

Expert Opinion

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How to design multi-target drugs: target search options in cellular networks

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Despite improved rational drug design and a remarkable progress in genomic, proteomic and high-throughput screening methods, the number of novel, single-target drugs has fallen much behind expectations during the past decade. Multi-target drugs multiply the number of pharmacologically relevant target molecules by introducing a set of indirect, network-dependent effects. Parallel with this, the low-affinity binding of multi-target drugs eases the constraints of druggability and significantly increases the size of the druggable proteome. These effects tremendously expand the number of potential drug targets and introduce novel classes of multi-target drugs with smaller side effects and toxicity. Here, the authors review the recent progress in this field, compare possible network attack strategies and propose several methods to find target-sets for multi-target drugs.

Keywords: antibiotics, disordered proteins, drug targets, fungicides, genomics, multi-target drugs, networks, network damage, pesticides, phosphorylation, protein kinases, proteomics, signaling networks

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1. Introduction: emergence and rationale of the multi-drug concept

Recent drug development strategies were based on the emergence of potential targets in genomic and proteomic studies. Therefore, the drug development paradigm followed at present can be summarized as to: i) find a target of clinical relevance; ii) identify the 'best-binder druggable molecule' by high-throughput screening (HTS) of large combinatorial libraries and/or by rational drug design based on the three-dimensional structure of the target; iii) provide a set of proof-of-principle experiments; and iv) develop a technology platform leading to clinical applications. However, despite all the considerable drug development efforts undertaken, the number of successful drugs and novel targets fell significantly behind the expectations during past decades [1-3].

A number of novel strategies have been developed to overcome the target shortage and to add novel classes of drugs to development pipelines. Many of these drug development directions aim to influence multiple targets in a parallel fashion. One of the most widespread multiple target approaches, combination therapy, is increasingly used to treat many types of diseases, such as AIDS, atherosclerosis, cancer and depression. As one of the newly developed combination therapies, 'multi-target lead discovery' is a promising tool for the identification of unexpectedly novel effects of drug combinations [4-8]. Recently, initial steps have been taken to develop aptamer combinations against complex sets of targets [9].

Multiple target strategies have only recently been rediscovered by drug developers. Snake and spider venoms are both multi-component systems and plants have

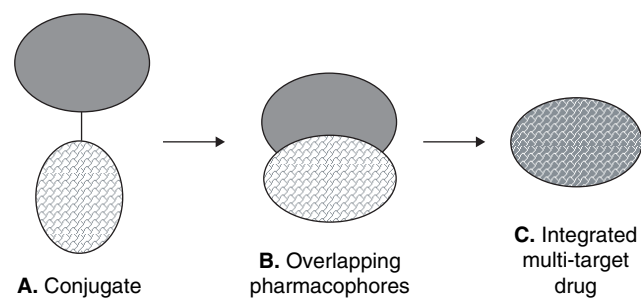


Figure 1. Variants of multi-target drugs. **A.** The increasing overlap of pharmacophores gives an almost continuous spectrum starting from conjugates. **B.** Via slightly overlapping pharmacophores. **C.** Until highly integrated multi-target drugs.

also developed a combinative strategy to defend themselves against pathogens. In addition, traditional medicaments and remedies often contain multi-component extracts of natural products [10,11]. All these examples show that multiple target strategies have benefits, which were used as medicaments by human ancestors several thousand years ago and have withstood a million-year evolutionary selection.

Agents aiming at only a single target ('single-hits') might not always affect complex systems in the desired way, even if they completely change the behavior of their immediate target. Single targets might have 'back-up' systems that are sometimes different enough so as to not respond to the same drug. Moreover, many cellular networks are robust and prevent major changes in their outputs, despite dramatic changes in their constituents [12-15]. These considerations are independent of whether or not the pharmacologic agent inhibits or activates its target.

2. Examples for multi-target strategies

Several efficient drugs, such as salicylate, non-steroidal anti-inflammatory drugs (NSAIDs), metformin, antidepressants, antineurodegenerative agents and multi-target kinase inhibitors (such as Imatinib, or the inhibitors of the kinase-maturing molecular chaperone, Hsp90), affect many targets simultaneously [7,16-24]. Multi-target antibodies (in forms of diabodies, triabodies, tetrabodies and recombinant polyclonal antibodies) are increasingly used in cancer therapy to delay the development of resistance [25,26].

