

Personalized network-based treatments in oncology

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Abstract

Network medicine aims at unraveling the cell signaling networks to propose personalized treatments for patients suffering from complex diseases. In this short review, we show the relevance of network medicine to cancer treatment by outlining the potential convergence points of the most recent technological and scientific developments in both drug design and signaling networks analysis.

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Introduction

For many years, cancer research has been focusing on developing new drug treatments, and especially personalized treatments, that aim to target the patient's cancer specifically. Personalized or targeted therapies have been proposed, based primarily on gene sequencing (Feero et al. 2011; Hieronymus et Sawyers 2012) or gene expression patterns (van 't Veer et Bernards 2008; Weigelt, Baehner, et Reis-Filho 2010; Colombo et al. 2011). A common significant limitation with these personalized therapies is that they are focused on identifying one single marker that will be measured to determine the optimal treatment. However, as was demonstrated by Janes and colleagues (Janes et al. 2005) in a landmark article, this simplistic approach can lead to wrong decisions. They found that the protein kinase JNK could have either a pro- or an anti-apoptotic effect depending on the state of the signaling network. This highlights a very important aspect of cellular-decision processes: signaling follows rules of complex systems, where the final outcome is dependent not only on the parameters of the system but also on the initial conditions (context-dependency). The importance of signaling networks architecture has direct implications on biomarker discovery, and several authors have advocated for a shift of the paradigm; from one or a few measurements to signaling networks (Barabási 2007; Erler et Linding 2010; Erler et Linding 2012; Barabási, Gulbahce, et Loscalzo 2011; Creixell et al. 2012; Pawson et Linding 2008).

Following the signaling network paradigm, which considers external cues to be processed by a series of protein-protein interactions and post-translational modifications, and results in phenotypic changes, the analysis of a disease is based on several signals or markers and the treatment is based on the assessment of the disease as a system. Suggested therapies take into account the capacity of the system to adapt to perturbation (e.g. drug resistance); therefore the proposal of combination therapies that would be able to overcome the systems robustness, by anticipating its adaptation mechanisms.

Combination therapies have been around for decades (DeVita, Young, et Canellos 1975; Al-Lazikani, Banerji, et Workman 2012), and a number of combination therapies with agents that target different so-called 'pathways' are in clinical trials. For example, in advanced melanoma, studies combining a BRAF inhibitor and a Pi3K inhibitor are currently recruiting patients ([Clinicaltrials.gov](#)). Even though these combination therapies have been designed with the knowledge that cells can adapt to one perturbation (Bozic et al. 2013), they haven't been designed following a systematic analysis of the cell signaling networks dynamics (i.e. how signals and networks themselves are changing in time) and of the crosstalk

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between these networks. A fundamental problem is the inherent incompleteness, non-context aware and even incorrect descriptions of dynamic network states as simplistic ‘pathway’ diagrams (Jørgensen et Linding 2010).

Thus, other ways to design combination treatments have been proposed, ranging from time-staggered application (Lee et al. 2012) to the use of several potentially nonspecific drugs (Hopkins 2008). In the case of Lee et al. the utilization of the systems dynamics to improve the efficacy of drugs is groundbreaking, and we predict many more studies like this will pave the way for new more powerful treatment strategies, even for combinations of drugs that hitherto or in previous clinical trials were deemed ineffective. [Figure 1](#) highlights the main differences between classical targeting strategies, hitting a single target, and network-based strategies that hit part of, or the whole, of a signaling network.

In this perspective, we review the state-of-the-art in network-based drugs and treatments and propose some ways to provide more effective treatments. We show that a better understanding of signaling networks is a critical step towards such treatments.

Network treatments

There is a growing amount of experimental evidence that shows the impact of network medicine on drug development. The initial work of Schoeberl *et al.* (Schoeberl et al. 2009) who built a computational model of the ErbB signaling network in order to detect the most effective ligands of ErbB, allowed the identification of ErbB3 and EGFR as key nodes for ligand response and the design of an antibody to specifically target those nodes that stopped the growth of tumors in xenografts mice. This research has been followed-up by a number of clinical trials, and the MM-121 antibody is now in phase II clinical trial (Clinicaltrials.gov; merrimackpharma.com/solutions/pipeline). Earlier on Huang *et al.* (Huang et al. 2007) determined a combination treatment with c-Met kinase inhibitor and either an EGFR kinase inhibitor or cisplatin resulted in an increased cytotoxicity. It also resulted in phase I and II clinical trials (Huang, Xu, et White 2009). Other examples can be found in the literature (Leung et al. 2012), proposing treatments attacking only one single or a very small number of nodes in these networks.

