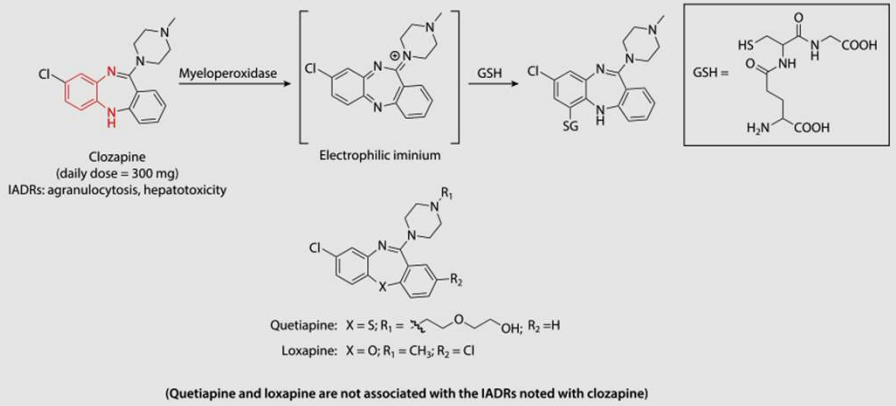

Figure 1

Structure-toxicity relationships for the dibenzodiazepine derivatives: clozapine versus loxapine and quetiapine. Abbreviations: GSH, glutathione; IADR, idiosyncratic adverse drug reaction.

Abstract

Because of the inability to predict and quantify the risk of idiosyncratic adverse drug reactions (IADRs) and because reactive metabolites (RMs) are thought to be responsible for the pathogenesis of some IADRs, the potential for RM formation within new chemical entities is routinely examined with the ultimate goal of eliminating or reducing the liability through iterative design. Likewise, avoidance of structural alerts is almost a standard practice in drug design. However, the perceived safety concerns associated with the use of structural alerts and/or RM screening tools as standalone predictors of toxicity risks may be overexaggerated. Numerous marketed drugs form RMs but do not cause idiosyncratic toxicity. In this review article, we present a critique of the structural alert/RM concept as applied in drug discovery and evaluate the evidence linking structural alerts and RMs to observed toxic effects. Pragmatic risk mitigation strategies to aid the advancement of drug candidates that carry a RM liability are also discussed.

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

Epigenetics and Complex Disease: From Etiology to New Therapeutics

Carolyn Ptak and Arturas Petronis

Annu. Rev. Pharmacol. Toxicol. 2008. 48:257–76

Abstract

Epigenetics is a new development in complex non-Mendelian disease, which may not only uncover etiologic and pathogenic mechanisms but may also provide the basis for the development of medications that would target the primary epigenetic causes of such diseases. Such epigenetic drugs would be novel, potentially possessing substantially higher therapeutic potential and a much lower rate of adverse effects in comparison to current symptomatic treatments. A collection of epigenetic drugs already exist at various stages of development and, although their effectiveness has yet to be maximized, they show great promise in the treatment of cancer, psychiatric disorders, and other complex diseases. Here we present a review of the epigenetic theory of complex disease and an evaluation of current epigenetic therapies, as well as predictions of the future directions in this expanding field.

There are three fundamental points that enable us to consider epigenetic factors as etiological candidates in complex disease. First, the epigenetic status of genes is more dynamic in comparison to DNA sequence and can be altered by developmental programs and the environment of the organism (8); furthermore, epigenetic changes may occur even in the absence of evident environmental differences, i.e., owing to stochastic reasons (9). Second, some epigenetic signals can be transmitted along with DNA sequence across the germline generations, i.e., such signals exhibit partial meiotic stability (10). Third, epigenetic regulation is critical for normal genomic function, such as segregation of chromosomes in mitosis, inactivation of parasitic DNA elements, and regulation of gene activity (34). Partial epigenetic stability, or metastability, and the primary role in controlling activities of DNA sequences can shed new light on non-Mendelian irregularities of complex diseases.

Epimutation: epigenetic changes that cause or predispose an organism to a disease

In some complex diseases, the risk to offspring depends on the sex of the affected parent. For example, asthma, bipolar disorder, and epilepsy are more often transmitted from the mother, whereas type 1 diabetes seems to be more often transmitted from the affected father (11). Parent-of-origin-dependent clinical differences have also been detected in schizophrenia (22). Molecular genetic studies, although rarely performed in a gender-specific fashion, also reveal parental origin effects in a wide variety of phenotypes, such as obesity (23), Alzheimer's disease (24), atopy and asthma (25), autism (26), and major psychosis (27). One of the most common mechanisms of parent-of-origin effects is genomic imprinting (28). The essence of genomic imprinting consists of the differential epigenetic modification of genes depending on their parental origin (29). Disruption of the normal imprinting pattern often causes diseases that affect cell growth, development, and behavior (30).