It may be found that a large number of terms used at present to describe ligands have multiple activities: the words balanced, binary, bivalent, dimeric, dual, mixed or triple are all used in combination with various suffixes, such as agonist, antagonist, blocker, conjugate, inhibitor or ligand. Various pharmacophores may have an increasing overlap, which gives an almost continuous spectrum starting from the conjugates (or cleavable conjugates, which are actually a novel chemical form of combinational therapies) to the overlapping pharmacophores, until the highly integrated multi-target drugs (Figure 1 [7,19]).

Multi-target drugs offer a magnification of the 'sweet spot' of drug discovery [1], meaning the overlap between pathways, which are interesting from the pharmacologic point of view, and the hits of chemical proteomics, which represent those proteins that can interact with druggable molecules (meaning small, hydrophobic molecules with a good bioavailability). The sweet spot represents those few hundred proteins, which are both parts of these interesting pathways and are druggable [1]. The option to allow indirect effects via network-contacts of multi-target drugs expands the first circle, as the number of those proteins, which are indirectly related to existing targets of pharmacologically important pathways, is by magnitudes greater than the number of the targets themselves. On the other hand, the low-affinity binding of multi-target drugs enlarges the second circle, as it eases the constraints of druggability. Small, hydrophobic molecules bind to only a small subset of proteins with high affinity. However, the very same molecules interact with 10 or even 100 times more proteins with increasingly lower and lower affinity. Here, low affinity binding describes interactions with dissociation constants in the higher macromolar or even close to the millimolar range. Low affinity binding also implies a more transient interaction (where the off-rate is comparable or higher than the on-rate). As a result of these combined effects, the sweet spot of drug discovery may easily become a wide candy-field (Figure 2).

3. Cellular networks: drug target maps

Cellular networks help us to understand the complexity of the cell. In the network concept, the complex system is perceived as a set of interacting elements that are bound together by links. Links usually have a weight, which characterizes their strength (affinity, or propensity). Links may also be directed links, when one of the elements has a larger influence than the other and vice versa. In cellular networks, the interacting molecules are considered as the elements and their interactions form the weighted, but not necessarily directed, links of the respective structural network. Alternatively, directed links may also be seen as representations of signaling or metabolic processes of the functional networks in the cell (Table 1 [27-29]). Cellular networks often form small worlds where two elements of the network are separated by only a few other elements. Networks of our cells contain hubs, that is, elements which have a large number of neighbors. These networks can be dissected to overlapping modules that form hierarchical communities [30-32]. However, this summary of the main features of cellular networks is largely a generalization and needs to be validated through a critical scrutiny of the data sets, sampling procedures and methods of data analysis at each network examined [33,34].

Cellular networks offer a lot of possibilities to point out their key elements as potential drug targets. An example of these possibilities, signaling networks have interdigitated pathways and multiple layers of cross-talk [35]. Special signaling elements, such as the PI3 kinase, the Akt kinase or the insulin receptor substrate family have been called 'critical nodes'.