Because signaling networks can and will rewire themselves after being attacked (Creixell et al. 2012), network drugs should be constituted of compounds that will have a significant coverage of the network. A classical way to investigate this strategy is to perform a systematic, genome-wide screen (Luo et al. 2009) with known compounds. This can highlight potential synthetic drugs, however it doesn't make use of any information about the network connectivity or dynamics. A major breakthrough in the field has been carried out in the Yaffe lab,¹⁶ who performed a detailed study of the network changes after time-staggered EGFR inhibition, making the cancer cell more sensitive to DNA-damaging drugs. This

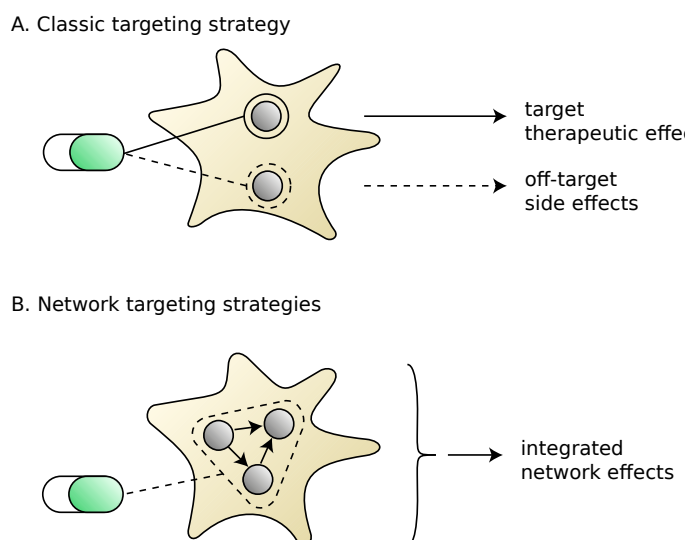


Figure 1: Classic versus network view of drug action. In the classic view (A), a drug as a target and off-target effects, which activate pathways of effectors to trigger therapeutic and side effects, respectively. In the network or systemic view (B), multiple targets of a signaling network are perturbed, resulting in integrated therapeutic and side effects.

effect was highly time-dependent, and simple co-administration of the drugs resulted in a radically decreased effect. The combination of both approaches, i.e. time-staggered, genome-wide RNAi screens, results in a very large number of putative combinations. Advanced algorithms need to be developed to make this approach feasible, and a better understanding of the regulation networks is a critical step towards that end (Pawson et Linding 2008).

Despite the accumulating evidence of its potential impact, network medicine is still in its infancy. However, network biology, as well as personalized approaches, are clearly expected to play significant role in the development of novel and more sustainable treatments in the future.

Personalized medicine

Beyond the buzzword, personalized medicine is the development of therapies that are targeted at the specific tumor affecting the patient (Creixell *et al.* 2012; Gonzalez-Angulo, Hennessy, et Mills 2010). With the scientific and technological advances discussed above, it becomes feasible to integrate sequencing, mass spectrometry and genome-wide screening data into predictive computer models. We refer to the ability to predict how cells respond to input cues or treatments from their current state of their signaling networks as biological forecasting. Similar to weather forecasts, super-computing facilities are required to model the complex networks of interactions and their effects on cellular phenotype. In the case of a cellular model, large-memory systems must hold the whole dataset in memory, as integrative and non-linear effects makes it impossible to split the problem into smaller sub-problems. Such models should integrate genetic (sequencing), expression (proteomics not mRNA expression), signaling (e.g. phospho-proteomics) and phenotypic (e.g. screening and imaging) data. Early integrative network biology studies were demonstrated by Janes *et al.* (Janes *et al.* 2005), Linding *et al.* (Linding *et al.* 2007), Jørgensen *et al.* (Jørgensen *et al.* 2009) and e.g. Bakal *et al.* (Bakal *et al.* 2007; Bakal *et al.* 2008) who modeled genetic and phospho-proteomic data with neural networks and other algorithms to derive information on the signaling network architecture. More advanced models of this type can then be used to predict which treatment will be most effective against a specific cancer (Creixell *et al.* 2012).

