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Systems pharmacology meets predictive, preventive, personalized and participatory medicine

Sherry L. Jenkins and
Department of Pharmacology & Systems Therapeutics, Systems Biology Center New York (SBCNY), Mount Sinai School of Medicine, New York, NY 10029, USA

Avi Ma'ayan
Department of Pharmacology & Systems Therapeutics, Systems Biology Center New York (SBCNY), Mount Sinai School of Medicine, New York, NY 10029, USA

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The vision of predictive, preventive, personalized, and participatory (P4) [1] medicine is expected to transform healthcare in the near future, but how exactly is this going to happen? Transformative changes that are relevant to P4 medicine are beginning to bud in the emerging sphere of a new discipline called systems pharmacology. Systems pharmacology combines high-throughput genome-wide experiments with advanced computation and modeling to understand drug action in cells and drug-induced events that perturb the human phenotype. Systems pharmacology combines systems biology with pharmacology but also involves genetics, genomics and computer science. It attempts to link drug perturbations of the molecular networks of cells to the human phenotype. Here we will discuss how the transformative potential of systems pharmacology touches different aspects of P4 medicine. We focus on two aspects of systems pharmacology: generating and analyzing drug-induced gene-expression signatures and mining drug/adverse event connections, as well as the potential synergy of these two activities.

Our ability to sequence DNA and RNA fast and inexpensively is opening doors to many applications that could transform medicine. For instance, whole-genome sequencing of millions of individuals could be used to detect mutations that can further characterize genetic disorders and identify novel drug targets [2]. In addition, gene expression, metabolomics or proteomics of cells from the blood [3], or sequencing of the microbiome from our stool, mouth or skin [4], can be used to monitor the health status of an individual over time with great accuracy [3]. Such data can be correlated with drugs taken by individuals and the adverse events they may experience. A related transformative approach involves the screening of drugs by applying them to stimulate human cells and then

Author for correspondence: Tel.: +1 212 659 1739, Fax: +1 212 831 0114, avi.maayan@mssm.edu.

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measuring genome-wide gene-expression changes induced by these drugs, in addition to phenotype assays such as measuring cell proliferation inhibition or programmed cell death [5]. This gene-expression signature-based approach to drug discovery adds a new dimension to drug–drug similarity networks, and such additions can potentially be used to find new connections between drugs, and molecular pathways or molecular networks, as well as between drugs and diseases or adverse events. The NIH Director Common Fund project, known as the library of integrated network-based cellular signatures (LINCS), supports this vision by providing funds to the development of a new version of the Connectivity Map database [5] through the application of the L1000 technology [101]. L1000 technology can be used to perform genome-wide gene-expression profiling at a very low cost, enabling a high-throughput alternative to standard cDNA microarrays or RNA-seq. However, the rapid drop in the cost of DNA sequencing is also poised to result in a similar transformation: measuring genome-wide mRNA expression at a very low cost, enabling the profiling of thousands of approved and experimental drugs on various human cells in different doses and in combination. The signature-based approach to drug discovery diverts us away from the single-target, structure-based approaches that dominated drug discovery for decades and are likely insufficient for a complete solution when complex diseases are considered [6]. The genome-wide view of drug perturbations also gives us the opportunity to understand the global dimension of how drugs can alter the cellular molecular networks and pathways of the human cell. Since drug-discovery costs keep rising because novel compounds rarely make it to US FDA approval, new approaches for drug development are now essential and the signature-based approach is refreshing. The LINCS project and similar efforts are expected to enable us to streamline the identification of new indications for approved and novel drugs, as well as their combinations, and to better 'predict' and 'prevent' side effects for new drugs before these occur at the postmarketing stage in the large population. There is also a potential to substitute animal testing with such *in vitro* assays [7].

While using low-cost, high-throughput screening to obtain genome-wide gene-expression signatures for many types of human cells treated with different drugs, as well as measuring gene expression after drug application in tissues extracted from model organisms, both bring great promise to drug discovery. It is also clear that measuring RNA and/or DNA alone may not be enough to explain drug responses and drug molecular mechanisms in individual patients, even when using cells from the individual patient. Technologies such as mass spectrometry proteomics, phosphoproteomics, single-cell analyses and metabolomics together with expression signatures can be linked computationally to pathways and networks to better identify the actual drug targets and the pathways these drugs alter [8]. These additional technologies are likely to be critical in order to allow real breakthroughs in the field of translational systems biology, systems pharmacology and the realization of P4 medicine.