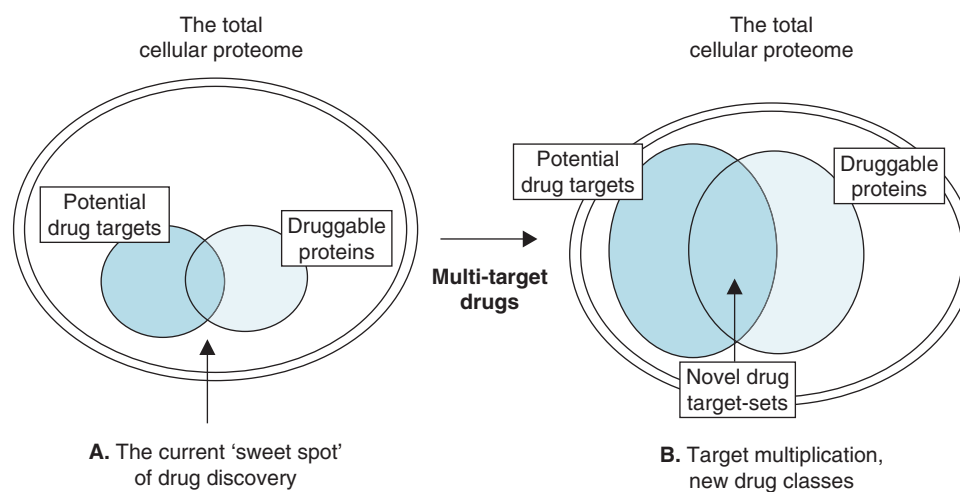


Figure 2. From the 'sweet spot' of drug discovery to a potential candy-field. Multi-target drugs may magnify the 'sweet spot' of drug discovery [1] to a whole candy-field. **A.** The overlap between pathways, which is interesting from the pharmacological point of view and the hits of chemical proteomics, representing those proteins that can interact with druggable molecules, constitutes the 'sweet spot' of drug discovery. **B.** Indirect effects of multi-target drugs expand the number of pharmacologically relevant targets, whereas low-affinity binding enlarges the number of druggable molecules.

These 'critical nodes' have multiple isoforms and are important junctions of signaling pathways [36]. Both the bridge elements of signaling networks, providing cross-talk and the critical nodes, can be important targets of network-based drug development. Domain-specific target analysis of protein-protein interaction networks extends the map of physical interactions towards functional understanding. Domain-specific targets offer a larger flexibility and may actually reflect a family of multiple targets due to the frequent re-use of domain variants as a result of modular evolution [37,38]. Elements of metabolic and cytoskeletal networks have also been analyzed as drug targets [39,40].

However, present databases of most cellular networks suffer a lot of uncertainties. Protein-protein interaction networks have a large number of false-positive entries, which makes the inclusion and assessment of low-affinity interactions especially difficult. Moreover, present databases mostly give an averaged probability of the particular interaction. This does not take into account if the two proteins are expressed at the same time or if they are located in the same cellular compartment at the same time. Most databases do not contain the information of the ratio of two interacting proteins in the given status of the particular healthy or the particular sick cell. Literature-derived, evidence-based databases suffer from the nomenclature and interpretation problems of the original data. However, recent advances connect protein-protein interaction databases with protein structure data, which make both the validation and prediction of protein-protein interactions more robust [41-43].

The above-mentioned problem may be overcome by using curated databases, which contain only the most valid and most accurate information. However, these databases will miss most low-affinity interactions and ~ 80% of the available

information is lost due to increased scrutiny. As an alternative approach, the authors keep all information – taking into account that the author's database becomes 'fuzzy' due to the inclusion of potentially false data. In this approach to correct the errors, highly integrated methods for network analysis are needed, which are able to build in all the above information and take into account those which are in contradiction with most of the others. It is advantageous to use these integrated analytical tools in a 'zoom-in' fashion, where the user may define the integration level of their choice. Low resolution network maps can be calculated faster and by directing the user's mind, showing the most important take-home messages of the analysis. Zooming in to a high-resolution analysis with the same, flexible method, will show the refined details of all available information and give the user a large number of correct (and false) ideas to think about and to test in experiments either in the primary 'hit areas' of the low-resolution analysis or the spots of specific interests based on other assumptions.

4. Multi-target drugs are often low-affinity binders

The development of a multi-target drug is likely to produce a drug that interacts with its target (having a lower affinity than a single-target drug) because it is unlikely that a small, drug-like molecule can bind to a number of different targets with equally high affinity. However, low-affinity drug binding is, apparently, not a disadvantage. For example, memantine (a drug used to treat Alzheimer's disease) and other multi-target non-competitive NMDA receptor antagonists show that low-affinity, multi-target drugs might have a lower prevalence and a reduced range of side effects than high-affinity, single-target

Table 1. Cellular networks as drug target maps.

Name of cellular network	Network elements	Network links	Potential drug targets
Protein interaction network	Cellular proteins	Transient or permanent bonds	Hubs, bridges, proteins in modular centers and overlaps
Cytoskeletal network	Cytoskeletal filaments	Transient or permanent bonds	Cross-linking proteins
Organelle network	Membrane segments (membrane vesicles, domains and of rafts of cellular membranes) and cellular organelles (mitochondria, lysosomes, segments of the endoplasmic reticulum, etc.)	Proteins, protein complexes and/or membrane vesicles, channels	Proteins and lipid rafts regulating inter-organellar junctions
Signaling network	Proteins, protein complexes, RNA (such as micro-RNA)	Highly specific interactions undergoing a profound change (either activation or inhibition) when a specific signal reaches the cell	Hubs, bridge, proteins of cross-talks, 'critical nodes'
Metabolic network	Metabolites and small molecules, such as glucose, or adenine, etc.	Enzyme reactions transforming one metabolite to the other	Metabolic switch enzymes and their regulatory proteins, channelling
Gene transcription network	Transcriptional factors or their complexes and DNA gene sequences	Functional (and physical) interactions between transcription factor proteins (sometimes RNAs) and various parts of the gene sequences in the cellular DNA	Hubs, bridges, proteins in modular centers and overlaps

