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Structure and dynamics of molecular networks: A novel paradigm of drug discovery A comprehensive review

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ABSTRACT

Despite considerable progress in genome- and proteome-based high-throughput screening methods and in rational drug design, the increase in approved drugs in the past decade did not match the increase of drug development costs. Network description and analysis not only give a systems-level understanding of drug action and disease complexity, but can also help to improve the efficiency of drug design. We give a comprehensive assessment of the analytical tools of network topology and dynamics. The state-of-the-art use of chemical similarity, protein structure, protein–protein interaction, signaling, genetic interaction and metabolic networks in the discovery of drug targets is summarized. We propose that network targeting follows two basic strategies. The "central hit strategy" selectively targets central node/edges of the flexible networks of infectious agents or cancer cells to kill them. The "network influence strategy" works against other diseases, where an efficient reconfiguration of rigid networks needs to be achieved. It is shown how network techniques can help in the identification of single-target, edgetic, multi-target and allo-network drug target candidates. We review the recent boom in network methods helping hit identification, lead selection optimizing drug efficacy, as well as minimizing side-effects and drug toxicity. Successful network-based drug development strategies are shown through the examples of infections, cancer, metabolic diseases, neurodegenerative diseases and aging. Summarizing >1200 references we suggest an optimized protocol of network-aided drug development, and provide a list of systems-level hallmarks of drug quality. Finally, we highlight network-related drug development trends helping to achieve these hallmarks by a cohesive, global approach.

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Abbreviations: ADME, absorption, distribution, metabolism and excretion; ADMET, absorption, distribution, metabolism, excretion and toxicity; FDA, USA Food and Drug Administration; GWAS, genome-wide association study; mTOR, mammalian target of rapamycin; NME, new molecular entity; QSAR, quantitative structure–activity relationship; QSPR, quantitative structure–property relationship; PPAR, peroxisome proliferator-activated receptor; SNP, single-nucleotide polymorphism.

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1. Introduction

'Business as usual' is no longer an option in drug industry (Begley & Ellis, 2012). There is a growing recognition that systems-level thinking is needed for the renewal of drug development efforts. However, interrelated data have grown to such an unforeseen complexity, which argues for novel concepts and strategies. The Introduction aims to convey to the Reader that the network description and analysis can be a suitable method to describe the complexity of human diseases and help the development of new drugs.

1.1. Drug design as an area requiring a complex approach

The population of Earth is growing and aging. Some of the major health challenges, such as many types of cancers and infectious diseases, diabetes and neurodegenerative diseases are in desperate need of innovative medicines. Despite of this challenge, fast and affordable drug development is a vision that contrasts sharply with the current state of drug discovery. It takes an average of 12 to 15 years and (depending on the therapeutic area) as much as 1 billion USD to bring a single drug into market. In the USA, pharmaceutical industry was the most R&D-intensive industry (defined as the ratio of R&D spending compared to total sales revenue) until 2003, when it was overtaken by communications equipment industry (Austin, 2006; Chong & Sullivan, 2007; Bunnage, 2011).

The increasingly high costs of drug development are partly associated

- with the high percentage of projects that fail in clinical trials,
- with the recent focus on chronic diseases requiring longer and more expensive clinical trials,
- with the increased safety concerns caused by catastrophic failures in the market and
- with more expensive research technologies.
- Moreover, direct costs are doubled, where the second half comes from the 'opportunity cost', i.e. the financial costs of tying up investment capital in multiyear drug development projects (Austin, 2006; Chong & Sullivan, 2007; Bunnage, 2011).

We have a few hundreds of targets of approved drugs from the >20,000 non-redundant proteins of the human proteome. Despite the considerably higher R&D investment after the millennium, the number of new molecular entities (NMEs) approved by the USA Food and Drug Administration (FDA) remained constant at an annual 20 to 30 compounds. The number of NMEs potentially offering a substantial advance over conventional therapies is an even more sobering number of 6 to 17 per year in the last decade (Fig. 1). However, it is worth to note that looking only at the number of new drugs without considering their therapeutic value omits an important factor in the analysis (Austin, 2006; Overington et al., 2006; Chong & Sullivan, 2007; Bunnage, 2011; Edwards et al., 2011; Scannell et al., 2012).

