Systems Pharmacology, Natural Products and Drug Discovery through Compound Libraries

Network Pharmacology

Rational drug design in the past has proceeded based on the reductionistic philosophy of the one disease-one gene-one drug paradigm. However, this approach has been questioned as to its effectiveness given the lack of success of the approach in some critical areas.

For example, the attrition rates in phase 2 and phase 3 drug trials, are on the rise, where approximately 30% of failures can be attributed either to a lack of efficacy or to questions about safety. [1] This failure is due in part to an apparent discrepancy between results at the bench and at the bedside and to an incomplete understanding of the pathways—and, importantly, the interrelationships of these pathways. In oncology, 59% of drugs entering phase 3 clinical trial fail. Overall, only about 1 in 9 drugs gets approved by US or European regulatory agencies. In some therapeutic areas, however, the rate approaches 1 in 5. Why do some therapeutic areas show a greater rate of success in drug approval (e.g. in cardiovascular disease)whereas others, such as oncology or CNS disorders show only 5-8% bench to bedside success rates? Is it because we understand the cardiovascular system better than we understand cancer or the function of the CNS? Or is it because the network(s) involved in cardiovascular disease are somewhat less complex than those involved in tumorigenesis and/or the CNS?

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One of the premises of network (or systems) pharmacology is that a drug, its ligand, its mechanism of action and the unwanted (or unsuspected) adverse drug effects are best examined using principles of systems biology, focusing on the complex network of interactions rather than the reductionistic approach of the past. It must of course be said in this regard that the reductionistic approach has provided us with the requisite tools to approach rational drug design in a more holistic or systems (network)based manner. In systems or network pharmacology and drug design, the focus is not on a search for a single target drug that suppresses or induces a gene, metabolic pathway or protein. In systems or

network pharmacology the goal is to "identify the perturbations in the disease-causing network."[2,3]

Another premise of network pharmacology is that the perturbations in any system that result in disease are multiple—that disturbance at a single node of the network will likely not affect any single function because of redundancy and compensatory signaling pathways built into the system. [4] For example, examining a number of animal model systems, less than 20% of genes examined are considered essential.[2,5,6] Thus, the loss of a single gene in knockout mice results in an estimated 10% that may have utility for rational drug design.[2,7]

The alternative approach of network pharmacology is through polypharmacology—understanding the effects of the binding of a drug to multiple biological targets. Many antibiotics for example affect a single target. The more effective antibiotics such as the β-lactams and the fluoroquinolones target two or more molecules. Knudson's two-hit hypothesis of tumorigenesis is perhaps an early example of the concept. If disease is rarely caused by a single event but instead caused by a series of perturbations in an interrelated network of molecular interactions, then it seems more clear that to "reset" the network, one must look at multiple targets.

The key challenges in network pharmacology are:

- The identification of node or nodes within the network that have been perturbed with disease resulting. One could imagine identifying a node or nodes that describe a "pre-disease state" as well—personalized medicine is a growing area of interest and is concerned with predicting, and preventing diseases and well as designing personalized and participatory approaches to health and wellness.[8]
- The identification and characterization of an agent or agents with the appropriate profile to "unperturb" the network.

It is believed that the structure or topology of the networks can provide vital clues for drug discovery—recent work on "betweenness centrality"[9-11], "bridging centrality"[10,12,13] and "degree centrality"[9,14-18]. Betweenness centrality has been defined as the "number of nonredundant shortest paths traveling through a node"[2]. Bridging centrality has been defined as the "nodes between and connecting subgraph clusters defined by the ratio of the number of interactions of a neighboring node in a subgraph over the number of remaining edges in the subgraph"[2,19] Degree centrality is defined as "the number of direct interactions intersecting a node"[2] Bottlenecks, areas with high degrees of betweenness rather than interconnectedness, appear to be critical in finding emergent essential proteins and emergent phenotypes. These proteins and phenotypes can then be the new targets for drug discovery. [20-22]

Methods in Network Pharmacology based on Systems Biology

Computational approaches are used to analyze the results of combinations of experiments measuring many cellular processes and to analyze the data sets resulting. Computational modeling is performed as an iterative process that can use non-intuitive hypotheses that may be validated and expanded. The computational approaches may be top-down (data-driven) or bottom-up (hypothesis-driven). The top-down methodologies (network modeling, for example) involve high through-put "omics" data and uses statistical modeling techniques for analysis. Bottom-up methodologies (e.g.dynamical or mechanistic modeling) are generally used on the smaller systems and require deriving the appropriate equations with various estimates employed for the quantitative details that may be lacking.