drugs [20,44]. The recent suggestion to use unstructured proteins as a novel and un-explored field of drug-targets uses the beneficial effects of low-affinity, but rather specific binding, which has been shown to be extremely useful in regulation and signaling [45]. Here again, low affinity binding denotes interactions with dissociation constants in the higher micromolar or even close to the millimolar range. Low affinity binding also implies a transient interaction, where the off-rate is comparable to or higher than the on-rate.

Does low-affinity binding predict a low-efficiency? Not necessarily. Most (> 80%) of the cellular protein, signaling and transcriptional networks are in a low-affinity or transient 'weak linkage' with each other. In metabolic networks, weak links are those reactions that have a low flux [29,46]. In this review, the authors use the term 'weak linker' to denote small molecules and drugs that interact with cellular proteins having a low-affinity. Thus, most multi-target drugs are weak linkers. Because most links in cellular networks are weak, a low-affinity multi-target drug might be sufficient to achieve a significant modification. A recent paper of B N Ames [47] on the potential impact of micronutrients on disease development is a good example of the profound effects emerging from seemingly minor interactions. Low affinity, imperfect binding allows the development of special, cooperative binding behavior, which may lead to a switch-type activation setting a threshold for various cellular events, such as DNA replication [48,49].

5. Identification of drug targets using the network approach: attack strategies

Drug design strategies are mostly based on target-driven approaches, where an efficient compound to influence disease-related molecular target is sought. The network approach examines the effects of drugs in the context of cellular networks. In this model, a drug-induced inhibition of a single target means that the interactions around a given target are eliminated, whereas partial inhibition can be modeled as a partial knockout of the interactions of the target.

Cellular networks are usually damaged by random failures, such as the oxidative damage of free radicals, the indirect effect of somatic mutations and the complex phenomenon of ageing [50]. Opposed to this, drug-driven network attacks are targeted to find the most efficient way to influence network behavior. Several classes of drugs, such as antibiotics, fungicides, anticancer drugs as well as numerous chemical compounds, such as pesticides, are designed to destroy the normal function of cellular networks.

Networks have a number of vulnerable points and, therefore, can be attacked in many ways (Figure 3). The first major insight identifying a set of weak points in natural networks may come from the work of A L Barabasi and co-workers [30,51], who discovered that many real-world networks (including cellular networks) have a scale-free degree distribution, which means