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) antidepressant, has been shown to induce genes encoding the MBDs MeCP2 and MBD1 by continuously activating the serotonergic (5-HT) system in the adult rat brain, suggesting that gene expression is repressed in the presence of fluoxetine. Induction of HDAC2 mRNA accompanied the protein increase, and decreased amounts of histone H3 were detected in three serotonin projection areas: the caudate-putamen, the frontal cortex, and the dentate gyrus of the hippocampus (109). Taken together, it appears that increased HDAC2 expression and recruitment to DNA plays a role in the regulation of histone acetylation and repression of gene expression in response to fluoxetine

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

Epigenetics and Complex Disease: From Etiology to New Therapeutics

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SUMMARY POINTS

1. Epigenetics is critical for normal functioning of the genome, and epimutation can be viewed as the first (etiological) step in the pathogenesis of complex diseases, which offers an explanation for their non-Mendelian characteristics.
2. Medications that target epimutations show great potential in the treatment of a variety of complex diseases, such as cancer and psychiatric disorders, although such medications are still in the early stages of development.
3. As techniques advance in the profiling of DNA methylation and histone modification patterns, disease epimutations may be detected and novel epigenetic drugs will emerge that have the potential to significantly improve the treatment of complex diseases.

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

Annu. Rev. Pharmacol. Toxicol. 2012. 52:21–35

Using Genome-Wide Association Studies to Identify Genes Important in Serious Adverse Drug Reactions

Ann K. Daly

Abstract

Genome-wide association (GWA) studies have detected novel associations for serious, idiosyncratic, adverse drug reactions including liver toxicity, hypersensitivity, skin rash, and myotoxicity. Human leukocyte antigen (HLA) genotype has been established as an important predictor of susceptibility to drug-induced liver injury, including injury with some drugs where immune-related toxicity was not suspected previously. Similarly, GWA studies have shown a key role for HLA genotype in susceptibility to carbamazepine-related skin rash and hypersensitivity. HLA genotype is not a risk factor for all forms of drug-induced liver injury or for myotoxicity or cardiotoxicity. For simvastatin-related myotoxicity, a strong association with *SLCO1B1*, which encodes the hepatic statin uptake transporter, has been detected. Genome-wide studies have not yet found clear associations for drug-induced cardiotoxicity, but for bisphosphonate-induced necrosis of the jaw, polymorphisms in the cytochrome P450 CYP2C8 may predict susceptibility. Larger GWA studies and whole-genome sequencing may provide additional insights into all these toxicities.

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

Annu. Rev. Pharmacol. Toxicol. 2012. 52:21–35

Using Genome-Wide Association Studies to Identify Genes Important in Serious Adverse Drug Reactions

Ann K. Daly

Table 1 Summary of published genome-wide association studies on serious adverse drug reactions

Type of toxicity	Number of published studies	Drugs involved	Genes implicated	Highest level of significance (lowest p value)	Reference(s)
Liver	4	Ximelagatran, Flucloxacillin, Lumiracoxib, Amoxicillin-clavulanate	HLA classes I and II	8.7×10^{-33}	37, 39, 40, 42
Skin and hypersensitivity	3	Carbamazepine plus miscellaneous agents	*HLA-A*	1.2×10^{-13}	58, 59, 62
Myotoxicity	1	Simvastatin	*SLCO1B1*	4.0×10^{-9}	68
QT prolongation	1	Iloperidone	*CERKL*	2.8×10^{-6}	78
Osteonecrosis of the jaw	1	Pamidronate, zoledronic acid	*CYP2C8*	6.2×10^{-6}	80

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

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Ann K. Daly

LIVER-RELATED ADVERSE DRUG REACTIONS

Idiosyncratic hepatotoxicity relating to drug exposure is usually referred to as drug-induced liver injury (DILI), a rare but clinically important problem. Drugs that give rise to this toxicity are

DILI:
organ-specific toxicity

The first study on a possible genetic association for DILI susceptibility appeared more than 20 years ago as a report showing an increased incidence in frequency of certain human leukocyte antigen (HLA) class II serotypes among DILI cases compared with controls (29). These cases included DILI induced by several drugs. A number of further reports of associations with particular HLA serotypes and genotypes followed, including, in particular, two independent reports suggesting that the HLA class II allele *DRB1*1501* was a risk factor for DILI induced by the antimicrobial agent, amoxicillin-clavulanate (30, 31). This form of DILI has been suggested to relate predominantly to the clavulanic acid component of the drug (32), though this has still not been demonstrated directly. Candidate-gene association studies have also led to the detection of several other associations with non-HLA genes, either for DILI due to individual drugs (33, 34) or for cases of this adverse drug reaction linked to a range of different drugs (35, 36).