Five areas in which these approaches have resulted in recent advances [23] include:

1. Drug-target networks showing interactions with multiple targets (polypharmacology). Promiscuous or dirty drugs can be designed based on existing libraries that bind to multiple targets with the potential of increasing clinical efficacy while decreasing adverse drug effects and toxicity—and thereby decreasing the rates of attrition mentioned above. Keiser *et al* have demonstrated that receptors can be related to each other based on ligand similarity. [24] Li *et al* have developed a disease-specific drug-protein computational framework to study potential molecular signature differences that may exist between classes of drugs in the context of a specific condition or disease state.[25]
2. Predictions of drug-target interactions. Cheng *et al* have determined that a network-based set of inferences performed best prediction drug-target interactions: they tested drug-based similarity inference (DBSI), target-based similarity inference (TBSI) and network-based inference (NBI).[26] They concluded that NBI could be "powerful tools in prediction of DTIs and drug repositioning."
3. Investigations of the adverse effects of drugs. Adverse drug effects (ADE) constitute one of the fundamental issues in drug attrition rates. *In silico* interactomes have indicated that drugs that share the same or very similar ADE profile also share drug-protein interactome profiles.[27,28]
4. Drug repositioning/repurposing has the potential to save time and reduce the risks of drug development. Iskar *et al* were able to identify drug-induced biclusters (transcriptional modules) that were conserved across human and rat cell lines. They were then able to predict and validate experimentally, modulators of PPARγ, hormone and adrenergic receptors and cell cycle inhibitors. [29]
5. Predictions of drug combinations. Time- and order-sensitive drug combinations can result in increase efficacy and safety. For example, for antitumor agents, Huang *et al* recently developed a computational approach,

DrugComboRanker to identify and prioritize drug combinations able to function synergistically. They also built disease-specific networks (based on individual genomes) and interactome data and identified specific combinations by searching drug libraries.[30]

Natural Products and Systems Pharmacology


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Interestingly, compound libraries are also being used in a form of "reverse pharmacoengineering" where natural products in the form of herbal combinations used for centuries in Traditional Chinese Medicine (TCM) are being studied using systems pharmacology approaches to elucidate mechanisms of action and forms of interactions. Using compound libraries such as DrugBank, PDTD, TTD, PharmGBK, MetaCore, CPDB, ChEMBL, MMsINC, CB, ChemSpider, ChemProt, LookChem and others as well as natural products databases such as HIT, CHMIS-C and specialized databases for TCM such as TD@T, TCMGeneDIT, TCM-ID, TCMID and others has lead to greater understanding of combinatorial rules, MOAs in complex disease and the disease process. In addition, comparing the data with that in existing libraries has led to new potential targets, new drug discovery potential and new potential combinations.[11,31] *in silico* strategies can be used to understand the complex interactions that exist in herbal medicines and as a platform for new drug discovery.[32]

For example, Liu *et al* examined two sets of herbs using a pattern recognition model, discriminant analysis, eADME prediction, target fishing and network analysis to clarify the herb-target associations and to construct networks. They found that one class of herbs (the energy (qi)-toning herbs) acted as an adjuvant and an anti-inflammatory while another class (the blood tonifying herbs)stimulated hematopoiesis.[33]

Others have used TCM herbs and natural products as a resource library for discovering anti-infectives and anti-inflammatory drugs, [34-36] cardioactive drugs, [37-39] and antineoplastic agents,[40 41 41] and acetylcholinesterase inhibitors. [11,42]

Herbs that are used in existing combinations which have a long history (albeit an often anecdotal history) of safety and efficacy can be studied using all the tools of systems pharmacology and serve as a platform for new drug discovery using existing compound libraries as the springboard. In addition, systems pharmacology methods can be used to elucidate potential interactions between natural products and prescription medications.[43-46]