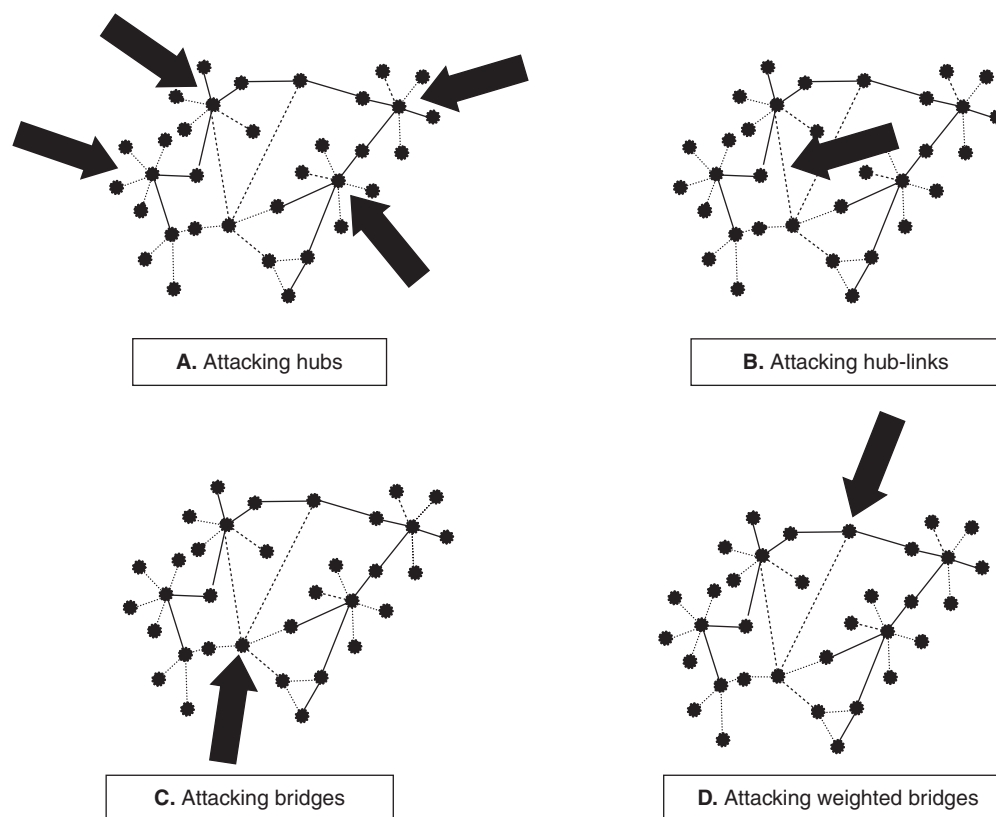


Figure 3. Attack scenarios on networks. In this figure the authors summarize a number of malicious attacks on vulnerable points of networks. **A.** Attacks on nodes with highest degree (hubs). **B.** Attacks on ‘hub-links’ with the highest degree of their end points. **C.** Attacks on bridging elements with links having a high betweenness centrality. **D.** Attacks on bridges having links with the highest weighted centrality.

(in simple terms) that these networks have hubs (e.g., nodes with a much greater number of neighbors than average). If hubs are selectively attacked, the information transfer in most scale-free networks soon becomes significantly hindered. In other words: hubs are central points of networks. Scale-free networks are, however, highly resistant against random damage. These two features can be summarized as having a robust, but fragile nature of scale-free networks. As an illustration for the robustness, 99% of the internet in a random-attack strategy may be deleted and the continuity of the network still remains, that is, the internet could still be used after such an attack, albeit it would be much slower than usual [52]. On the contrary, malicious attacks on hubs may follow a ‘greedy’ strategy, meaning that degrees are continuously recalculated after each attack and network elements are re-ranked. This greedy strategy is often more powerful than using the original degrees of network elements throughout the whole process [53].

Hubs are the centers of networks only from the point of local network topology. Another approach for pinpointing central elements of network communication is to find those elements (or links) that are in a centered position, not in the local, but in the global topology. The “betweenness of centrality” of a link refers to the number of shortest paths between any

two elements of the network across the given link. The betweenness centrality was worked out initially in social networks [54], but later it became a preferred centrality measure to assess the presumed effect of targeted attacks on network stability. Inverse geodesic length (also called network efficiency), meaning the sum of the inverse of the shortest paths between network elements, is widely used as an indicator of network damage after the removal of links or elements [53,55,56]. Alternative measures of the damaging element or link removal have also been worked out by Latora and Marchiori [57], which are based on monitoring of the performance of the whole network.

Recent studies take into account the weights and directness of network links. This is much closer to the real, cellular scenario, where protein–protein interactions are characterized by their affinity and/or prevalence (link weight) as well as direction (e.g., in form of signaling). The removal of the links with the highest weighted centralities is often more devastating to network behavior than the removal of the most central links based on the unweighted version of the same network topology [58].

Another recent approach is to take into account mesoscopic centrality network topology measures, which are neither based

on local information (such as hubs) or global information (such as betweenness centrality), on network structure. Motter *et al.* [59] found that the removal of long-range links connecting elements a long distance from each other has a profound impact on small-world networks; however, it fails to affect many scale-free networks. Another complication is caused by multi-layered networks [101], where various communities and modules are organized in a hierarchical fashion. These studies reveal that the use of the complex structural information of real world networks needs more sophisticated methods, such as an integrated assessment of link density and network topology (Kovacs *et al.*, manuscript in preparation).

The network approach helped to gain ground in drug target analysis. Flux-balance analysis (or metabolic control analysis) uses a large database of experimental data and calculates all of the metabolic rates of the metabolic network, assuming that the rates of reactions producing a metabolite must be equal with the rates of reactions that consume it. Flux-balance analysis of metabolic networks uncovers vulnerable points of parasite or pathologic metabolisms providing potential targets for efficient drug action [39,60-62]. Comparison of cellular (transcriptional, signaling, protein-protein interaction etc.) networks from various genomes helps to identify the function of novel proteins and, thus, increases the number of potential drug targets [63,64]. Analysis of protein-protein interactions identifies protein contact surfaces as potential sites of drug action [65] and neural networks have long been applied to help in methodological and computational drug design [66].