Table 2 Genome-wide association studies on drug-induced liver injury

Drug	Number of cases	SNP(s)[a] showing lowest p value	p value[b]	Odds ratio (95% CI)[b]	Gene and allele tagged by SNP	Reference
Ximelagatran	74	rs2858869	6.0×10^{-6}	Not done	*HLA-DRB1*0701-DQA1*0201*	37
Flucloxacillin	51	rs2395029	8.7×10^{-33}	45 (19.4–105)	*HLA-B*5701*	39
Lumiracoxib	41	rs9270986	2.8×10^{-10}	5.3 (3.0–9.2)	*HLA-DRB1*1501-DQB1*0602*	40
Amoxicillin-clavulanate	201	rs9274407	4.8×10^{-14}	3.1 (2.3–4.2)	None	42
		rs9267992	6.8×10^{-13}	3.1 (2.3–4.2)	None	
		rs3135388	3.5×10^{-11}	2.8 (2.1–3.8)	*HLA-DRB1*1501-DQB1*0602*	
		rs2523822	1.8×10^{-10}	2.3 (1.8–2.9)	*HLA-A*0201*	

[a]SNP, single-nucleotide polymorphism.
[b]Based on allele frequency for SNP.

ΤΟΞΙΚΟΤΗΤΑ ΦΑΡΜΑΚΩΝ

Annu. Rev. Pharmacol. Toxicol. 2012. 52:21–35

Using Genome-Wide Association Studies to Identify Genes Important in Serious Adverse Drug Reactions

Ann K. Daly

DRUG-INDUCED MYOPATHY

A number of different drugs are associated with myopathy, which usually involves subacute manifestation of myopathic symptoms such as muscle weakness, myalgia, creatine phosphokinase (CPK) elevation, or myoglobinuria. The precise disease phenotype is somewhat dependent on the individual drug (63). Most cases are not serious and are readily reversible by drug withdrawal, but a more severe form of disease resulting in rhabdomyolysis followed by death also occurs rarely.

example of pharmacogenomic-based, SNP- related, toxicity (myopathy)

Understanding the genetic basis of susceptibility to simvastatin-induced myopathy was greatly increased by a GWA study of 85 cases of myopathy and 90 simvastatin-exposed controls without evidence of myopathy (68). The cases and controls were all of European ethnic origin. A highly significant association ($p = 4 \times 10^{-9}$) was seen for a single SNP in *SLCO1B1* with an odds ratio of 4.5 per copy of the variant allele. This effect was confirmed in 21 cases of myopathy from a separate replication cohort. *SLCO1B1* encodes an anionic drug transporter located on the sinusoidal face of the hepatocyte, which is the main inward transporter for a number of different statins (65). The significant SNP was in strong linkage disequilibrium with a nonsynonymous SNP in the *SLCO1B1*15* allele (also present in the rarer *SLCO1B1*5* allele) that is associated with higher plasma levels of statins owing to impaired transport (69). This association is, therefore, very biologically plausible. The significant polymorphism is common with a variant allele frequency

ΒΑΣΗ ΤΗΣ ΑΛΛΗΛΕΠΙΔΡΑΣΗΣ

Απορρόφηση
Αλλαγή απορρόφησης
Συνήθως μειώνει δραστικότητα, άρα συνήθως δεν συνδέεται με τοξικότητα, πχ αντιμυκητησιακές αζόλες
η τετρακυκλίνες με αντιόξινα

Φαρμακοκινητική
- Εκτόπιση απο θέση δέσμευσης σε πρωτείνες πλάσματος
- Αλληλεπίδραση στον (ηπατικό) μεταβολισμό
- Αλληλεπίδραση στην αποβολή

Φαρμακοδυναμική
Αλληλοενίσχυση βιοδραστικότητας

Ποιά φάρμακα ενέχονται;

Φάρμακα που χορηγούνται συχνά και για μεγάλο διάστημα

Αντι-υπερτασικά η αντιαρρυθμικά

Αντιπηκτικά

Αντιβιοτικά

ΜΣΑΦ

Αντι-καταθλιπτικά

Πόσο καλά διαγιγνώσκουν πιθανό πρόβλημα οι γιατροί;

Σε έρευνα που έγινε στις ΗΠΑ, μόνο 40% των γιατρών «διέγνωσαν» πιθανή τοξικότητα λόγω αλληλεπίδρασης απο ταυτόχρονη θεραπεία με 2 ή παραπάνω φάρμακα

Επιπλοκές – Καταστάσεις που συνεισφέρουν στο πρόβλημα:

Οι περισσότεροι ασθενείς που πηγαίνουν στο φαρμακείο παίρνουν τουλάχιστον 2 φάρμακα