In addition, the drug-signature screening approaches can become 'personalized' by screening drugs using human cells directly derived from patients. Epithelial cells collected from a buccal swab can now be reprogrammed to induced pluripotency stem (iPS) cells to be maintained and expanded indefinitely in culture [9]. Such cells can then be differentiated into desired lineages before they are used for a drug screen that can measure drug-induced gene-expression signatures in those patient-derived cells. A similar approach is to profile the response of drugs in xenograft mouse models created with cells extracted from individuals with the purpose of tailoring a treatment personalized to the individual. This 'mini-me' approach is expensive but now also possible [10].

At the same time, the patient is becoming increasingly involved in their own health decisions, especially where online forums enable patients to obtain information about their condition and, most critically, donate their own data to the pool of human knowledge about

drug effects in individuals. We are moving towards a new future in which, besides being an organ donor, patients will be asked to be a data donor. In addition to donating their own genome information, patients will be asked to donate information about how they feel, what they eat, what medications they use, how much exercise they do and how many hours they slept last night. Many people already engage in such data donation activity without even realizing it.

For example, data mining systems can extract side-effect information for drugs taken by patients from user-generated content websites, such as Facebook and Twitter. A web crawler can scan these sites to mine user-generated content from user posts and blogs. Such systems can extract health-related information, such as drugs and side-effect data, from the vast amount of user posts using text mining, and then apply statistics on the results to extract knowledge, finding correlations between drugs and indicative symptoms, including side effects, to build drug/side-effect networks. Web systems such as KEGG Medicus [11] will enable patients to donate their experience with the medications they are taking, and to find other patients with similar profiles to their own, enabling 'participatory' medicine. The trend of the formation of social groups of patients with similar disease profiles where such communities exchange and share health information among each other is expected to continually grow. While active participation of patients to make sound health decisions is currently unreliable at a global scale, other methods to extract drug/side-effect information at the postmarketing stage is currently carried out by physicians. The FDA Adverse Event Reporting System (FAERS) [102] is an open and free resource containing a treasure of information about drug effects in humans, where millions of records have been collected for many years; however, such data has not yet been largely utilized for knowledge extraction and decision-making. However, there are many pioneering examples that creatively used FAERS for finding interesting connections, including the following [12–14]. Data collected from patients treated with various drugs are expected to grow rapidly. In the near future, the mobile patient will be streaming real-time data about their health-related status into servers that will integrate this for knowledge extraction and better health-decision choices.

When the dust settles and modern systems pharmacology becomes more co-ordinated, sophisticated algorithms will be able to find patients with similar properties, histories and retrospective trajectories based on different drug-treatment experiences, environmental conditions, genomic backgrounds and more. Such systems will be able to find similar drugs based on their collected properties, including gene-expression signature patterns in various human cells, and connect these drug-induced changes to pathways and networks. This will inform future decisions for individuals by optimizing drug and dose to the individual patient. The consequences of such decisions will be fed back into the global expert system to improve its performance, just like the way the Google search engine or the Amazon Recommender system are continually improving by processing the successes and failures of users' searches, clicks and purchases. This vision has previously been realized in the 1970s [15] but now we see the results that show that such systems can become more complete and effective; realistically outperforming or at least assisting an experienced physician.

New expert systems may already have enough of the data and algorithms needed to successfully improve standard methods of making health decisions personalized for individuals. For example, one such knowledge-based decision support system, IBM Watson [16], was shown to perform better than a human expert playing Jeopardy or chess. IBM's Watson, or a similar a system, can potentially be programmed to implement machine learning algorithms to compute the best drug treatment at the best dose for an individual patient by synthesizing information from data collected from systems pharmacology, including patient history, symptoms, genotype and environmental conditions by comparing similar patients; and using data about drugs, including global similarity among drugs based

on drug effects on the molecular networks they perturb in different human cells, as well as other drug relevant properties.

While the future of systems biology, systems pharmacology and pharmacogenomics is mostly unpredictable because it requires the merger of technologies, policies and further innovations [17], changes are being seen, gradually realizing the vision of P4 medicine. Once new attitudes and technologies are widely accepted, systems pharmacology will be synergistic and transformative.

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