Most of the above network-related methods have been used so far to steer target identification attempts to single targets and a systematic network-based analysis of multi-target drug action is still to come. In the authors' earlier study [55,67], a multi-target attack on the genetic regulatory networks of the bacterium *Escherichia coli* or the yeast *Saccharomyces cerevisiae* was modeled. A comparison of various strategies suggested that multiple, but partial, attacks on carefully selected targets were almost inevitably more efficient than the knockout of a single target. For example, the largest damage to the *E. coli* regulatory network was reached by removing an element with 72 connections. However, the same damage could be achieved if three to five nodes were partially inactivated. Multiple attacks have proven to be more efficient than a single attack even if the number of affected interactions remained the same [55,67]. Thus, the reason underlying the efficiency of multi-target attacks was proven not to be trivial, even from a theoretical point of view: multi-target attacks were not only better because they affected the network at more sites, but they could, especially if distributed in the entire network, perturb complex systems more than concentrated attacks even if the number of targeted interactions remained the same.

6. Network diseases

The authors' initial network-based analysis of the potential efficiency of multi-target drugs [55,67] was based on the topology

of bacterial and yeast gene regulatory networks, which may be regarded as an initial model of the multi-target action of antibiotics and fungicides, where network damage corresponds well to the desired drug action. For the analysis of multi-target drugs affecting specific disease models (e.g., antihypertensive, antipsychotic and antidiabetic drugs), more specific signaling, metabolic and transcriptional network models are needed. As a prelude of this process, several complex multifactorial diseases have already been described as 'network diseases'. Cancer was assessed as a systems biology disease by Hornberg *et al.* [68]. The complexity of intra- and extra-cellular cancer-specific changes in signaling, gene-regulatory (and, most probably, protein-protein interaction) networks, the profound reorganization of cellular metabolism, the multiple types and interactions of cells involved and the complexity of all these events at various types and subtypes of malignant transformation make the name 'systems biology disease' well deserved for all stages of tumor development.

Network effects of continuously changing functional neuron assemblies may provide an explanation of the daily fluctuations in the symptoms of neurodegenerative diseases. This approach may show novel pathways of drug development, leading to shorter and cheaper clinical trials that concentrate on the short-term attenuation of symptom fluctuations, instead of waiting for and monitoring the long-term and rather elusive benefits of inhibited neurodegeneration [69]. As increased fluctuations of this efficiency may reflect a general decline in the stability of the overall network, which is related to the reduction of weak links [29,46] – multi-target drugs might be an ideal choice to prevent further functional loss in this sense. The complexity of neuronal networks also led to the concept of network disease in the case of depression aiding the design of novel, multi-target antidepressants [7].

Last, but by no means least, ageing has also been conceived as a network disease [50,70]. The multiple reasons and stages of biological ageing, the increasing variability of symptoms and malfunctions, both from one elderly person to the other and from one day to another, all call for a network-based analysis of the increasing amount of data collected so far.

7. Target-sets of multi-target drugs: the help of networks

How should we find the relevant target-sets of multi-target drugs? In the last decade several experimental and modeling approaches have been developed to identify single targets in a network context [39,60,61,71-74]. Appropriate modifications of these approaches may constitute the first step for zooming in to a smaller set of potential targets. A high-throughput combinative screen of all possible combinations may be a daunting task and prospect [5]. How can we pin point those target combinations that might be relevant in the clinical setting?

Surprisingly, old-fashioned drug development might come back here to help: *in vivo* pharmacology (i.e., whole-animal

studies) might become important again [75]. However, for more efficient *in vivo* testing, better animal models are needed. Better animal models can be achieved by humanizing the metabolic and signaling network of test animals.

Can the network approach help suggest potential target sets? The answer is not known at present. However, the authors have many promising tools to assess the relevance of their present, network-based knowledge on the complexity of the cell in pathologic states. The authors will list these in the Expert Opinion section.