Πιθανή επιδείνωση προβλήματος λόγω

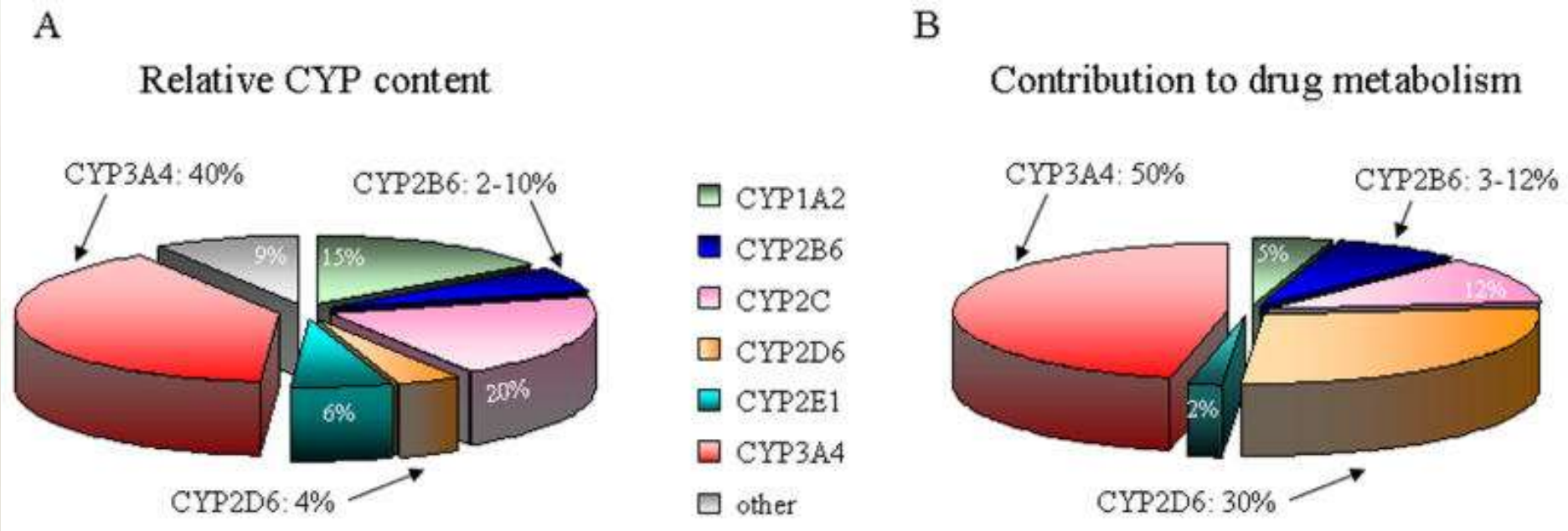
- φαρμάκων χωρίς συνταγή

- φυτικών σκευασμάτων και συμπληρωμάτων

Υπενθύμιση:

όλα τα CYP δεν συνεισφέρουν το ίδιο στον μεταβολισμό των φαρμάκων

Το CYP3A4 και το CYP2D6 είναι τα πιο σημαντικά

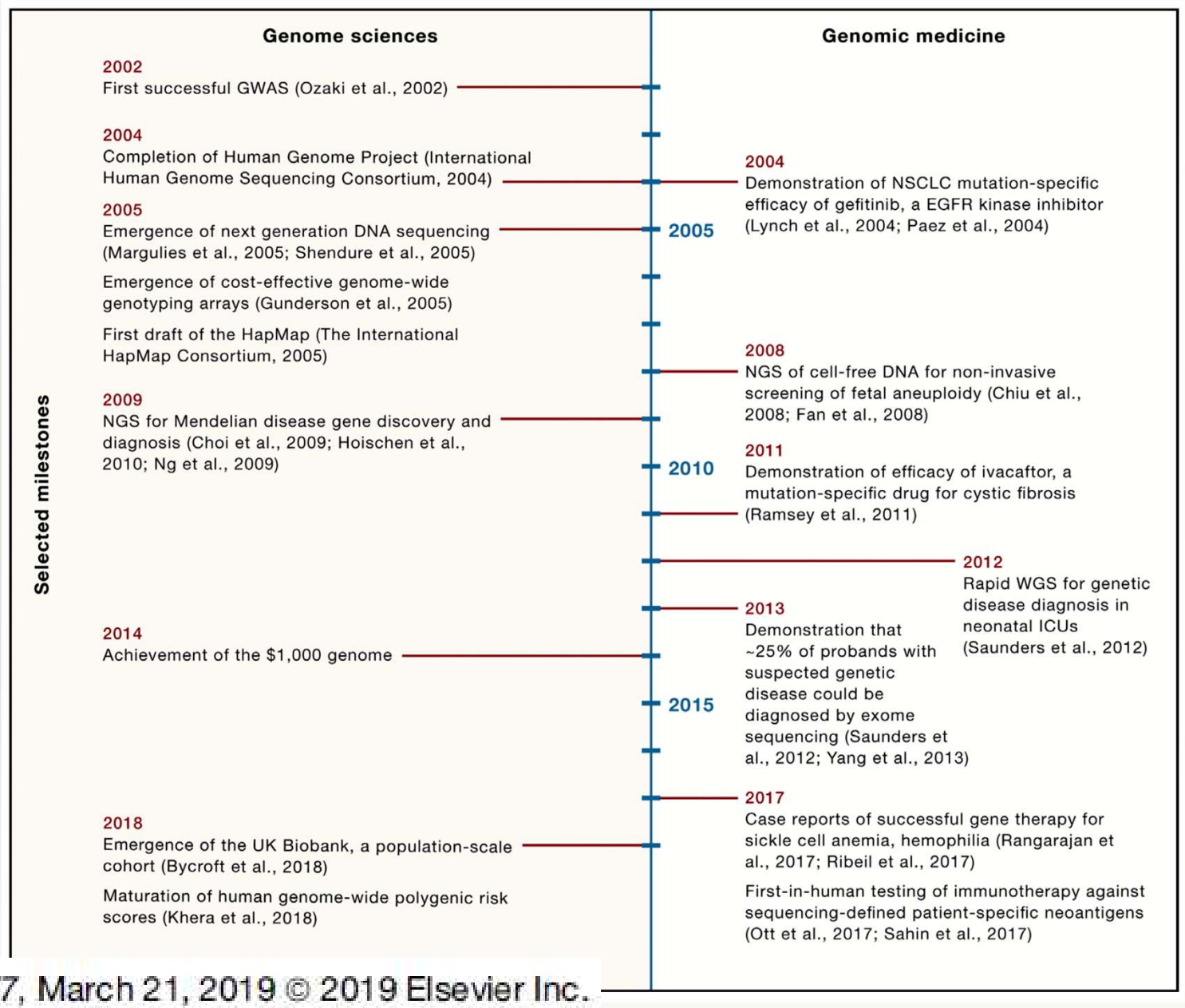


Pie charts for hepatic CYP expression and their contribution to metabolism of clinically-used drugs. (A) Relative hepatic expression of CYP content. (B) Contribution to drug metabolism. Due to substrate overlap among CYP isozymes, the total of contributions is moderately >100%.

Curr Drug Metab. 2008 September; 9(7): 598–610.

Τι πιθανότητες έχουν 2 φάρμακα να μεταβολίζονται απο το CYP3A4;

GENOMIC MEDICINE
Σταθμοί:



GENOMIC MEDICINE

Μελλοντικές προκλήσεις:

Grand challenges

Genome sciences

- A spatiotemporally resolved molecular atlas of all human cell types, throughout the lifecycle, and in both health and disease
- A comprehensive catalog of common genetic variants in which all human populations, as well as all classes of genetic variation, are well represented
- A "telomere-to-telomere" ungapped reference representation of the human genome
- A functionally validated catalog of human regulatory elements, annotated with the gene(s) that they regulate and the cellular, developmental, and/or disease contexts in which they are active
- The definitive identification of causal variants and genes for thousands of GWAS associations
- A comprehensive understanding of the genetic basis of all Mendelian disorders
- A basic understanding of the primary function(s) of every human gene
- Algorithms that can accurately predict the consequences of arbitrary genetic variants at the molecular/cellular level

Genomic medicine

- A database of whole genome sequences for at least 0.1% of living humans, integrated with electronic medical records and other phenotypes, and broadly accessible for research
- The routine use of exome or genome sequencing to diagnose the vast majority of suspected cases of Mendelian disease
- The routine use of genome-wide genotyping and polygenic risk scores for common disease risk prediction
- The generation of catalogs of clinically meaningful functional scores for all possible SNVs in all "clinically actionable" genes
- The routine use of exome or genome sequencing to guide cancer treatment, including for patient-specific immunotherapy
- The successful exploitation of cell-free DNA for early (or at least earlier) detection of common cancers
- Algorithms that can accurately predict the consequences of arbitrary genetic variants at the organismal level

Cell *177*, March 21, 2019

ΤΟΞΙΚΟΓΟΝΙΔΙΩΜΑΤΙΚΗ

Μερικοί ορισμοί:

Glossary

Adverse outcome pathways (AOPs): a conceptual framework connecting a molecular initiating event and key events with outcome and adverse effects in risk assessment.

DrugMatrix: one of the largest toxicogenomic reference resources, consisting of 638 compounds tested under microarray technology and their corresponding pathology data in rat, which covers 137 mechanism of toxicity-related pathways and 50 pathological endpoints.

FAIRsharing community: a web-based, searchable portal of three interlinked registries, containing both in-house and crowdsourced manually curated descriptions of standards, databases, and data policies, combined with an integrated view across all three types of resource.

Gene Expression Omnibus (GEO): the world's largest functional genomics data repository developed by the National Center for Biotechnology Information.

Idiosyncratic toxicity: is not dose-dependent and unpredictable. Idiosyncratic toxicity is caused by drug- and patient-related risk factors. Drug-related risk factors include metabolism, bioactivation and covalent binding, and the inhibition of key cell functions. Patient-related risk factors include genetic background, underlying disease, age, gender, comedications, and activation of the innate immune system.