References Cited

1. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? . Nat Rev Drug Discov 2004;3:711-6.
2. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nature Chemical Biology 2008;4:682-90.
3. Martin F, Thomson TM, Sewer A, et al. Assessment of network perturbation amplitudes by applying high-throughput data to causal biological networks. BMC Systems Biology 2012;6:54-.
4. Kitano H. Towards a theory of biological robustness. . Mol Syst Biol 2007;3:#137.
5. Woods S, Coghlan A, Rivers D, et al. Duplication and retention biases of essential and non-essential genes revealed by systematic knockdown analyses. Plos Genetics 2013;9:e1003330-e.
6. Georgi B, Voight BF, Bućan M. From mouse to human: evolutionary genomics analysis of human orthologs of essential genes. Plos Genetics 2013;9:e1003484-e.
7. Zambrowicz BP, Sands AT. Knockouts model the 100 best-selling drugs–will they model the next 100?. Nat Rev Drug Discov 2003;2:38–51
8. Jenkins SL, Ma'ayan A. Systems pharmacology meets predictive, preventive, personalized and participatory medicine. Pharmacogenomics 2013;14:119-22.
9. Li M, Zheng R, Zhang H, Wang J, Pan Y. Effective identification of essential proteins based on priori knowledge, network topology and gene expressions. Methods (San Diego, Calif) 2014;67:325-33.
10. Hwang WC, Zhang A, Ramanathan M. Identification of information flow-modulating drug targets: a novel bridging paradigm for drug discovery. Clinical pharmacology and therapeutics 2008;84:563-72.
11. Gu J, Gui Y, Chen L, Yuan G, Lu H-Z, Xu X. Use of natural products as chemical library for drug discovery and network pharmacology. Plos One 2013;8:e62839-e.
12. Faustino RS, Terzic A. Bioinformatic networks: molecular reticles for pinpointing pharmacological target selection. Clinical pharmacology and therapeutics 2008;84:543-5.
13. Chen L, Wang Q, Zhang L, et al. A novel paradigm for potential drug-targets discovery: quantifying relationships of enzymes and cascade interactions of neighboring biological processes to identify drug-targets. Molecular Biosystems 2011;7:1033-41.
14. Li M, Wang J, Chen X, Wang H, Pan Y. A local average connectivity-based method for identifying essential proteins from the network level. Computational Biology And Chemistry 2011;35:143-50.
15. Li M, Zhang H, Wang J-x, Pan Y. A new essential protein discovery method based on the integration of protein-protein interaction and gene expression data. BMC Systems Biology 2012;6:15-.
16. Ozgür A, Vu T, Erkan G, Radev DR. Identifying gene-disease associations using centrality on a literature mined gene-interaction network. Bioinformatics (Oxford, England) 2008;24:i277-i85.
17. Xiong W, Xie L, Zhou S, Guan J. Active learning for protein function prediction in protein–protein interaction networks. Neurocomputing: An International Journal 2014.
18. Zhang X, Xu J, Xiao W-x. A new method for the discovery of essential proteins. Plos One 2013;8:e58763-e.
19. Yu H, Kim PM, Sprecher E, Trifonov V, Gerstein M. The importance of bottlenecks in protein networks: correlation with gene essentiality and expression dynamics. . PLoS Comput Biol 2007;3.
20. Gálvez J, Gálvez-Llompart M, García-Domenech R. Molecular topology as a novel approach for drug discovery. Expert Opinion On Drug Discovery 2012;7:133-53.

