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Developing New Drug Treatments in the Era of Network Medicine

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Introduction

Although impressive advances have been made in determining the genetic and molecular causes of disease, treatment for many complex diseases remains inadequate. Despite compelling unmet medical needs and new insights into disease pathobiology, new drug approvals for complex diseases have stagnated. A new paradigm for drug development is needed, and key concepts from network medicine and systems pharmacology may be essential to this effort.

Overview of Network Medicine and Systems Pharmacology

Network medicine is the developing new field which applies network science and systems biology approaches to understand complex diseases and systems pharmacology approaches to develop treatments for these diseases[1]. The classical single target-based drug development paradigm focuses on the identification of a key molecular component of the disease, which can be regulated with a small molecule that will act as a specific and effective "magic bullet." However, for common, complex diseases like coronary artery disease, asthma, and diabetes mellitus, this single target approach oversimplifies the complex pathobiological mechanisms of these chronic illnesses. Moreover, this approach tends to neglect the complex perturbations that drugs cause within the cellular molecular network, which can lead to serious adverse events as unanticipated ("off-target") effects. Better phenotyping of patients with complex diseases, using a combination of clinical, physiological, and imaging approaches, will also be critical to characterize disease heterogeneity and to personalize drug development and treatment.

A recent NIH White Paper on Systems Pharmacology pointed out the importance of viewing drug development within a network context; the cellular molecular network has emergent properties (unique characteristics resulting from the specific combination of network elements) that are not apparent if single molecules are studied in isolation[2]. The authors

recognized that these biochemical networks vary by tissue, genetic variation, disease state, and environmental exposures. Stochastic effects also play an important role in cell-to-cell variability and limiting accuracy of biochemical circuits. They proposed an integrated definition of systems pharmacology, which focuses on interactions between multiple elements including molecules, cells, and tissues. Few drugs fail today due to problems with pharmacokinetics; the key challenge is coming up with new and better drug targets for disease. The reductionist approach to drug discovery has worked well in some cases, such as the development of antiretroviral agents for HIV; however, the failure of this paradigm in most complex diseases suggests that alternative approaches are needed. Since complex diseases likely result from multiple genetic, epigenetic, and environmental factors acting in a developmental context, targeting multiple components of disease pathways may be necessary for effective treatment. Approaches from network medicine and systems pharmacology may be helpful for selecting optimal drug targets, for determining which patients should be treated with which drugs, and for assessing the efficacy and adverse effects of new treatment regimens. The differences between the current paradigm for most drug development efforts and a network medicine/systems pharmacology approach are shown in Figure 1.

Selecting Drug Targets: Systems Pharmacology Approaches

In order to use network medicine approaches to select drug targets for a complex disease, the molecular interaction network of genes and proteins relevant to that disease must be known. Tools such as yeast two-hybrid assays and tandem affinity purification/mass spectrometry have provided initial, unbiased maps of the overall cellular molecular interaction network, but they remain quite incomplete. The identification of genetic determinants of complex diseases could provide a useful foothold by which to identify disease-specific modules of the cellular molecular interaction network if the functional consequences of these natural perturbations could be characterized. However, the low power of genome-wide association studies to identify main genetic effects and, most notably, epistatic interactions in complex diseases has limited the utility of purely genetic approaches. Genetic analysis methods that focus on specific biochemical pathways and which integrate multiple –omics data types (e.g., transcriptomics, metabolomics, and proteomics as well as environmental modifications of them, such as oxidized post-translational modifications of the proteomics) may have greater power to identify relevant interactions. Once the disease pathway is elucidated and its molecular components are defined, dynamic systems analysis can be applied to determine which (combination of) drug targets yields the optimal benefit with minimal adverse consequences -- an emergent property of the system not discernible by conventional pharmacologic reductionism.