***In vitro* to *in vivo* extrapolation (IVIVE):** can be broadly defined as an approach extrapolating the experimental results or observations made *in vitro* to predict *in vivo* phenomena qualitatively or quantitatively.

KEGG: Kyoto Encyclopedia of Genes and Genomes database, a collection of data resources that takes account of the complex relationship among biological pathways, diseases, and chemical substances/drugs.

OmicsMapNet: an approach to transform omics data to 2D images as an input for building deep convolutional neural network (CNN).

Open TG-GATEs: a large-scale toxicogenomics database that stores gene expression profiles, pathological

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ΤΟΞΙΚΟΓΟΝΙΔΙΩΜΑΤΙΚΗ

Σχηματική προσέγγιση
ποιές τεχνολογίες → λήψη αποφάσεων σε κλινικό ρυθμιστικό επίπεδο;

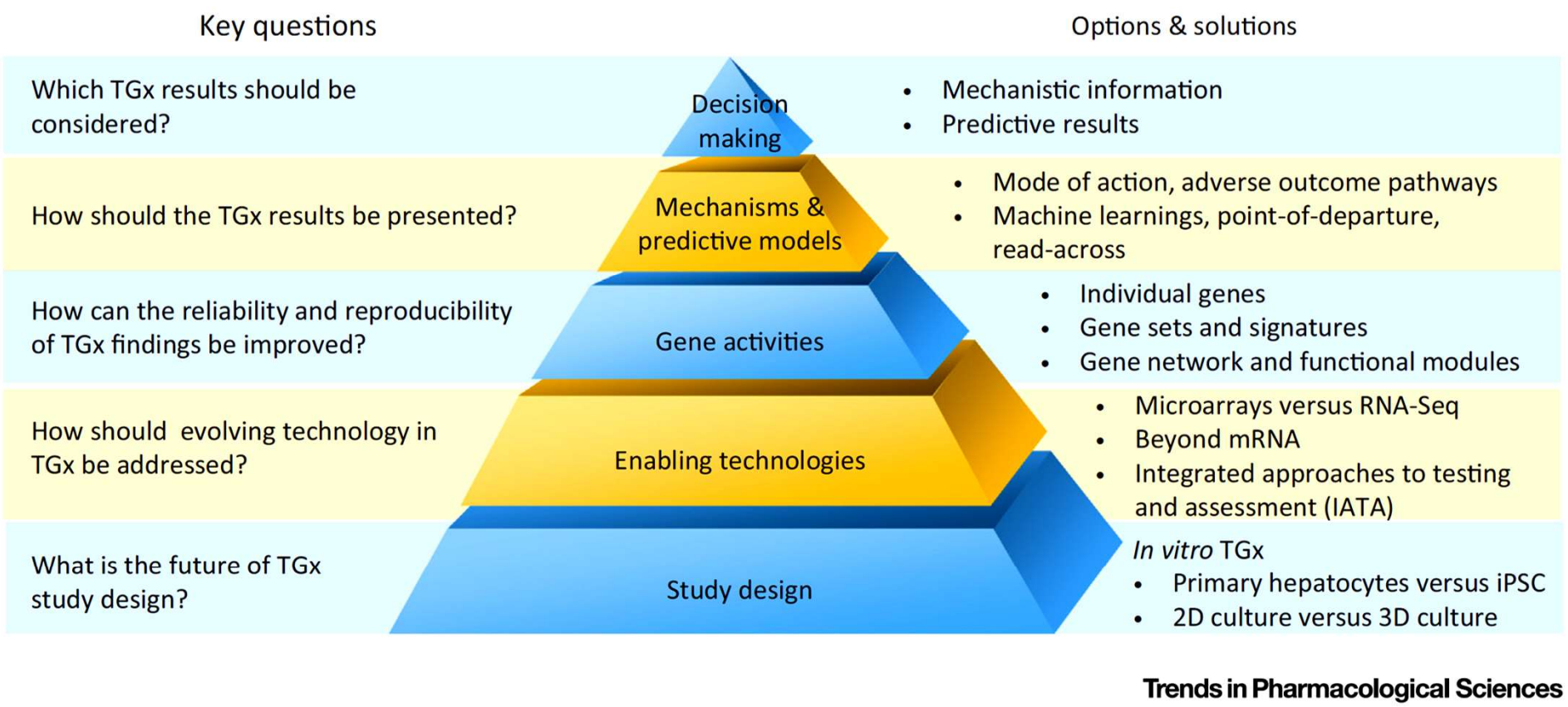

Figure 1. The Pyramid of Toxicogenomics (TGx) towards Regulatory Decision Making. Some outstanding questions and potential solutions for promoting TGx in respect of decision making are shown. iPSC, Induced pluripotent stem cell.