Practically, several network-targeting strategies are available and the most important ones are shown in Figure 2. A network drug can target a single, central node of a signaling network (Figure 2A). But more complex, multi-target therapies can be developed as well, with either a single multi-targeted drug hitting several nodes (Figure 2B), or several specific drugs each hitting a different node of the signaling network (Figure 2C). Alternatively, one can also imagine multiple multi-target kinase inhibitors (Figure 2D) may result in a specific overall impact on the tumor cells signaling networks which can be beneficial from the therapeutic point of view.

However, the limited number of drugs approved by the US FDA currently reduces the choice of potential targets available. In 2006, Overington *et al.* (Overington, Al-Lazikani, et Hopkins 2006) estimated that the pharmacopoeia available at this time contained 324 distinct molecular drug targets. This relatively small number of targets must be mitigated with the relative lack of specificity of many drugs, also termed promiscuity, meaning most drugs actually hit several targets (Nobeli, Favia, et Thornton

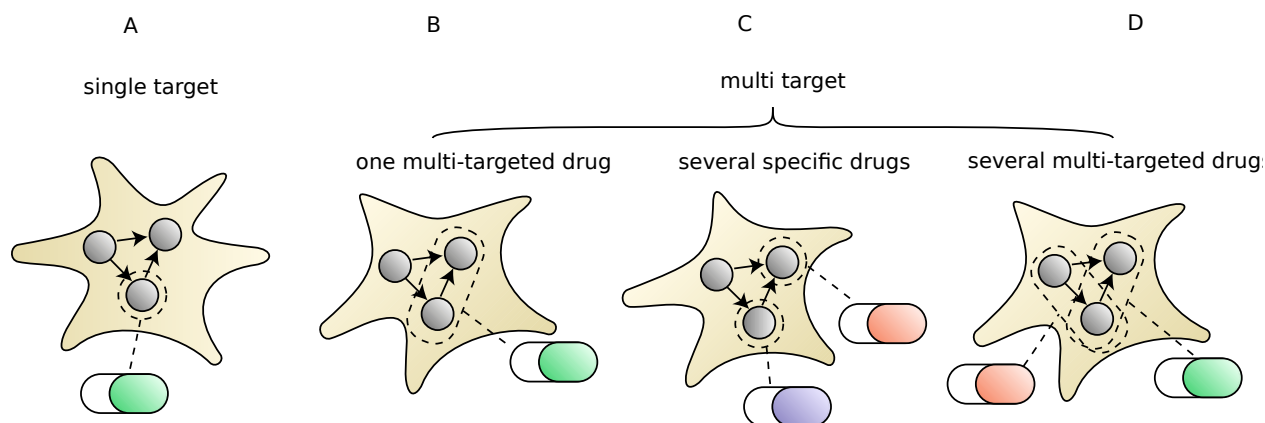


Figure 2: The three most important network-targeting strategies. A single drug can be used to target a single node of the network (A) or multiple nodes can be targeted with one multi-targeted (B) or several specific (C) or multi-targeted (D) drugs.

2009; Hopkins 2009). Kinase inhibitors in particular have been shown not to be very selective (Karaman *et al.* 2008; Davis *et al.* 2011; Anastassiadis *et al.* 2011). Some researchers such as Andrew Hopkins argued that promiscuity is part of a drug's efficacy and that one could take advantage of this lack of specificity to design drugs hitting several targets at once and maximize the drug's clinical effect (Hopkins 2008; Hopkins, Mason, *et al.* Overington 2006). This is indeed supported by Gleevec and many other drugs being approved for secondary indications, or having extensive off-label usage (Kesselheim *et al.* 2012). A potentially interesting advantage of designing network-based treatment strategies could be the possibility of using lower doses of each drug to maintain, or improve, efficacy whilst reducing side-effects, as proposed by Lötsch and Geisslinger (Lötsch *et al.* Geisslinger 2011).

Unfortunately, the pharmaceutical industry is still essentially focusing on developing drugs that hit a given target as specifically as possible. We question this strategy that, while it may be useful in identifying the best drug for a given node, does not equal the best treatment strategy, nor the best target. Such knowledge must be derived through systematic biological studies of the signaling networks associated with the disease or cancer type. A notable exception is Merrimack Pharmaceuticals Inc. (Cambridge, MA, USA) that develops multi-targeted, network-attacking antibodies named MM-111 (Kirouac *et al.* 2013), MM-141 and MM-151 (merrimackpharma.com/solutions/pipeline).