Part of the slow progress is related to the high risks of investments. The development of an NME-drug costs approximately four times more than that of a non-NME. Moreover, the 'curse of attrition' steadily remained the biggest issue of the pharmaceutical industry in the last decades (Fig. 2). Each NME launched to the market needs about 24 development candidates to enter the development pipeline. Attrition of phase II studies is the key challenge, where only 25% of the drug-candidates survive. The 25% survival includes new agents against known targets (the 'me-too' or 'me-better' drugs), and therefore may be a significant overestimate of the survival rate of drug-candidates directed towards new targets. The low survival rate is exacerbated further by the very high costs of a failing compound at this late development stage (Brown & Superti-Furga, 2003; Austin, 2006; Bunnage, 2011; Ledford, 2012). These high risks made the drug industry cautious, and sometimes perhaps over-cautious. As the pharmacologist and Nobel Laureate James Black said: "the most fruitful basis for the discovery of a new drug is to start with an old drug" (Chong & Sullivan,

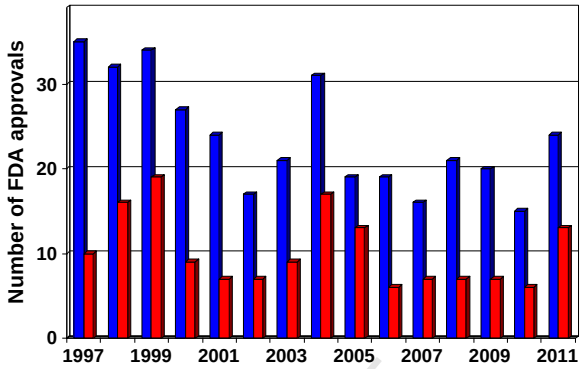

Fig. 1. Number of new molecular entities (NME, a drug containing an active ingredient that has not been previously approved by the US FDA) approved by the US Food and Drug Administration (FDA). Blue bars represent the total number of NMEs, whereas red bars represent "priority" NMEs that potentially offer a substantial advance over conventional therapies. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Source: http://www.fda.gov/Drugs/default.htm.

2007). In fact, analysis of structure–activity relationship (SAR) pattern evolution, drug–target network topology and literature mining studies all showed the same behavior trend indicating that more than 80% of the new drugs tend to bind targets, which are connected to the network of previous drug targets (Cokol et al., 2005; Yildirim et al., 2007; Iyer et al., 2011a).

Improving the quality of target selection is widely considered as the single most important factor to improve the productivity of the pharmaceutical industry. From the 1970s target selection was increasingly separated from lead identification. Drug development process often fell to the 'druggability trap', where the attraction of working on a chemically approachable target encouraged development teams to push forward projects having a poor target quality. Additionally, chemical leads were often discovered to have unwanted side-effects and/or be toxic at later development phases (Brown & Superti-Furga, 2003; Hopkins, 2008; Bunnage, 2011).

The decline in the productivity of the pharmacological industry may stem partly from the underestimation of the complexity of cells, organisms and human disease (Lowe et al., 2010). We will illustrate the high level of this complexity by three examples.

- Under ideal conditions only 34% of single-gene deletions in yeast resulted in decrease in proliferation. However, when knockouts were screened against a diverse small-molecule library and a wide range of environmental conditions, 97% of the gene-deletions demonstrated a fitness defect (Hillenmeyer et al., 2008).
- Many of the most prevalent diseases, such as cancer, diabetes and coronary artery disease have a genetic background including a large number of genes (see Section 5 and Brown & Superti-Furga, 2003; Hopkins, 2008; Fliri et al., 2010). Following a treatment with a chemotherapeutic agent almost all of 1000 tagged proteins of cancer cells showed a dynamic response, when their temporal expression levels and localization were tracked (Cohen et al., 2008).
- As Loscalzo and Barabasi (2011) summarized in their excellent review, diseases are typically recognized and defined by their late-appearing manifestations in a partially dysfunctional organ-system. As a part of this, therapeutic strategies often do not focus on truly unique, targeted disease determinants, but (rightfully) address the patho-phenotypes of the already advanced disease stage. These advanced patho-phenotypes have a large number of symptoms, which are not primarily disease-specific (such as inflammation). This definition of disease may obscure subtle, but potentially important differences among patients with clinical presentations, and may also neglect pathobiological mechanisms extending the disease-defining organ system. Loscalzo and Barabasi (2011) argue that the complexity of

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