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Table 1. Gene–Drug Combinations with Actionable Pharmacogenetics[a,b]

Drug	Gene/allele	ADR
Abacavir	*HLA-B:57:01*	Hypersensitivity
Acenocoumarol, phenoprocoumon	*CYP2C9*, *VKORC1*	Bleeding
Allopurinol	*HLA-B*58:01*	Hypersensitivity
Atazanavir	*UGT1A1*	Jaundice
Azathioprine, mercaptopurine, thioguanine	*TPMT*	Myelotoxicity
Azathioprine	*HLA-DRB1*, *HLA-DQB1*	Pancreatitis
Capecitabine, fluorouracil, tegafur	*DPYD*	Neutropenia, mucositis, neuropathy
Carbamazepine	*HLA-B*15:02*, *HLA-A*31:01*	SJS, hypersensitivity
Clopidogrel	*CYP2C19*	Myocardial infarction, stroke, bleeding
Clozapine	*HLA-B_158 T*, *HLA-DQB1*05:02*	Agranulocytosis
Codeine	*CYP2D6*	Respiratory depression
Daunorubicin, doxorubicin	*RARG*, *SLC28A3*	Cardiotoxicity
Oral hormonal contraceptives	Factor V (*FV*) *Leiden*	Venous thromboembolism
Irinotecan	*UGT1A1*	Neutropenia, diarrhea
Phenytoin	*CYP2C9*, *HLA-B*15:02*	Hypersensitivity
Rasburicase	*G6PD*	Acute hemolytic anemia
Simvastatin	*SLCO1B1*	Muscle toxicity
Tacrolimus	*CYP3A5*	Supratherapeutic concentrations, hypertension and nephrotoxicity
Thioridazine	*CYP2D6*	QT prolongation
Warfarin	*CYP2C9*, *VKORC1*	Bleeding

[a]Guidelines for genetic testing have been issued by the Clinical Pharmacogenomics Implementation Consortium (CPIC), the Royal Dutch Pharmacists Association, the Pharmacogenetics Working Group, the French Joint Working Group comprising the National Pharmacogenetics Network (RNPGx) and the Group of Clinical Onco-Pharmacology (GPCO-Unicancer), the Canadian Pharmacogenomics Network for Drug Safety Clinical Recommendation Group, and other professional societies (www.pharmgkb.org/view/dosing-guidelines.do). These are examples of potentially preventable adverse drug reactions where a genotype is already available or undertaken specifically before a patient is started on the drug.

[b]Abbreviations: CYP, cytochrome P450; DPYD, dihydropyrimidine dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; HLA, human leucocyte antigen; RARG, retinoic acid receptor γ; SJS, Stevens–Johnson syndrome; SLC, solute carrier transporter; TPMT, thiopurine methyltransferase; UGT1A1, UDP glucuronosyltransferase family 1A.

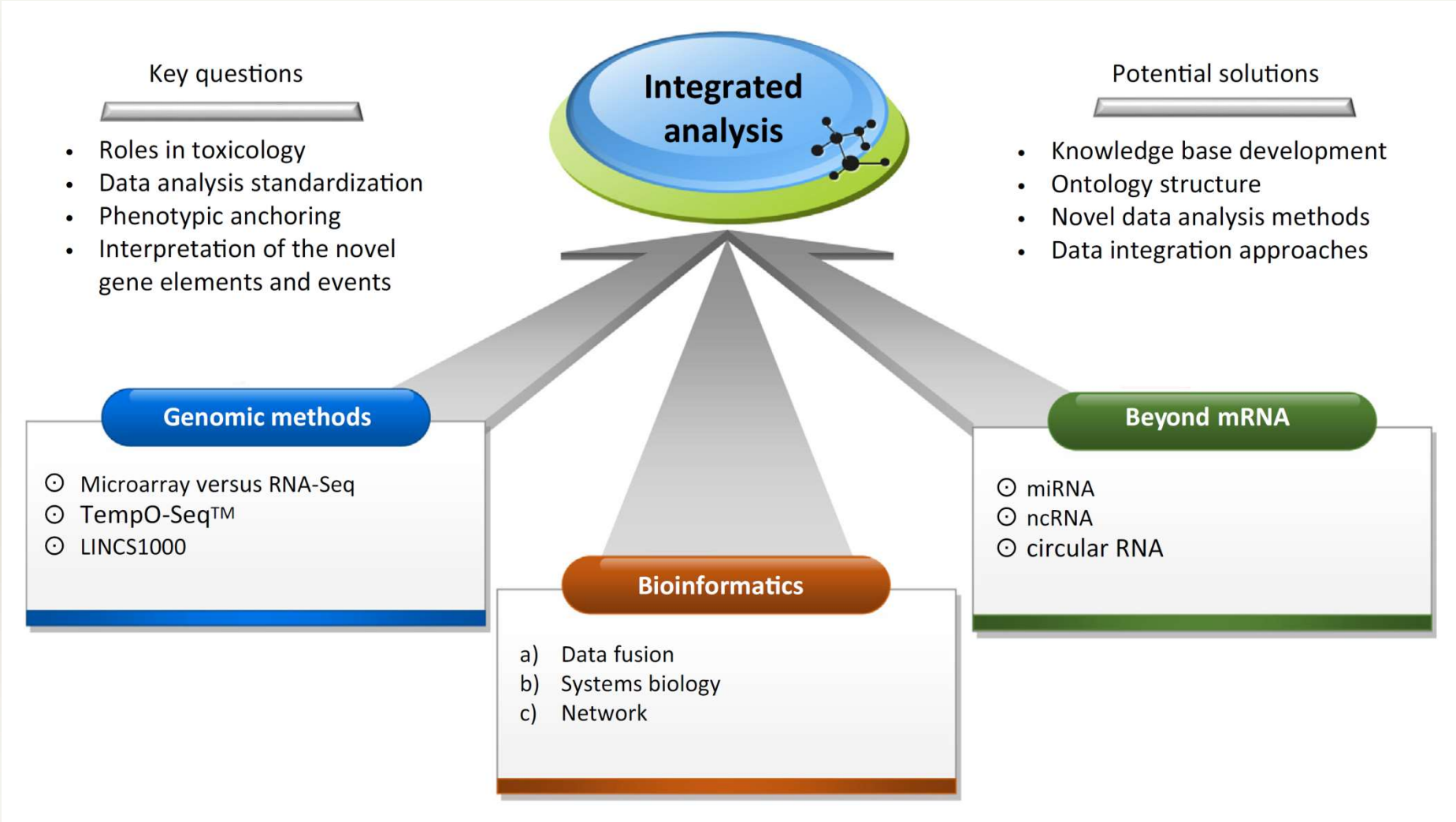
ΤΟΞΙΚΟΓΟΝΙΔΙΩΜΑΤΙΚΗ
Δοκιμές *in vitro* στην τοξικογονιδιωματική