New strategies for drug development are being developed that will eventually provide a larger catalog of potential drugs to choose from and combine. Initiatives to establish this catalog are ongoing (Paolini *et al.* 2006), with the DrugBank (Knox *et al.* 2011), CANSar (Halling-Brown *et al.* 2011) and ChEMBL (Gaulton *et al.* 2011) databases providing mapping between drugs and their targets. A new class of drugs that we predict will soon expand this catalog are siRNA molecules that suppress the expression of a gene. Upon entering the cell, the siRNA molecule will trigger the assembly of the RISC complex, and bind with the target mRNA which will be cleaved. The main barrier to the design of siRNA-based drugs is the delivery of a charged molecule to the target tissue. This challenge is addressed with the development of a large variety of groundbreaking carrier nanoparticles (Lee *et al.* 2012; Whitehead, Langer, *et al.* Anderson 2009). The first clinical trials are ongoing (Burnett *et al.* Rossi 2012), and will hopefully soon deliver a genome-wide catalog of potential treatments and treatment combinations from which a personalized treatment can be chosen. Furthermore, research is ongoing to develop the delivery of combinations of siRNA with other drugs (Meng *et al.* 2013).

Perspectives

At the moment even with the relatively low number of FDA approved drugs it would be impractical to screen all possible combinations across all cell types and secondary or higher order alternate input cues (Janes *et al.* 2005). If we include all potential candidate drugs, the number of combinations scales to an unfeasible level. A better understanding of the signaling networks, together with biological forecasting models, will be needed to guide the relevant questions and hypothesis to test in drug screens (Creixell *et al.* 2012). Such models can also help explore parts of the networks' state spaces otherwise non-reachable through screening (Creixell *et al.* 2012). Lee *et al.* (Lee *et al.* 2012) demonstrated the complexity of signaling networks, and a proof of concept that complex treatments strategies can deal with this complexity. However, more systematic approaches based on signaling network models are required to efficiently drive the development of more network therapies.

Several important issues remain to be solved. What data can we reasonably collect from the patient? While it seems realistic to obtain a tissue sample from the primary tumor that can be genotyped and analyzed by mass-spectrometry for (phospho-)proteomics profiling, it could be impractical to collect such data in certain cases, for instance from metastatic sites where the cells are spread through the patient's body and often undetectable. In some cases this can be counter acted by single-cell technology, for example the CyTOF single-cell mass-cytometer (Bodenmiller *et al.* 2012). Research is ongoing to exploit tumour cells and DNA markers circulating in blood to gain additional information on the tumour (De Mattos-Arruda *et al.* 2013) like initial or acquired mutations, drug sensitivity and early relapse detection (Crowley *et al.* 2013). Then again there still remains the question of how we can verify whether the treatment is having an effect? The most elaborated approach to monitoring cancer treatment response is imaging using PET, CT or (DW-)MRI to estimate tumor size, shape, texture, structure and dynamics (Thoeny *et al.* Ross 2010). These techniques can also be used to detect therapeutic

effects on tumor metabolism (18F-Fluorodesoxyglucose uptake) and cell proliferation (18F-Fluorothymidine incorporation) (Avril, Sassen, et Roylance 2009). However, often metastatic sites are missed due to non-comprehensive data analysis or tumor cell colonies below the detector limit surviving treatment.

An interesting alternative to patient sample collection is being developed at the M. D. Anderson Cancer Center under the codename "T9 project" where immunocompromised mice are used as xenograft models. A small biopsy of the patient tumours is transplanted into mice, which are then treated with various drugs in order to establish which one induces the strongest effect (Gonzalez-Angulo, Hennessy, et Mills 2010). Such in vivo testing could complement in vitro and in silico models and eventually lead to better and more personalized drug treatments.

Conclusion

Network medicine holds the promise of delivering more personalized and efficient treatments of cancers. With the larger sets of candidate drugs that will be available in the near future, network-based analysis could be the bridge that will point out which treatment, either a single drug, a combination of drugs, time-staggered or other complex treatment, will most efficiently treat a given patient. This will also pave the way for sustainable medicine of the future.

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