A recent seminal study of breast cancer cell lines by Lee and colleagues demonstrated several key principles for future therapeutic applications of network medicine[3]. These investigators studied cell lines from triple negative (i.e., estrogen receptor; progesterone receptor; and HER2 oncogene-negative) breast cancer, which is notoriously difficult to treat, with seven genotoxic drugs and eight signaling inhibitors in various combinations and dosage schedules. They found that combination treatment with epidermal growth factor receptor (EGFR) inhibition and DNA-damaging chemotherapy (doxorubicin) led to substantial killing of triple-negative BT-20 cells, but only when the EGFR inhibition preceded the DNA-damaging chemotherapy by at least four hours. Thus, not only was the application of combination treatment important, but the sequence and timing of the administration of the multiple therapeutic agents was essential. This response relates to the dynamic effects of the cellular molecular interaction network, which was rewired in response to EGFR inhibition. Importantly, some other breast cancer cell lines (both triple negative and non-negative) were not responsive to this ordered drug treatment combination,

demonstrating the importance of accurate phenotypic characterization of disease subtypes. These investigators used microarray analysis to demonstrate that EGFR inhibition caused many gene expression changes in BT-20 cells--but not in breast cancer cell lines unresponsive to combination treatment with EGFR inhibition and doxorubicin--thus showing the utility of –omics readouts in assessing therapeutic effects. They found that EGRF inhibition enhanced the apoptotic response to doxorubicin, which was mechanistically related to caspase-8 cleavage and activation.

Selecting Patients for Treatment: Reclassifying Disease Using Network Approaches

Complex diseases likely represent syndromes composed of multiple disease entities which are grouped together based on our limited understanding of disease pathogenesis. Current classification schemes in most complex diseases are typically based on expert opinion and literature review. In describing the challenges of nosology, which involves the development of terminology and classification schemes for diseases, Snider pointed out that etiology becomes a defining characteristic of diseases whenever an etiology is known (*e.g.*, specific genetic defect in sickle cell anemia)[4]. However, when the etiology is not known, pathology, pathophysiology, and clinical features are used to create defining features of disease—potentially with compound definitions from several of these categories. Recently, several groups of classic Mendelian disorders, including Marfan syndrome, genetic skeletal disorders, and inherited ichthyoses, have undergone revisions of disease classification. In each case, expert panels agreed that clinical characteristics should remain the primary approach for classifying these diseases. However, molecular genetic testing was recognized to provide extremely useful information to ensure accurate diagnosis and to offer the potential for splitting groups that cannot be distinguished based on their clinical and radiographic appearance. As the field of network medicine develops, complex diseases may be reclassified based on a combination of multiple –omics data types along with genetic variants and clinical, physiological, and radiological criteria. Presumably, different disease subtypes will require different treatment strategies.

In addition to providing insights into disease pathogenesis, pharmacogenetics may identify individuals likely to benefit (or not benefit) from treatment. Further research will be required to determine how to integrate pharmacogenetic effects efficiently into network models of drug development and efficacy.

Determining if Drugs Work: Network Approaches to Drug Assessment

One of the major challenges in developing new drug treatments for chronic diseases is that very long observation periods may be needed to assess a therapeutic effect. For example, chronic obstructive pulmonary disease is a gradually progressive complex disease characterized by irreversible obstruction to airflow. Determining whether a new drug changes the rate of lung function decline may require years of observation in thousands of subjects. Currently available molecular biomarkers for complex diseases likely do not capture the underlying network influences on these diseases. By incorporating assessment of multiple –omics approaches in a network context, more rapidly changing biomarkers of disease from genomics, proteomics, or metabolomics may be developed. Demonstration of a therapeutic effect in human studies will still be required, but such biomarkers could guide the selection of drugs and their dosages in early stages of drug development.

Adverse drug events are major causes of morbidity, and they limit the use of therapeutic agents that would otherwise be highly beneficial. There are three types of drug toxicity: on-target, on-pathway (toxicity is the result of the same effect as therapeutic efficacy); on-

target, off-pathway (toxicity results from a second effect of the correct molecular target); and off-target (effect on molecules other than the molecular target)[2]. Applications of network science may allow computational predictions of adverse drug effects. For example, Huang and colleagues applied computational biology approaches (support vector machines and logistic regression) to publicly available databases of drug targets (DrugBank), drug side effects (SIDER), protein-protein interactions (HAPPI), and biological pathways (GO). They demonstrated that including protein-protein interaction or biological pathway information provided substantially improved prediction of cardiotoxicity-related drug adverse events[5].

In order to incorporate network science and systems pharmacology information into an efficient pipeline for drug development, novel clinical trial designs may be required. Adaptive clinical trials provide flexibility to incorporate newly discovered information during the trial, such as pharmacogenetic effects, in order to redesign the trial while it is in progress. Applications of an adaptive clinical trial approach that integrate information regarding dynamic combinations of drug treatments could be essential to the implementation of network medicine. Similarly, the evolution of network and systems-based therapeutics coupled with well-defined disease phenotyping will optimize the successful achievement of personalizing therapies.