Table 1. Examples of *In Vitro* Models Used in Toxicogenomics

Model	Organ	Species	Advantages	Disadvantages	Refs.
Tissue slices	Liver	Rat/mouse/ human	• Liver structure is maintained with all cell types • Good correlation with *in vivo* regarding **xenobiotic metabolism** and zone-specific cytochrome activity • **Phase II enzymes**, gluconeogenesis, and albumin production could be retained with 20–96 hours	• Necrosis occurs after 48–72 hours • Metabolic enzyme levels decreased after 6 72 hours • Drug metabolism and intrinsic clearance rates are lower than primary hepatocytes	[52]
Primary hepatocytes	Liver/ kidney	Rat/mouse/ human	• Functional activities could be maintained for 24–72 hours • Ideal for assessing the interspecies and interindividual differences in metabolism • Suitable for enzyme induction and inhibition studies	• Hepatocyte de-differentiation changes function, gene expression, cell morphology • Microenvironment lost • Cytochrome P450 expression decline quickly after 24–48 hours	[53]
Immortalized cell lines (e.g., HepaRG and HepG2)	Liver	Rat/mouse/ human	• High proliferative capacity and stable karyotype • Expression level of most liver functions and phase I/II enzymes can be retained in a lower percentage than primary hepatocytes	• Individual donor phenotype can be retained • Limited predictive power of toxicity is retained in population level	[54]
Three-dimensional culture systems	Liver	Rat/mouse/ human	• Hepatocyte functions are improved compared with monolayer culture • Cell types are retained and longevity is extended • Good correlation with *in vivo* toxicity • Cell interaction, morphology is more stable	• Limited successful co-culture (mainly with fibroblasts cells) • Standard culture construction protocol is needed • Not fully high throughput	[55]
Embryonic stem cells	Liver/ cardio/brain	Rat/mouse/ human	• Easily studied with most established omics techniques • Define phenotypes for many organ toxicity • Developmental toxicity	• Lower expression for metabolism-related genes • Not fit for long-term experiments • Bioengineering required	[51]
Induced pluripotent stem cells	Liver/ cardio/brain	Rat/mouse/ human	• Individual variability can be assessed • **Idiosyncratic toxicity** • Defined phenotype (multiple disease models) • Easily studied with most established omics techniques	• Bioengineering required • Lack of robust and reproducible differentiation protocols • Loss of the functionality of native hepatocytes • Lower expression level of metabolism-related genes	[56]
Organoids	Multiple organs	Rat/mouse/ rat and other species	• Limited amounts of starting material required • Can be propagated for a long time • Can be derived from multiple tissues and species • Good preservation of physiological features	• The native microenvironment of derived tissues could not be well maintained • Unable to mimic *in vivo* growth factor • Limited use in modeling inflammatory responses of tissues	[57]

ΤΟΞΙΚΟΓΟΝΙΔΙΩΜΑΤΙΚΗ

Συμπερίληψη νέων τεχνολογιών



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