8. Conclusion

Combinatorial therapies have recently become one of the most successful drug development strategies. Multi-target drugs can be perceived as siblings of combinatorial therapies, where the different agents (often as many as five to six of them) are compressed into a single, integrated chemical entity. Multi-target drugs expand the number of pharmacologically relevant target molecules by introducing a set of indirect, network-dependent effects. Multi-target drugs usually have a low affinity towards their targets. An increasing amount of evidence shows that low affinity, especially if multiplied, does not mean low efficiency. On the contrary, several signaling and regulatory events are actually based on low-affinity interactions. Moreover, low-affinity binding of multi-target drugs eases the constraints of druggability and significantly increases the size of the druggable proteome. These effects tremendously expand the number of potential drug targets and will introduce novel classes of multi-target drugs with smaller side effects and toxicity. Cellular networks offer a large number of possibilities, such as hubs and bridges with high betweenness centrality to find target-sets of multi-target drugs. However, the ‘fuzziness’ (meaning uncertain and incomplete information) of cellular networks and the data sets on network diseases, such as cancer, diabetes and neurodegeneration, need a more sophisticated approach.

9. Expert opinion: network-based, smart multi-target drugs of the future

We predict that in 5 – 10 years multi-target drugs will be much more common than it is today. The emerging knowledge of recent years strongly suggests that these drugs have a better chance of affecting the complex equilibrium of whole cellular networks than drugs acting on a single target. Target expansion to indirect targets will lead to the discovery of several novel classes of drugs. Moreover, it is sufficient that these multi-target drugs affect their targets only partially, which multiplies our target choices from the point of druggability.

Low-affinity, multi-target drugs might have another advantage. Weak links have been shown to stabilize complex networks, including macromolecular networks, ecosystems and social networks, buffering the changes after system perturbations.

If multi-target, low-affinity drugs inhibit their targets, they change a strong link into a weak link, instead of eliminating the link completely. A weak activation also results in a weak link in most of the cases. Thus, multi-target drugs can increase the number of weak links in cellular networks and, thus, stabilize these networks, in addition to having multiple effects. Stabilization of the cells becomes especially important if we take into account that cells of stressed, sick and ageing organisms are at the ‘verge of chaos’, showing a much greater instability than their healthy counterparts [29,46,70,76,77]. Thus, multi-target drugs may have multiple beneficial effects:

- they can be designed to act on a carefully selected set of primary targets, which help to sum up the action of the drug on key, therapeutically relevant secondary targets
- via the above-mentioned, indirect approach and their low affinity binding multi-target drugs may avoid the presently common dual-trap of drug resistance and toxicity
- finally, the low affinity, weak links of multi-target drugs have an important side effect: they stabilize the sick cell, which may be sometimes at least as beneficial as their primary therapeutic effect.

What is the 5 – 10 year perspective on finding the relevant target-sets of multi-target drugs? Here, our increasing knowledge of cellular networks will certainly play a key role in the future. The increasing complexity of the data sets requires more sophisticated tools to direct our attention to relevant areas of the information universe. In the last part of this review, we list a few ideas for future directions in the development of network analysis tool-kits:

- overlaps of network communities [31], which have a key role in the regulation of complex systems [29], may be efficient guides to restrict the initial target pool in search of target sets for multi-target drugs
- differential analysis of relevant cellular networks, (such as signaling networks, gene-regulatory networks, metabolic networks and protein–protein interaction networks) of healthy and sick cells may provide an even more efficient screen
- finally, the present development of analytical tools to assess the evolution and dynamism of whole cellular networks will reveal search methods to deconvolute the hidden masterminds of the primary target sets from the presently known, pharmacologically relevant secondary targets (Kovacs *et al.*, patent application submitted). A variant of this approach has been called ‘reverse-engineering’, which deciphers potential targets by the analysis of the effect of a limited set of experimental perturbations [71,78–80]. These approaches open the way to finding multiple-targets and to designing alternative target sets to mimic the action of existing, successful drugs

In summary, 10 years from now we will have a multitude of expanded cellular data sets having detailed and differential information on variable pairs of healthy and sick cells. These data sets will have graded information, which enables the

building of weighted and directed networks. Analytical tools will be developed to assess the complexity of these networks, keeping all data and giving a zoom in picture of any resolution in a computationally accessible, short time. Multi-target drugs will magnify the presently available target field by introducing thousands of secondary targets, as well as other thousands of druggable proteins. This will all lead to the discovery of several entirely novel drug classes. Finally, we will enjoy the network option of fine-tuning of drug action of multi-target drugs by the targeted manipulation of certain

elements of the already existing target sets of multi-target drugs, which may lead to the development of personalized medicines – at a low cost.

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