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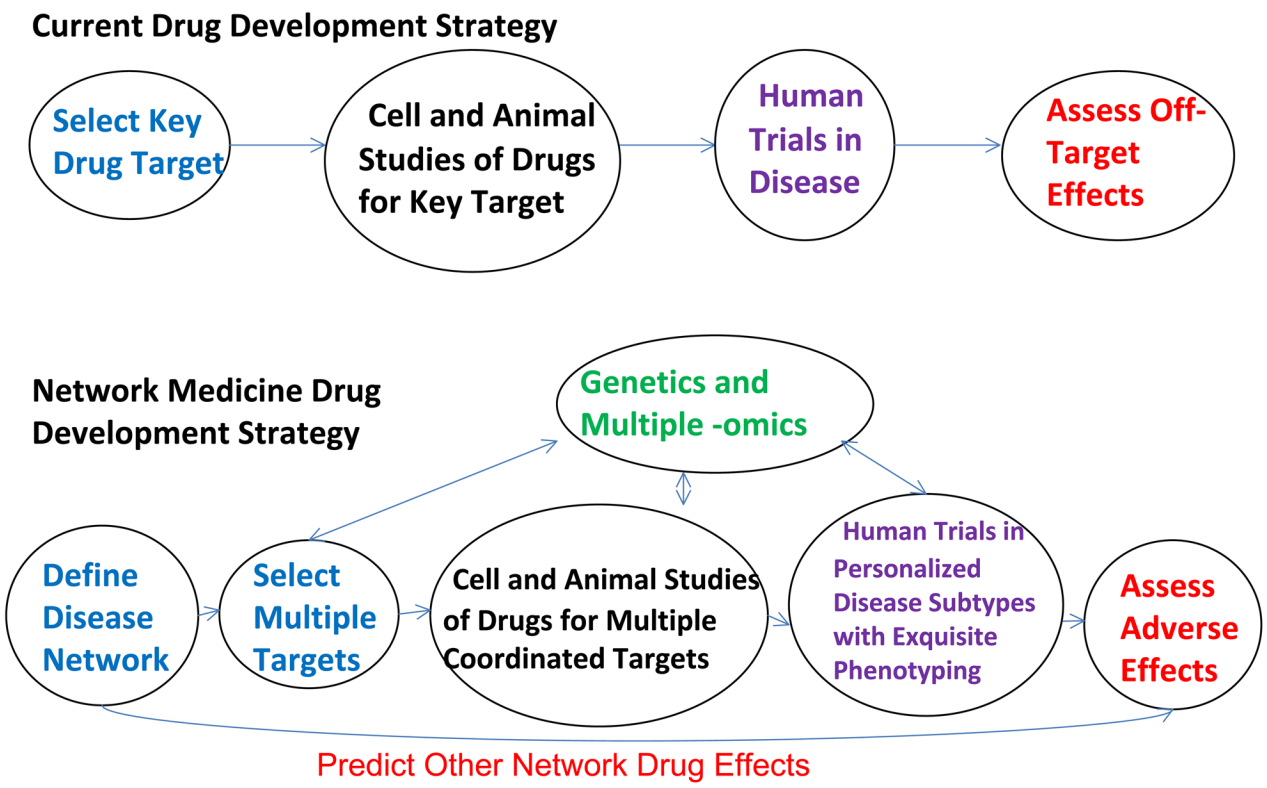

Figure 1.

Current and Network Medicine Approaches to Drug Development for Complex Diseases. The single target approach to drug development (top) begins by selecting a key molecular target for drug development from a variety of potential sources, including genetic studies, cell-based assays, or animal models of disease. Drugs are developed, typically by high throughput screening, against this key molecular target and tested in cell-based and animal model systems. If the safety profile is adequate, human trials are performed; unanticipated adverse events are often found, which are typically attributed to off-target effects. As network medicine and systems pharmacology are applied to drug development (bottom), we anticipate that determination of the disease molecular network will provide multiple targets for drug development. Studies of coordinated combinations of drugs will be assessed with various –omics read-outs in cell-based systems, animal models, and human trials. Human trials will have a higher likelihood of success if patients with the same pathophysiological subtype of disease, determined by the integration of comprehensive phenotyping, genetics, and multiple –omics approaches (including transcriptomics, proteomics, and metabolomics), are studied. Determination of the disease network will allow prediction of specific adverse events, which may promote pharmacogenetic testing to avoid treatment of individuals at high risk for these events.