21. Gálvez J, Gálvez-Llompart M, García-Domenech R. Introduction to molecular topology: basic concepts and application to drug design. Current Computer-Aided Drug Design 2012;8:196-223.
22. Audigier Y, Picault F-X, Chaves-Almagro C, Masri B. G Protein-Coupled Receptors in cancer: biochemical interactions and drug design. Progress In Molecular Biology And Translational Science 2013;115:143-73.
23. J. Z, Zheng M, Li G, Su Z. Advanced systems biology methods in drug discovery and translational biomedicine. Biomed Res Int 2013;2013.
24. Keiser J, Roth B, Armbruster B, Ernsberger P, Irwin J, Shoichet B. Relating protein pharmacology by ligand chemistry Nature Biotechnology 2007;25:197–206.
25. Li J, Zhu X, Chen J. Building disease-specific drug-protein connectivity maps from molecular interaction networks and PubMed abstracts PLoS Computational Biology 2009;5.
26. Cheng F, Liu C, Jiang J, et al. Prediction of drug-target interactions and drug repositioning via network-based inference PLoS Computational Biology 2012;8.
27. Yang L, Chen J, He L. Harvesting candidate genes responsible for serious adverse drug reactions from a chemical-protein interactome PLoS Computational Biology 2009;5.
28. Yang l, Wang K, Chen J. Exploring off-targets and off-systems for adverse drug reactions via chemical-protein interactome—clozapine-induced agranulocytosis as a case study PLoS Computational Biology 2011;7.
29. Iskar M, Zeller G, Blattmann P, et al. Characterization of drug-induced transcriptional modules: towards drug repositioning and functional understanding. Mol Syst Biol 2013;9:662.
30. Huang L, Li F, Sheng J, et al. DrugComboRanker: drug combination discovery based on target network analysis. Bioinformatics 2014;30:i228-i36.
31. Hur M, Campbell AA, Almeida-de-Macedo M, et al. A global approach to analysis and interpretation of metabolic data for plant natural product discovery. Natural Product Reports 2013;30:565-83.
32. Liu H, Wang J, Zhou W, Wang Y, Yang L. Systems approaches and polypharmacology for drug discovery from herbal medicines: an example using licorice. Journal of Ethnopharmacology 2013;146:773-93.
33. Liu J, Pei M, Zheng C, et al. A Systems-Pharmacology Analysis of Herbal Medicines Used in Health Improvement Treatment: Predicting Potential New Drugs and Targets. Evidence-based Complementary & Alternative Medicine (eCAM) 2013:1-17.
34. Ding W, Gu J, Cao L, et al. Traditional Chinese herbs as chemical resource library for drug discovery of anti-infective and anti-inflammatory. Journal of Ethnopharmacology 2014.
35. Wang X, Xu X, Li Y, et al. Systems pharmacology uncovers Janus functions of botanical drugs: activation of host defense system and inhibition of influenza virus replication. Integrative Biology: Quantitative Biosciences From Nano To Macro 2013;5:351-71.
36. Wells TNC. Natural products as starting points for future anti-malarial therapies: going back to our roots? Malaria Journal 2011;10 Suppl 1:S3-S.
37. Gu J, Gui Y, Chen L, Yuan G, Xu X. CVDHD: a cardiovascular disease herbal database for drug discovery and network pharmacology. Journal Of Cheminformatics 2013;5:51-.
38. Li P, Chen J, Wang J, et al. Systems pharmacology strategies for drug discovery and combination with applications to cardiovascular diseases. Journal of Ethnopharmacology 2014;151:93-107.
39. Zhou W, Wang Y. A network-based analysis of the types of coronary artery disease from traditional Chinese medicine perspective: potential for therapeutics and drug discovery. Journal of Ethnopharmacology 2014;151:66-77.
40. Luo F, Gu J, Chen L, Xu X. Systems pharmacology strategies for anticancer drug discovery based on natural products. Molecular Biosystems 2014;10:1912-7.

41. Lu B, Hu M, Liu K, Peng J. Cytotoxicity of berberine on human cervical carcinoma HeLa cells through mitochondria, death receptor and MAPK pathways, and in-silico drug-target prediction. Toxicology In Vitro: An International Journal Published In Association With BIBRA 2010;24:1482-90.
42. Schuster D, Kern L, Hristozov DP, et al. Applications of integrated data mining methods to exploring natural product space for acetylcholinesterase inhibitors. Combinatorial Chemistry & High Throughput Screening 2010;13:54-66.
43. Zhang Y, Wang D, Tan S, Xu H, Liu C, Lin N. A Systems Biology-Based Investigation into the Pharmacological Mechanisms of Wu Tou Tang Acting on Rheumatoid Arthritis by Integrating Network Analysis. Evidence-based Complementary & Alternative Medicine (eCAM) 2013:1-12.
44. Xue R, Fang Z, Zhang M, Yi Z, Wen C, Shi T. TCMID: Traditional Chinese Medicine integrative database for herb molecular mechanism analysis. Nucleic Acids Research 2013;41:D1089-D95.
45. Ru J, Li P, Wang J, et al. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. Journal Of Cheminformatics 2014;6:13-.
46. Mukherjee P, Venkatesh P, Ponnusankar S. Ethnopharmacology and integrative medicine - Let the history tell the future. Journal of Ayurveda & Integrative Medicine 2010;1:100-9.